Australian Government
Department of Health
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan (Consultation version) for

DIR 185

Clinical trial with genetically modified *Bordetella pertussis* (BPZE1) for the prevention of whooping cough

Applicant: Novotech (Australia) Pty Ltd

30 September 2021

This RARMP is open for consultation until 4 November 2021.

Written comments on the risks to human health and safety and the environment posed by this proposed clinical trial of the GM whooping cough vaccine are invited. You may make your submission

via mail to: The Office of the Gene Technology Regulator, MDP 54 GPO Box 9848, Canberra ACT 2601

or

via email to: ogtr@health.gov.au.

Please note that issues regarding patient safety and the quality of the vaccine **do not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

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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)

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

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*.

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.

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Abbreviations

AICIS	Australian Industrial Chemicals Introduction Scheme
aP	Acellular pertussis vaccine
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
CCI	Confidential Commercial Information
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
FSANZ	Food Standards Australia New Zealand
g	gram
GM	Genetically modified
GMO	Genetically modified organism
GTTAC	Gene Technology Technical Advisory Committee
HGT	Horizontal gene transfer
IATA	International Air Transport Association
IN	Intranasal
IBC	Institutional Biosafety Committee
min	Minute
ml	Milli litre
OGTR	Office of the Gene Technology Regulator
PCR	Polymerase chain reaction
RARMP	Risk Assessment and Risk Management Plan
RNA	Ribonucleic acid
TGA	Therapeutic Goods Administration
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
USA	United States of America
WHO	World Health Organization
wP	Whole cell pertussis vaccine

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.

4. The *Risk Analysis Framework* (RAF) (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR website).

5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Risks to the health and safety of people or the environment posed by the proposed supply are assessed within this context. Chapter 1 describes the risk assessment context for this application.

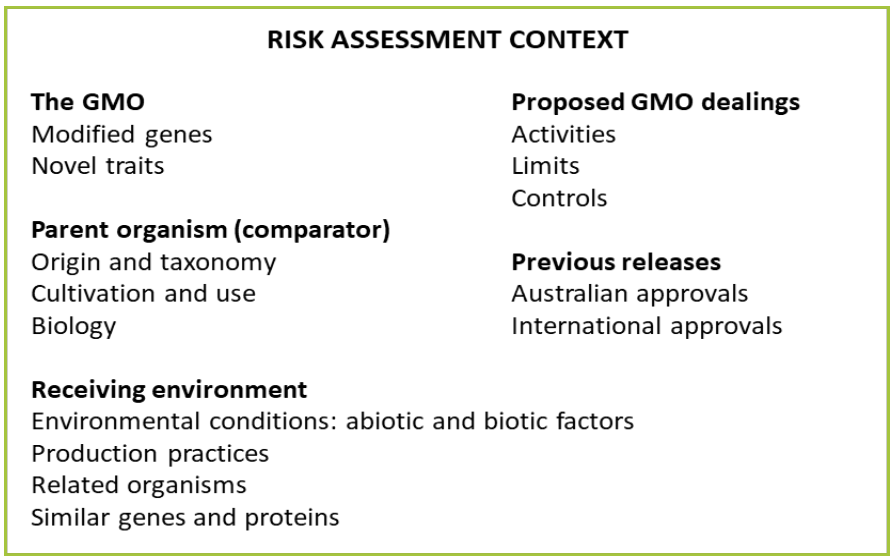

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. In accordance with Section 50A of the Act, this application is considered to be a limited and controlled release application, as the Regulator was satisfied that it meets the criteria prescribed by the Act. Therefore, the Regulator was not required to consult with prescribed experts, agencies and authorities before preparation of the RARMP.

7. Section 52 of the Act requires the Regulator to seek comment on the consultation RARMP from agencies - the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities or agencies prescribed in the Regulations, Australian local councils and the Minister for the Environment - and from the public.

1.1 Interface with other regulatory schemes

8. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. The GMOs and any proposed dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including Food Standards Australia New Zealand (FSANZ), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA), the Australian Industrial Chemicals Introduction Scheme (AICIS) and the Department of Agriculture, Water and the Environment (DAWE).

9. Medicines and other therapeutic goods for use 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 TGA is responsible for administering the provisions of this legislation. Clinical trials of therapeutic products that are experimental and under development, prior to a full evaluation and assessment, are also regulated by the TGA through the Clinical Trial Approval (CTA) scheme or the Clinical Trial Notification (CTN) scheme.

10. For clinical trials, the TGA has regulatory responsibility for the supply of unapproved therapeutic products. In terms of risk to individuals participating in a clinical trial, the TGA (as the primary regulatory agency), the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles in ensuring participants' safety under the *Therapeutic Goods Act 1989*. However, where the trial involves a GMO, authorisation is also required under gene technology legislation. To avoid duplication of regulatory oversight, and as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment. This includes risks to people preparing and administering the GM vaccine, and risks associated with import, transport and disposal of the GMO.

11. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guidelines for Good Clinical Practice (ICH-GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH 1996). The guideline was developed with consideration of the current good clinical practices of the European Union (EU), Japan, and the United States of America (USA), as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). The TGA has adopted the ICH-GCP in principle as Note for Guidance on Good Clinical Practice (designated CPMP/ICH/135/95) (Therapeutic Goods Administration 2000), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

12. The National Health and Medical Research Council (NHMRC) has issued the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council et al., 2018). This document sets the Australian standard against which all research involving humans is reviewed. The *Therapeutic Goods Act 1989* requires that the use of a therapeutic good in a clinical trial must be in accordance with the ethical standards set out in this document.

13. Approval by a Human Research Ethics Committee (HREC) is also a fundamental requirement of a clinical trial. HRECs conduct both ethical and scientific assessment of the proposal and in addition often consider issues of research governance. Other elements of governance of clinical trials that are considered by HRECs include appropriate informed consent, specific inclusion and exclusion criteria, data monitoring and vaccine accounting and reconciliation.

14. The Department of Agriculture, Water and the Environment administers Australian biosecurity conditions for the importation of biological products under the *Biosecurity Act 2015*. Biological products include animal or microbial derived products such as foods, therapeutics, laboratory materials and vaccines (including GM vaccines). Import of GM vaccine is subject to regulation by the Department of Agriculture, Water and the Environment and the Regulator.

15. All clinical trial sites would be located at medical facilities including out-participant settings, hospitals and associated pharmacies. Analysis of biological samples collected from trial participants administered with the GMO would occur at clinical trial sites, or at pathology laboratories. These facilities are regulated by State and Territory governments and adhere to professional standards for safety (NSQHS), disease control (Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019) and handling of pathology samples (NPAAC).

16. The state and territory governments regulate hospitals and other medical facilities in Australia. All public and private hospitals and day procedure services need to be accredited to the National Safety and Quality Health Service (NSQHS) Standards developed by the Australian Commission on Safety and Quality in Healthcare (the Commission) and endorsed by the state and territory Health Ministers. The Commission coordinates accreditation processes via the Australian Health Service Safety and Quality Accreditation (AHSSQA) scheme. The NSQHS Standards provide a quality assurance mechanism that tests whether relevant systems are in place to ensure that the minimum standards of safety and quality are met. The safety aspects addressed by the NSQHS Standards include the safe use of sharps, disinfection, sterilisation and appropriate handling of potentially infectious substances. Additionally, the Commission has developed the National Model Clinical Guidance Framework, which is based on, and builds on NSQHS Standards to ensure that clinical governance systems are implemented effectively and to support better care for patients and consumers.

17. The National Pathology Accreditation Advisory Council (NPAAC) advises Commonwealth, State and Territory health ministers on matters relating to the accreditation of pathology laboratories. NPAAC plays a key role in ensuring the quality of Australian pathology services and is responsible for the development and maintenance of standards and guidelines for pathology practices. The standards include safety precautions to protect the safety of workers from exposure to infectious microorganisms in pathology laboratories. While compliance with NPAAC standards and guidelines is not mandatory, there is a strong motivation for pathology services to comply, as Medicare benefits are only payable for pathology services if conducted in an appropriate Accredited Pathology Laboratory (APL) category, by an Approved Pathology Practitioner (APP) employed by an Approved Pathology Authority (APA). Accreditation of pathology services is overseen by Services Australia (formerly Department of Human Services), and currently, the only endorsed assessing body for pathology accreditation is the National Association of Testing Authorities (NATA).

18. Hospitals and pathology laboratories, including their workers, managers and executives, all have a role in making the workplace safe and managing the risks associated with handling potentially infectious substances including the proposed GMO. There are minimum infection prevention practices that apply to all health care in any setting where health care is provided. These prevention practices were initially developed by the Centers for Disease Control and Prevention (CDC), and are known as the standard precautions for working with potentially infectious material. The standard precautions are described in the Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019).

Section 2 The proposed dealings

19. Pertussis or more commonly known as ‘whooping cough’ is an acute respiratory disease caused by the bacteria *Bordetella pertussis* (*B. pertussis*). Vaccination against whooping cough has been mainly targeted at infants and young children because the disease can be more severe and

possibly lead to deaths in these age groups. Despite a good global vaccine coverage, there has been around 145, 000 reported cases of whooping cough worldwide in 2019 (WHO, 2020b).

20. Novotech (Australia) Pty Ltd (Novotech) is seeking authorisation to carry out a clinical trial to assess the safety and efficacy of a genetically modified (GM) vaccine (BPZE1) in school aged children to prevent the incidence of the disease and its spread.

21. The dealings involved in the proposed clinical trial are:

(a) import the GMO;

(b) conduct the following with the GMO:

i. preparation of the GMO for administration to trial participants;

ii. administration of the GMO to clinical trial participants by inhalation;

iii. collection of samples from trial participants;

iv. analysis of samples from trial participants;

(c) transport the GMO;

(d) dispose the GMO;

and may possess (including storage), supply, use or store the GMO for the purposes of, or in the course of, any of these dealings.

2.1 The proposed limits of the trial (duration, scale, location, people)

22. The clinical trial is proposed to take place over a five-year period from the date of issue of the licence. Up to 300 patients in Australia would receive the GMO.

23. The clinical trial would take place at clinical trial sites in Australia.

24. The applicant has proposed several controls to minimise exposure to the GMO, and to restrict the spread and persistence of the GMOs in the environment. These include:

- ensuring the GM treatment is administered by authorised, appropriately trained medical staff in clinical facilities;
- requiring that clinical trial staff handling and/or administering the GM treatment wear and use personal protective clothing and equipment;
- requiring decontamination of materials and equipment, potentially in contact with the GMOs at clinical trial sites, using effective disinfectants, or disposal in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation;
- requiring participants to remain at the clinical trial site for a specified duration after administration as mentioned in the CCI attachment; and providing them with instructions for good hand hygiene and coughing etiquette;
- excluding participants with frequent contact with children under 6 months of age; participants who live in the same household with individuals with known immunodeficiencies; or individuals on immunosuppressants; and
- transport, storage and disposal of the GMO and any contaminated waste generated at a clinical trial site would be in accordance with the current version of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs.*

2.2 Details of the proposed dealings

2.2.1 Manufacturing of the GMO

25. The GMO will be manufactured overseas in accordance with Good Manufacturing Practice (GMP) guidelines. The lyophilised product will be packaged into 1 ml glass vials as primary containment and will be packaged into a secondary (CO_2-protected bags) and tertiary (International Air Transport Association; IATA approved) cryoboxes for importation into Australia. The applicant has estimated that up to 1,911 vials would be imported for this trial.

2.2.2 Transport, supply and storage of the GMO

26. The GMO would be imported into Australia from overseas by specialist courier companies such as World Courier. Importation of the GMO will be carried out in accordance with International Air Transport Association (IATA) guidelines UN3245 (GMOs that are not classified as category A or B infectious substances). Briefly, the vials will be shipped on dry ice in a validated shipping container with a temperature monitoring device using IATA approved cryoboxes and additionally sealed within CO_2-protected bags, to a secure third-party storage site prior to transport to clinical trial sites.

27. Biological samples (e.g. blood, urine and mucosal fluid) from trial participants that may contain GMOs would be collected and transported to pathology laboratories for analysis. Transport within Australia of the GMO and biological samples would be carried out according to the packaging requirements of the OGTR's *Transport, Storage and Disposal Guidelines* (TSD) by commercial courier companies (e.g. World Courier). In brief, the GMO will be packaged in a container; and the details (name, address, and contact information) of the consignor and consignee, OGTR licence number, instructions in the event of a spill and indication that the shipment contains GMOs would be present on the outer packaging.

28. For transport from the pharmacy to the designated treatment room, the GMO would be contained in a capped syringe and transported in a sealed, unbreakable, rigid-sided container; recorded to ensure no loss; and staff transporting the GMOs would be trained as in Section 2.2.10. A spill kit would always be available in the facilities.

29. Storage of the GMO would be within a third-party storage site or clinical trial site(s) in a secure fridge or freezer with access restricted to authorised personnel.

2.2.3 Clinical trial sites

30. The clinical trial would be carried out at clinical trial sites, which are yet to be confirmed. Each site would be assessed by the applicant for suitability in accordance with the requirements of *Good Clinical Practice (GCP)* as per standard practice of the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)* and the capability to meet the OGTR TSDs and licence conditions.

2.2.4 Trial design

31. The applicant proposes a Phase 2b, multi-centre, placebo-controlled randomised study of BPZE1 as an intranasal pertussis vaccine in healthy school age children. The study involves BPZE1 as a single dose with or without the administration of a tetanus, diphtheria and pertussis vaccine, currently used in early childhood vaccination program in Australia. Up to 120 participants could also elect to participate in a sub-study. Additional details of the sub-study are indicated in a CCI attachment to the RARMP. Relevant CCI will be made available to the prescribed experts and agencies that are consulted on the RARMP.

2.2.5 Selection of trial participants

32. Relevant inclusion criteria proposed by the applicant include that:

- participants may be of any gender;

- participants must be between 6 and 15 years of age (inclusive) at day 1 of vaccination;
- participants must be medically healthy, as determined by the Investigator;
- participants and/or legal guardian must be able to understand, provide consent and comply with requirements of the trial;
- female trial participants:
    - must not be breastfeeding; and
    - must agree not to attempt to become pregnant; and
    - of childbearing potential, must agree to be heterosexually inactive for 21 days prior to enrolment and use an acceptable method of highly effective contraception at 21 days prior to enrolment through to at least 90 days after the last dose of study; and
- participants must agree to refrain from routine nasal sprays (including steroid sprays) or washes for at least 7 days following any study vaccination.

33. Relevant exclusion criteria proposed by the applicant include that include:

- any chronic lung disease, autoimmune and immunodeficiency disorders; and
- persons that has routine and/repeated contact with, or is currently living in a household with, an immunocompromised individual;
- persons that reside or may reside with an infant less than 6 months of age
- vaccination with another clinical trial product 6 months prior to administration or is planning to participate in any other clinical trial in the duration of the study.

34. In addition, participants may be excluded for any reason that, in the opinion of the investigator, makes the participant unsuitable for the study.

2.2.6 Preparation of the GMO for administration

35. The GMO doses for administration would be prepared in approved areas (e.g. pharmacies) within the clinical facilities by authorised trained personnel wearing appropriate PPE (goggles, face mask, disposable gloves and gowns). A material safety data sheet (MSDS) or equivalent document describing the occupational hazards and recommended handling procedures will be provided if required and would be available upon request from the sponsor.

36. The preparation area would be decontaminated with 70% alcohol prior and after the reconstitution of the GMO. One ml of sterile water would be added into the vial containing the lyophilised GMO to form the final dose. This would be carried out aseptically using syringes to transfer solutions. Therefore, there would not be open transfer of solutions outside of the syringe or vaccine vial as all solutions would be contained within the sealed primary vial or syringe. The filled capped syringe containing the GMO would be transported to the administration area as described in Section 2.2.2.

2.2.7 Intranasal administration of the GMO

37. The GM vaccine will be administered intranasally (IN) at clinical trial sites. The applicant has proposed that the IN administration will be carried out by authorised trained personnel who would be wearing appropriate PPE (goggles, face mask, disposable gloves and gowns).

38. Prior to administration, the filled syringe would be capped with an atomiser, which will be used to create an aerosolised mist and deliver the dose directly into the nasal passage.

39. During administration, clinical trial participants will be reclined at 45 degrees or have their head tilted back. Participants would then be required to stay in a recumbent position for 30s after administration of the GMO.

40. Participants and their carers would be informed of appropriate hygiene measures following administration of the GMO (e.g. coughing etiquette and hand washing) and remain in the clinical trial site for a specified duration as required by the study.

2.2.8 Decontamination and disposal of the GMO

41. Following administration, all residual GMO and associated waste which has come in to contact with the GMO (such as syringes, swabs and PPE) would be disposed of in accordance with the relevant State and Territory legislated procedures for clinical/medical waste disposal. Any unused vials of the GMO would also be disposed using the same process and logged for accountability. Disposal would be carried out by external service providers.

42. The dedicated treatment area/room (e.g. work bench, chairs and surfaces) would be decontaminated with chemical decontaminants appropriate for the GMO (e.g. hypochlorite, 0.5M sodium hydroxide, hospital grade disinfectant or 70% alcohol) as per clinical trial site procedures after the last administration of the GMO.

2.2.9 Sample collection and analysis

43. Following administration of the GMO, routine safety samples (e.g. urine pregnancy test) and trial specific samples (e.g. blood and mucosal samples) will be collected from trial participants at various time points to determine effectiveness of the vaccination and evaluate patient safety.

44. Clinical trial staff involved in sample collection and in the clean-up of potential spills would wear a disposable gown, gloves, face mask and eye protection (safety glasses or face-shields).

2.2.10 Training

45. The applicant's IBC declares that the training and experience of individuals involved in these dealings is satisfactory. Staff handling the GMO would be trained on the licence conditions during the site inspection visit. Training of additional staff commencing after the site inspection visit will be carried out by existing trained staff.

2.2.11 Accountability and Monitoring

46. A log detailing the dates and quantities of the GMO will be maintained by the investigator/pharmacist, or delegated person and will be verified by the unblinded study monitor during site visits.

47. All documentation (e.g. receipts, authorisation for use, dispensing, destruction, temperature monitoring) will be filed on-site and be available for inspection by the applicant. The applicant may also audit selected sites to ensure compliance with ICH GCP and licence conditions.

2.2.12 Contingency plans

48. A detailed contingency plan to address adverse effects related to GMO transmission and the unintentional release of the GMO (e.g. spills) have been provided. In summary, the incident would be reported to Novotech who will convene a teleconference with ILiAD within 24 hours of notification from the Principal Investigator (PI). The PI would be required to complete a 'Report of Exposure to Infectious Material Form'. The incident would then be reviewed by ILiAD and the Institutional Biosafety Committee (IBC) and a documented action plan specific to the event would be developed and implemented. This could include the identification of exposure pathways; appropriate medical treatment of affected persons; and prevention of spread and persistence of the GMO. The incident would then be reported to the OGTR. A detailed report of the incident would be prepared and documented. Further ongoing follow-up of the incident would be carried out as needed.

Section 3 Parent organism

49. The GM vaccine is derived from *Bordetella pertussis* (Tohama I strain). *B. pertussis* is a member of the genus *Bordetella* in the Alcaligenaceae family and is classified as a Risk Group 2 microorganism (Standards Australia/New Zealand, 2010). The characteristics of the parent organism provide a baseline for comparing the potential for harm from dealings with the GM vaccine. As such, the relevant biological properties of *B. pertussis* will be discussed here.

50. The bacteria *Bordetella* have been classified into nine species (*B. pertussis*, *B. parapertussis, B.bronchiseptica, B. petrii, B. avium, B. holmesii, B. hinzii, B. trematum, B. ansorpii)* (Park et al., 2012). The classical or mammalian Bordetellae are *B. pertussis*, *B. parapertussis* and *B. bronchiseptica*. Bioinformatics studies have suggested that *B. pertussis* and *B. parapertussis* have evolved from *B. bronchiseptica* through large scale gene loss or inactivation resulting in human host specificity (Parkhill et al., 2003). *B. pertussis* is a strict human pathogen and no natural animal reservoirs have been currently identified (Locht, 2016).

51. *B. pertussis* is a small, gram-negative, encapsulated, coccobacilli with outer pili that does not produce spores (Public Health Agency of Canada, 2010). To date, *B. pertussis* is not known to contain any plasmid(s) or integrate into a host's genome.

52. To date, thirteen strains of *B. pertussis* have been isolated and sequenced (Tohama I, CS, B0558, B1193, B1831, B1834, B1917, B1920, 12822, MO149, D445, Bbr77, 18323) (Park et al., 2012). The Tohama I strain was isolated from a patient in Japan in 1954 and is the basis of the current vaccine used in Australia (Heikkinen et al., 2007; Park et al., 2012). It is one of the first strains to be sequenced and used widely in laboratory studies (Parkhill et al., 2003). The Tohama I strain is also used as a reference strain to compare different strains of *B. pertussis* isolated from patients (Arnal et al., 2015; Bouchez et al., 2018). The parent strain of the GMO (Tohama I strain) is resistant to streptomycin and nalidixic acid (Mielcarek et al., 2006).

3.1 Pathology

53. There are three stages of infection associated with *B. pertussis,* the catarrhal stage, the paroxysmal stage and the convalescent stage (Melvin et al., 2014). The catarrhal stage lasts for 1-2 weeks and commonly involves non-specific symptoms such as malaise, runny nose, sneezing, low-grade fever and cough (Public Health Agency of Canada, 2010). This is then followed by the paroxysmal phase, which can last between 1-10 weeks (Melvin et al., 2014). It is during this phase of the infection that patients experience intense and frequent coughing fits (paroxysmal coughs) with the known 'whooping' sound (Public Health Agency of Canada, 2010; Melvin et al., 2014). The patient then goes through the convalescent stage, where the cough becomes less persistent and can last up to 1 month but can also persist much longer (Finger H., 1996). The disease is most contagious during the catarrhal and paroxysmal stages of the infection (Gregory, 2006).

54. In rare cases, whooping cough can lead to further lung related complications and death (Melvin et al., 2014). Pertussis infection in older adults can also cause rare non-respiratory complications that include brain disease (e.g. stroke and encephalopathy), tear in arteries, and herniated lumbar discs (Kilgore et al., 2016). The incidence of these serious complications is more common in unvaccinated individuals or those with an incomplete vaccination.

3.2 Bacterial infection and replication

55. *B. pertussis* is predominantly spread via the inhalation of aerosolised respiratory droplets containing the bacteria from an infected person (Melvin et al., 2014; Australian Technical Advisory Group on Immunisation (ATAGI), 2019). The bacteria is passively transported to the respiratory tract where it then binds to and replicates in the ciliated epithelial cells and innate immune cells (macrophages and dendritic cells) (Higgs et al., 2012; Melvin et al., 2014). During its replication, *B. pertussis* produces various toxins and virulence factors that affect the host's immune response,

damages the epithelial cells, and causes excessive secretion of mucus that leads to the pathogenesis observed with infection (Figure 2).

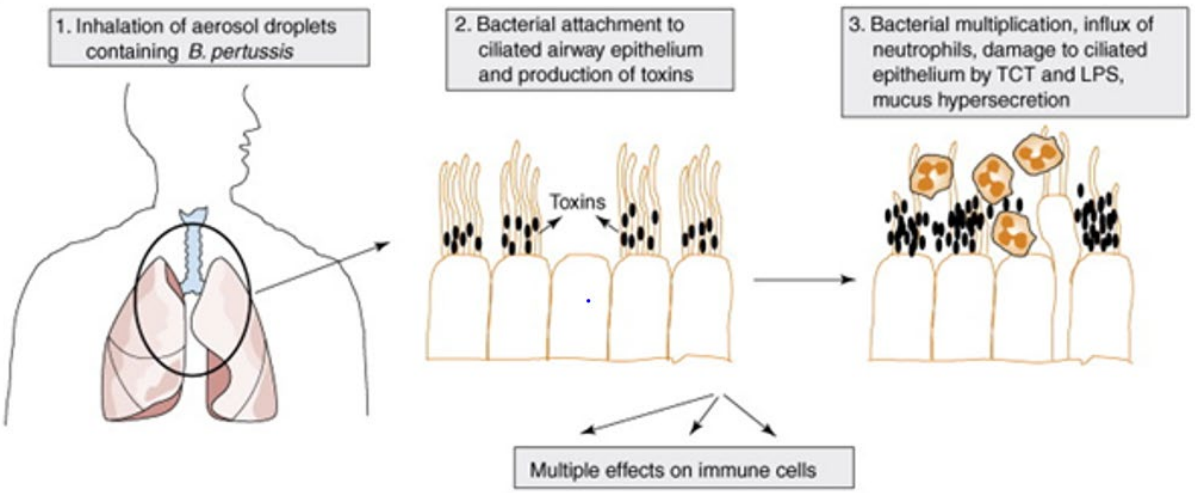

Figure 2: Transmission and infection of B. pertussis (Carbonetti, 2007).

3.3 Epidemiology

3.3.1 Host range and transmission

56. Humans are the natural host for *B. pertussis*. *B. pertussis* is highly contagious and is primarily transmitted from an infected individual via inhalation of aerosol droplets produced during coughing or sneezing (Warfel et al., 2012; Department of Health Australia, 2021). If untreated, infected persons can be infectious for up to 5 weeks (most infectious up to 2 weeks after cough begins), but with treatment with antibiotics, this infectious period can be reduced to 5-10 days (Finger H., 1996; CDC, 2019). Due to global vaccination programs, it mainly causes disease in unvaccinated individuals, especially infants too young to be vaccinated (Parton, 1999; Melvin et al., 2014; Kilgore et al., 2016). Adolescents, adult and older school age children are important reservoirs for *B.pertussis* and are often the source of infection (Public Health Agency of Canada, 2010; CDC, 2020).

57. Experimentally, mice, rats, pigs, rabbits and baboons have been infected with *B. pertussis* to study the pathogenesis of the disease (Parton, 1999; Melvin et al., 2014; Kilgore et al., 2016). However, only baboons have been shown to experience paroxysmal coughing (Locht et al., 2017). No natural infections of non-human hosts have currently been described or reported and there is currently no known animal or environmental reservoir of *B. pertussis*.

3.3.2 Bio-distribution

58. The predominant natural tropism of *B. pertussis* is the respiratory tract. Following natural infection, bacteria colonises the respiratory tract. Currently, there is no available evidence that *B. pertussis* can be found in the blood, urine, or faeces. Due to its strict requirements for survival as discussed in Section 3.3.5, it is unlikely to distribute and shed from the blood, urine or faeces.

3.3.3 Prevalence

59. Globally, there were about 145, 000 cases reported in 2019 and there has been a steady decline in number of infections due to a global vaccination program worldwide (Figure 5).

60. In Australia, epidemics of the disease occurs every 3-4 years, with the most recent epidemic occurring between 2008 and 2012 (Figure 5) (National Centre For Immunisation Research & Surveillance, 2019). In the last epidemic, infants (<6 months) and children (5-9 years old) had the highest rates of the disease (National Centre For Immunisation Research & Surveillance, 2019).

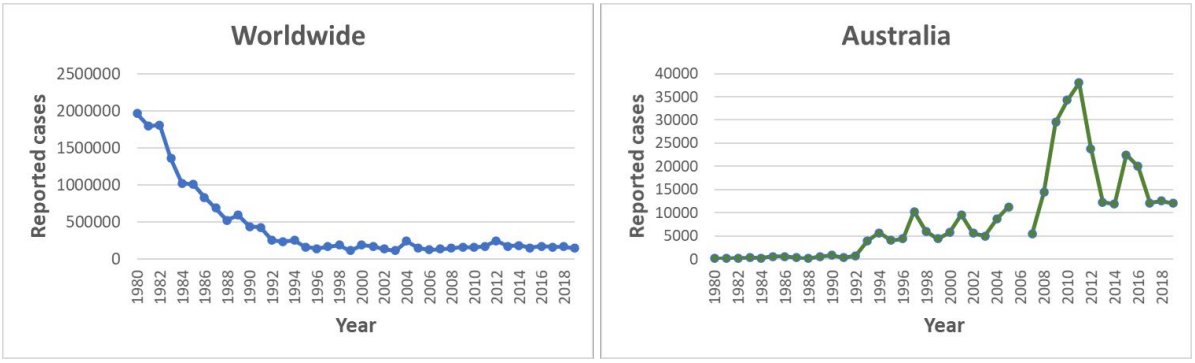

Figure 5: Reported cases of B. pertussis infection worldwide and in Australia (graphs plotted based on data from (WHO, 2020b)

3.3.4 Vaccinations

61. Vaccination against *B. pertussis* were introduced in the 1940s and nearly eradicated the disease by the 1970s. Initial pertussis vaccination used whole-cell pertussis (wP) vaccine, which consists of an inactivated form of the bacteria. However, due to some reported associations of wP vaccines with serious side effects, later shown to be unfounded, many countries and pharmaceutical companies have shifted towards acellular pertussis (aP) vaccines, containing purified protein components of *B. pertussis,* which will be discussed in Section 3.4. Initial aP vaccines consisted of two components of the bacteria, pertussis toxin (PT) and filamentous haemagglutinin (FHA) as they were shown to confer protection to mice infected with B. pertussis. Subsequently, the addition of pertactin and fimbrae were shown to increase the vaccine efficacy (Sato and Sato, 1999). Current aP vaccines in Australia contain all four components (Australian Technical Advisory Group on Immunisation (ATAGI), 2019).

62. As present, both wP and aP vaccines are still currently used worldwide based on the WHO vaccine-preventable diseases: Monitoring system. 2020 global summary. The vaccine is recommended as a 3 dose-primary series in infants including those who are HIV positive (6 weeks, 10-14 weeks, and 14-18 weeks) and a subsequent booster shot for children around 1-6 years of age (WHO, 2016). Both types of vaccines have shown to be effective in conferring immunity towards pertussis infection but there is more rapid waning of immunity and plausible reduced impact on transmission with aP compared to wP vaccines (WHO, 2016).

63. wP vaccines have been used worldwide in the 1940s and 1950s during the third trimester of pregnancy with good protection and no serious adverse events (Healy, 2016). Similarly, aP vaccines used in pregnant women did not show increased risks of serious adverse events and pregnancy outcomes (National Centre For Immunisation Research & Surveillance, 2019). Currently aP vaccines are the recommended vaccine for pregnant women (WHO, 2016).

64. Whole-cell vaccines were used in Australia in the 1940s and were shown to be effective in preventing deaths related to the disease (McIntyre et al., 1998). However, currently in Australia, only aP vaccines are used. The vaccine is recommended and is available as part of the National Immunisation Program (NIP) for children at 2, 4, 6, 18 months and 4 years of age; a booster shot via school-based programs at 12-17 years of age (Australian Technical Advisory Group on Immunisation (ATAGI), 2019). The pertussis vaccine is given in combination with diphtheria and tetanus vaccines (Australian Technical Advisory Group on Immunisation (ATAGI), 2019). It is also recommended for pregnant women between 20 and 32 weeks of pregnancy; adults above 65 years of age; and adults that may encounter vulnerable people (e.g. early childhood educators, carers, household contact and healthcare workers) (Australian Technical Advisory Group on Immunisation (ATAGI), 2019). The average percentage of completion of the third dose of pertussis vaccination in Australia between 1990-2019 is 92% and the coverage for the past 3 years has been 95% (WHO, 2020a).

3.3.5 Control, environmental stability and decontamination methods

65. Antibiotic treatment such as azithromycin, clarithromycin and erythromycin are recommended within 3 weeks (persons older than 1 years of age) or 6 weeks (infants younger than 1 years of age and pregnant women) following exposure to pertussis infection (CDC, 2019). The Department of Health Australia has recommended these antibiotic treatments for a duration of 5-7 days (Department of Health Australia, 2013). These treatments, if given early, may reduce the severity and prevent transmission of the disease to other people (Australian Technical Advisory Group on Immunisation (ATAGI), 2019).

66. *B. pertussis* is unable to survive for long outside the human body. The bacteria can survive for 3-5 days on dry inorganic surfaces, 5 days on garments, 2 days on paper and 6 days on glass (Public Health Agency of Canada, 2010). As mentioned in Section 3, the bacteria have very strict requirements for growth. It is a strict aerobe that grows optimally between 35°C and 37°C and has very specific nutritional requirements. Its growth can be inhibited by the presence of fatty acids, metal ions, sulphides and peroxides in the media (Public Health Agency of Canada, 2010; Kilgore et al., 2016). The inability of *B. pertussis* to survive in the environment is most likely attributed to the loss of genes involved in the use of alternative nutrient source (Parkhill et al., 2003).

67. *B. pertussis* is sensitive to various chemical decontamination agents such as glutharaldehyde, chlorine, 70% ethanol and phenolics such as orthophenylphenol, ortho-benzyl-para-chlorophenol, and peracetic acid (Public Health Agency of Canada, 2010). Moist or dry heat inactivates most vegetative bacteria like *B. pertussis* (Public Health Agency of Canada, 2010). *B. pertussis* is also shown to be sensitive to pH as the bacteria is not able to multiply below pH 5 and does not survive below pH 4.5 in *in vitro* studies (Schneider et al., 2000).

3.3.6 Horizontal gene transfer

68. Bacteria pathogens encounter a vast amount of selective pressures impacting their ability to establish, replicate and transmit from one host to another. This evolutionary process can promote the selection of bacteria gaining or losing capabilities through horizontal gene transfer (HGT) (Brinig et al., 2006). As mentioned in Section 3, bioinformatic studies proposed that the evolution of *B. pertussis* from *B. bronchiseptica* occurred roughly 0.7-3.5 million years ago and was mediated by gene loss rather than gene acquisition (Parkhill et al., 2003) and resulted in human host specificity. Genome analysis also suggested that HGT of pertussis toxin (PT) gene maybe have occurred from *B. bronciseptica* to *B. pertussis* and *B. parapertussis* because the whole gene is present in both bacteria (Park et al., 2012). However, as mentioned in Section 3.4.1, PT is not expressed in *B. parapertussis* and *B. bronchiseptica*.

69. Sequencing of *B. pertussis* Tohama I strain revealed a high load of insertion sequence elements which are associated with mediating the gene loss or inactivation from its ancestor *B. bronchiseptica* (Parkhill et al., 2003). Although the presence of insertion sequence elements could provide sites for homologous recombination, there is very little evidence of gene acquisition due to HGT (Brinig et al., 2006). Analysis of 137 strains of *B. pertussis* isolated from patients from Japan (Tohama I strain), USA, Netherlands, Italy and Australia showed very high level of gene conservation and no detection of any new genes suggesting that gene acquisition by *B. pertussis* is rare (Brinig et al., 2006).

3.4 Toxin and Virulence factors

70. There are a variety of toxins and surface structures that cause the pathogenesis of *B. pertussis*. These include the pertussis toxin (PT), adenylate cyclase toxin (ACT), dermonecrotic toxin (DNT), type III secretion system (T3SS), tracheal cytotoxins (TCT), filamentous hemagglutinin (FHA), fimbriae, pertactin, tracheal colonisation factor and lipopolysaccharide (Melvin et al., 2014). These virulence factors are regulated by a BvgAS master regulatory system (Melvin et al., 2014). As PT, DNT and TCT have a greater relevance to the GMO, they will be discussed in greater detail in Sections below.

3.4.1 Pertussis toxin

71. Pertussis toxin is specific to *B. pertussis* and not the genus (Kilgore et al., 2016) and is one of the most extensively characterised virulence factors of *B. pertussis*. PT is encoded by the *ptx* gene. Both *B. parapertussis* and *B. bronchoseptica* possess the *ptx* gene. However, they do not produce PT due to mutations in the promoter region impacting the expression of the gene (Parkhill et al., 2003). PT is an enzyme made up of a catalytic subunit A (SA) and a pentameric membrane binding subunit B (SB) (Melvin et al., 2014). SB enables the interaction of PT with the host cell receptor and SA is responsible for the biological role of the toxin (Melvin et al., 2014). PT is assembled in the bacterial periplasm and exported by a type IV secretion system (Parkhill et al., 2003) into the external environment (i.e. epithelial cells in the airway during an infection).

72. PT enters the hosts' cell via receptor-mediated endocytosis. It is then transported into the Golgi apparatus and the endoplasmic reticulum (ER) (Figure 3) (Melvin et al., 2014). In the ER, SA dissociates from SB, traffics to the cytoplasm, binds to NAD^+ substrate and transfers an ADP-ribose group from NAD^+ to the α-subunit of heterotrimeric G protein, which regulates multiple enzymes involved in various metabolic processes. This results in a dysregulated immune response as shown in Figure 4, (Scanlon et al., 2019).

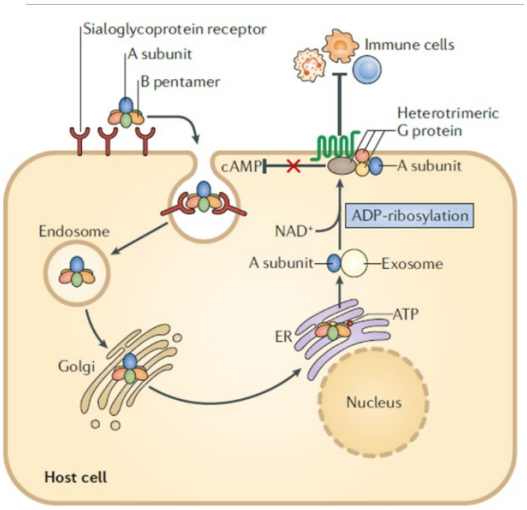

Figure 3: Mechanism of pertussis toxin (Melvin et al., 2014).

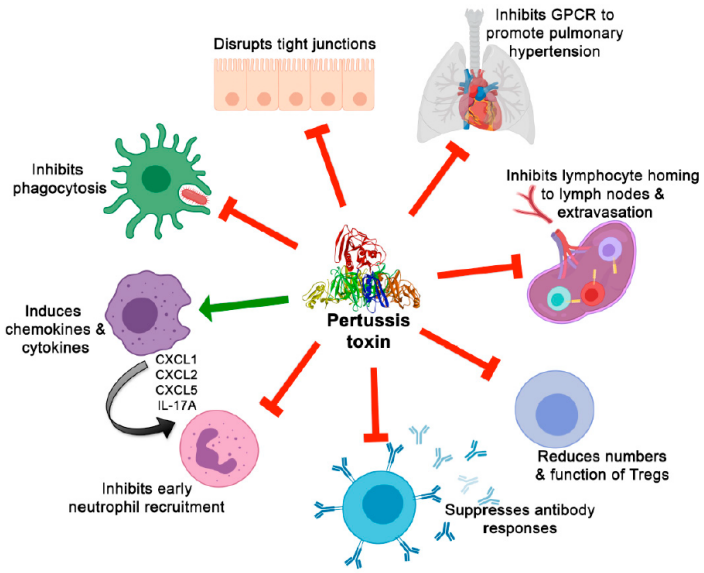

Figure 4: Effects of pertussis toxin during infection (Scanlon et al., 2019).

73. Due to the broad range of effects of PT, the precise role during human infection has not been elucidated. In mice, the production of PT has been associated with decreased production of pro-inflammatory cytokines; decreased neutrophil and macrophage recruitment to the lungs early in infection (Melvin et al., 2014; Scanlon et al., 2019). At the peak of infection, PT is associated with a high influx of white blood cells (lymphocytosis); an exacerbated inflammation and pathology in the airways; and increased bacterial burden in mice (Melvin et al., 2014; Scanlon et al., 2019).

74. Studies in infant mice also showed that PT contributes to the pathogenicity of *B. pertussis* but is not involved in the ability of the bacteria to colonise the lungs (Goodwin and Weiss, 1990). Studies in animal models have also alluded that PT may play a role in the symptomatic coughing caused by *B. pertussis*. Rats and baboons infected with PT-deficient strains of *B. pertussis* did not develop paroxysmal coughing (Parton et al., 1994; Scanlon et al., 2019).

75. In humans, the production of PT positively correlates to lymphocytosis (elevated white cells) in patients with pertussis infection and antibodies against PT protect against severe disease (Melvin et al., 2014; Scanlon et al., 2019). Evidence from both animal and human studies suggests that PT helps establish the infection by supressing the early innate immune responses, contributes to the inflammatory pathology at the peak of infection and plausibly causes symptomatic coughing.

76. PT is currently a component of acellular vaccines (Australian Technical Advisory Group on Immunisation (ATAGI), 2019; Dewan et al., 2020). The lack of widespread occurrence of PT-deficient strains in the era of acellular vaccines suggest the importance of PT in the pathogenesis and/or transmission of *B. pertussis* (Cauchi and Locht, 2018).

3.4.2 Tracheal cytotoxin

77. Tracheal cytotoxin (TCT) is a peptidoglycan produced during the remodelling of the bacterial cell wall (Higgs et al., 2012; Melvin et al., 2014). TCT is typically recycled by most Gram-negative bacteria via a transmembrane protein AmpG. This process is inefficient in *B. pertussis* and results in large amounts of TCT in the extracellular environment (Melvin et al., 2014). TCT seems to be somewhat conserved in pathogenic *Bordetella,* as they produce chemically identical TCT molecules causing similar respiratory pathology in humans, dogs and turkeys (Scanlon et al., 2019).

78. In a hamster model, TCT was shown to work synergistically with lipo-oligosaccharide to stimulate pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS), resulting in damage to ciliated epithelia cells in the respiratory tract and causing the forced removal of dead cells from the epithelial surfaces (Heiss et al., 1993; Flak and Goldman, 1999). These observations were also confirmed using an *in vitro* human tracheal model (Kessie et al., 2020).

79. TCT may also have a role in inhibiting the mucosal clearance, resulting in consistent coughing to clear mucous manually (Marzouqi et al., 2010) and leading to the hypothesis that TCT may cause the specific 'whooping' sound (Kilgore et al., 2016). However, this has not been confirmed with a suitable animal model. TCT has also shown to inhibit the migration of neutrophil *in vitro* and hence may also be a contributing factor to the survival of *B. pertussis in vivo (Cundell et al., 1994)*.

80. Currently, acellular vaccines do not contain TCT, while previously whole cell vaccines would have likely contained TCT. It has been speculated that the lack of TCT in acellular vaccines may contribute to their waning immunogenicity (Scanlon et al., 2019).

3.4.3 Dermonecrotic toxin

81. Dermonecrotic toxin (DNT) was one of the first *B. pertussis* toxins discovered and is produced by all members of the genus, but research is still lacking on its role in pertussis infection (Walker and Weiss, 1994). Using *in situ* hybridisation with *B. pertussis* DNT gene fragment as a probe, DNT genes were shown to be conserved in *B. pertussis, B. parapertussis* and *B. bronchispetica* but less so with *B. avium* (Walker and Weiss, 1994).

82. Early studies, showed that DNT is sensitive to heat, can cause skin lesions in mice when injected subcutaneously and can result in death if injected intravenously (Livey and Wardlaw, 1984; Stanek et al., 2020). A DNT deficient mutant *B. pertussis* did not affect the virulence of the bacteria when compared to wildtype in a mouse model (Walker and Weiss, 1994). However, mutations knocking out other virulence genes (PT, FHA and ACT) in *B. pertussis* did not affect the capability of *B. pertussis* to cause skin lesions, further suggesting the role of DNT in causing the lesions (Walker and Weiss, 1994). The induction of skin lesions is attributed to the interaction of DNT with the host binding protein Rho (Marzouqi et al., 2010; Stanek et al., 2020).

83. In primates, DNT can induce vasoconstriction (Kilgore et al., 2016). There is also evidence that DNT contributes to the ability of *B. bronchiseptica* to induce lung pathology in pigs (Melvin et al., 2014).

84. Earlier studies suggested that DNT does not have an export sequence signal and is therefore not secreted from the bacterial cell. Hence, its function is limited to the bacterial cytoplasm (Melvin et al., 2014). More recently, a cellular receptor for DNT has been identified (Teruya et al., 2020). These receptors were mainly expressed in nerve cells. Hence, implicating DNT as a potential neurotoxin and involvement with brain damage, which is a rare complication during pertussis infection.

85. Like TCT, current acellular vaccines do not contain DNT, most likely due to the possibility that it may cause lesions with intramuscular injection.

3.4.4 Other toxins and virulence factors

86. Other components, currently used in acellular vaccines, are filamentous hemagglutinin (FHA), pertactin and pertussis fimbriae. All three virulence factors are shown to contribute to the adherence of *B. pertussis* to the epithelium of the respiratory tract (Kilgore et al., 2016). FHA assists in the initial binding of the bacterium to the respiratory tract and then promotes the infection from the upper to the lower respiratory tract (Kilgore et al., 2016). FHA may also contributes to the distribution of other virulence factors such as adenylate cyclase toxin (ACT) (Melvin et al., 2014). It is thought the presence of pertactin in acellular vaccines is responsible for the selection of bacteria lacking pertactin. Some cases of *B. pertussis* cultured from patients lacking pertactin were reported (Melvin et al., 2014). Fimbriae is essential in the adherence and suppression of the initial immune response allowing the colonisation of the mucosa in the lower respiratory tract. Type 3 and 4 fimbriae are components of acellular vaccines (Australian Technical Advisory Group on Immunisation (ATAGI), 2019).

87. Other virulence factors that are not currently used in acellular vaccines are adenylate cyclase toxin (ACT), type III secretion system (T3SS), lipopolysaccharide (LPS) and other surface proteins. ACT has been shown to be critical for the colonisation of *B. pertussis* in infant mice (Goodwin and Weiss, 1990) and has been isolated from baboon and human clinical samples (Eby et al., 2013). Studies showed that ACT blocks the bactericidal secretions produced by macrophages and inhibits the cytotoxic effect of a variety of immune response cells (Kilgore et al., 2016). Antibodies towards this virulence factor is produced when a patient acquires whopping cough or has the whole-cell vaccine (Kilgore et al., 2016).

88. Type III secretion system (T3SS) has been shown to cause necrosis in various cells *in vitro*, possibly by transporting bacterial proteins into host's cells and dysregulating the immune response during lung infection (Kilgore et al., 2016). Bacteria lacking T3SS activity showed decreased persistence in the lower respiratory tracts in rats and mice that were intranasally inoculated (Melvin et al., 2014).

89. Lipopolysaccharide (LPS) in *Bordetella* species is known to stimulate cells involved with the early detection of the bacteria by the host immune system (Kilgore et al., 2016). The stimulatory capacity of *B. pertussis* LPS is lower than that of *B. bronchiseptica,* and may facilitate the immune

evasion properties and persistence of *B. pertussis* in the human host (Melvin et al., 2014). LPS is not an ingredient in the acellular vaccines, but it is present in whole-cell vaccines and can cause fever post injection (Kilgore et al., 2016).

90. There are various other surface proteins (BrkA, TcfA, BapC, BatB, Vag8, SphB1 and Phg) involved in mediating adherence, serum resistance, immune evasion and other interactions with other surface proteins but their exact roles in the pathogenesis of *B. pertussis* is not known (Melvin et al., 2014; Kilgore et al., 2016)

Section 4 The GM vaccine - nature and effect of the genetic modification

91. The GMO (BPZE1) is an attenuated *B. pertussis* (Tohama I strain) and designed as a whooping cough vaccine. The attenuation of the bacteria is carried out by the modification or removal of virulence factors that are involved with the pathogenesis of *B. pertussis*. The three genes targeted are the pertussis toxin (PT), tracheal cytotoxin (TCT) and dermonecrotic toxin (DNT). The safety profile of BPZE1 is consistent with the criteria of the definition of a Risk Group 1 microorganism according to the Standards Australia/New Zealand, 2010. BPZE1 is currently considered as a Risk Group 1 pathogen in several countries (Thorstensson et al., 2014).

4.1 The genetic modifications and effects

92. The insertion or deletion of genes in BPZE1 was carried out using allelic exchange, which is a method of bacterial genome engineering where a specific region of DNA is exchanged or deleted via homologous recombination (Mielcarek et al., 2006). DNA sequencing of the whole BPZE1 chromosome was carried out to verify the absence or presence of the modified DNA.

93. As previously mentioned in Section 3.4.1, PT toxin consists of 2 subunits A and B, which are encoded by the *ptx* gene. The catalytic SA binds to the NAD^+ substrate (substrate binding) and transfers an ADP-ribose group to protein G (catalytic enzyme activity). In the GMO, SA of PT was modified by replacing two amino acids in key residues involved with substrate binding (Arg-9 with Lys) and enzyme activity (Glu-129 with Gly). This was carried out by first removing the *ptx* gene, which encodes the protein and inserting the mutated version of the gene. This modification resulted in the detoxification of PT and slightly lower production of PT compared to WT (Mielcarek et al., 2006). More recent structural studies showed that the modified PT is virtually identical to WT PT and the differences in function is due to changes in the conformation dynamics of the enzyme's active site (Ausar et al., 2020).

94. The *B. pertussis ampG* gene was replaced with the *ampG* gene from *E. coli*, which is more efficient in the internalisation of TCT. This modification resulted in significantly lower TCT detected in in culture supernatant (Mielcarek et al., 2006), possibly due to the more efficient internalisation of TCT by the *E. coli* AmpG transmembrane protein.

95. The *dnt* gene, which encodes DNT was removed from BPZE1. As a result, no DNT is produced by BPZE1 (Mielcarek et al., 2006).

4.2 Characterisation of the GMO

96. As a result of these modifications, BPZE1 was shown in pre-clinical and clinical studies to be able to replicate and colonise the upper respiratory tract and induce a protective immune response without causing disease (Mielcarek et al., 2006; Feunou et al., 2010; Skerry and Mahon, 2011; Jahnmatz et al., 2014; Schiavoni et al., 2014; Thorstensson et al., 2014; Locht et al., 2017; Jahnmatz et al., 2020; Lin et al., 2020). Data obtained from pre-clinical and clinical trials has also been used to characterise the GMO.

4.2.1 Genetic stability and molecular characterisation

97. BPZE1 will be manufactured according to Good Manufacturing Practice (GMP) as a biological medicinal product for investigational use in humans. To determine the genetic stability of BPZE1, the GMO was serially propagated for 20-27 weeks in cells and mice (20 times and 9 times respectively). The absence of *dnt and B. pertussis ampG* genes, the presence of *E. coli ampG* genes and of the two mutations in the *ptx* gene, and the overall genomic stability of the GMO were confirmed using polymerase chain reaction (PCR); DNA sequencing; and DNA microarrays respectively (Feunou et al., 2008). These tests showed that BPZE1 is genetically stable as the propagated BPZE1 was genetically identical to the non-propagated BPZE1 indicating no reversion had occurred (Feunou et al., 2008). The lyophilisation of BPZE1 for commercial use also did not affect its genetic and vaccine potency (Thalen et al., 2020).

98. *B. pertussis* is not known to integrate into the host genome and the modification in BPZE1 does not affect this trait of the parent organism.

99. BPZE1 can be distinguished from WT *B. pertussis* by PCR detection of *E. coli ampG* gene, absence of *dnt* gene and quantitative PCR to target the mutations in *ptx* gene (Feunou et al., 2008; Thalen et al., 2020)

4.2.2 Stability in the environment and decontamination

100. The stability of BPZE1 in the environment (surfaces, water types and sediments) has not been tested. However, as mentioned in Section 3.3.5, *B. pertussis* does not survive long outside the human body. Therefore, it is expected that the survival of BPZE1 in the environment would be similar.

101. Methods of decontamination effective against the parent organism, *B. pertussis*, are expected to be equally effective against the GMO (see Section 3.3.5).

4.2.3 Pre-clinical studies using BPZE1

102. Details of the pre-clinical studies have been extensively reviewed in (Locht, 2016; Cauchi and Locht, 2018). However, a summary of the findings is described below.

103. Initial pre-clinical studies showed that the growth rate and adherence of BPZE1 is comparable to WT *B. pertussis* in cell culture (Mielcarek et al., 2006). Furthermore, mice studies demonstrated that BPZE1 was able to colonise and persist in the lungs similarly to the WT but the bacterial load of BPZE1 in the early time points of infection (day 7) was significantly lower (Mielcarek et al., 2006). Vaccination of adult and infant mice; and baboons also showed that BPZE1 does not cause disease and confers protection from *B. pertussis* infection (Mielcarek et al., 2006; Skerry and Mahon, 2011; Locht et al., 2017). A similar observation was seen in BPZE1-vaccinated immunocompromised adult and infant mice (Skerry et al., 2009).

104. BPZE1 was also shown to confer protection to vaccinated mice from *B. parapertussis* (Mielcarek et al., 2006; Feunou et al., 2010); Respiratory Syncytial Virus infection and allergen induced airway inflammation (Schnoeller et al., 2014); and decreased mortality of virulent mouse-adapted Influenza A (Cauchi and Locht, 2018).

105. Offspring of female mice vaccinated with BPZE1 were also shown to be protected from *B. pertussis* infection although this protection waned quickly. This protection was reduced if infant offspring were vaccinated with BPZE1 (Feunou et al., 2016). Although not confirmed in humans, this suggests that it may be advisable to use different vaccines for vaccinating mother and their infants.

4.2.4 Clinical trials using BPZE1

106. Several clinical trials using BPZE1 in adults were completed in Sweden and USA as summarised below:

a. Phase 1: Safety and immunogenicity; completed Jan 2012 (NCT01188512)

b. Phase 1b: Higher dosage; completed Dec 2017 (NCT02453048)

c. Phase 2a: Optimal dose response study; completed May 2020 (NCT03541499)

d. Phase 2b: Prime boost study; completed June 2020 (NCT03942406)

107. Participants were vaccinated with 10^3, 10^5 or 10^7 colony forming units (CFU) of the vaccine in initial Phase 1 trials. The trial showed that BPZE1 given at the highest dose was better at colonising the respiratory tract (up to 28 days post-inoculation), able to elicit a good immune response and had a good safety profile (Jahnmatz et al., 2014; Thorstensson et al., 2014). Acute adverse events were mild to moderate and transient (slight cough and fever), with no difference observed between placebo and treatment groups (Jahnmatz et al., 2014; Thorstensson et al., 2014). There was no reported vaccine related serious adverse events (Jahnmatz et al., 2014; Thorstensson et al., 2014).

108. To increase the colonisation rate of BPZE1, a Phase 1b study was carried out with 10^7, 10^8 and 10^9 CFU (Jahnmatz et al., 2020; Lin et al., 2020). Vaccination with 10^9 CFU of BPZE1 vastly improved the colonisation rate. The highest detected levels of live GMOs were in the nasal swabs at Day 4 (75% of patients) and the presence of the bacteria steadily declined (Jahnmatz et al., 2020). BPZE1 also elicited a good immune response and displayed a good safety profile (Jahnmatz et al., 2020; Lin et al., 2020). Similarly, adverse events were mild to moderate and no vaccine related serious adverse event were reported. There were no reports or documented transmission to staff administering the vaccine or the participant's close contacts. However, it is important to note that this was a passive surveillance, whereby reporting was voluntary.

109. Phase 2a and 2b studies to determine the optimal dose and prime boosting in combination with an acellular vaccine have just recently been completed. Some relevant data from the Phase 2b study is indicated in a CCI attachment to the RARMP. Relevant CCI will be made available to the prescribed experts and agencies that are consulted on the RARMP.

110. Interestingly, a study of samples collected from masks, fingertips, multiple surfaces, and air (e.g. bedroom, standardized aerosolization and provoking procedures such as talking and coughing) of vaccinated adult volunteers, intranasally infected with *B. pertussis* did not detect the bacteria by PCR or cultures. (de Graaf et al., 2020). The same study also tested the recovery of *B. pertussis* in a controlled environment using nebulised air with various particle size and concentration. They detected a median of 17% of *B. pertussis* of the total nebulised bacteria (de Graaf et al., 2020). The authors proposed that the lack of detectable bacteria following vaccination is plausibly due to the volunteers having immunity against *B. pertussis* from wP vaccines given during infancy or that the methods used to detect the bacteria was not sensitive enough. This study suggests that the shedding of *B. pertussis* from reinfection in vaccinated individuals is highly unlikely and since the GMO is attenuated compared to the WT strain, the likelihood of shedding of the GMO from patients may be further reduced.

Section 5 The receiving environment

111. The receiving environment forms part of the context for assessing risks associated with dealings with GM vaccine (OGTR, 2013). It informs the consideration of potential exposure pathways, including the likelihood of the GMO spreading or persisting outside the site of release.

5.1 Site of vaccination

112. The intended primary receiving environment will be the nose and upper respiratory tract of the clinical trial recipient as the GMO will be delivered via the IN route using a syringe and an atomiser.

113. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and the waste disposed of. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance

with institutional policies based on standard precautions for handling potentially infectious substances and in accordance with *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) (ICH GCP).*

114. The principal route by which the GMO may enter the wider environment following vaccination is via shedding. The GMO may be shed in the event of the trial participant sneezing during or after the administration of the GMO or when they return home. Further, GMO may also enter the environment via accidental spills of unused vaccine.

5.2 Presence of related bacterial species in the receiving environment

115. The presence of related bacteria may offer an opportunity for introduced genetic material to transfer between the GMO and other organisms in the receiving environment.

116. As mentioned in Section 3, there are nine species of *Bordetella*. *B. pertussis* (only infects humans); *B. parapertussis* (infects humans, sheep, goat, pig and cattle), *B. broncoseptica* (infects humans, pigs, cat, dog and rabbit); *B. avium* and *B. hinzii* (infects humans and birds); *B. holmessi*, *B. trematum*, *B. petrii* and *B. ansorpi* (infects humans) (Kilgore et al., 2016).

117. The prevalance of *B. pertussis* in Australia based on the reported cases is low (around 12, 000 cases reported in Australia in 2019) and as mentioned in Section 3.3.3, this number can vary during an epidemic outbreak.

5.3 Presence of similar genetic material in the environment

118. The balance of a system could be perturbed by the introduction of new genetic material through HGT or through release of GMO into the environment. However, the effect of perturbation would be relatively small if the genetic material was already present in the system and did not confer any selective advantage to an organism that gained this genetic material.

119. BPZE1 only contains genes derived from the naturally occurring *B. pertussis* apart from the modified PT gene and the naturally occurring *E. coli ampG* gene. The modification of PT inactivated the activity of the toxin and presence of *ampG* gene from *E. coli* reduces the activity of TCT. Hence, these modifications would not confer any selective advantage to the BPZE1 in the environment. *E.coli* is a gut bacterium which is naturally present in the environment.

Section 6 Previous authorisations

120. This GMO has not been previously authorised for commercial supply in any region or country but has been used for various clinical trials as mentioned in Section 4.2.4.

Chapter 2 Risk assessment

Section 1 Introduction

121. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by or as the result of gene technology (Figure 2). Risks are identified within the established risk assessment context (Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

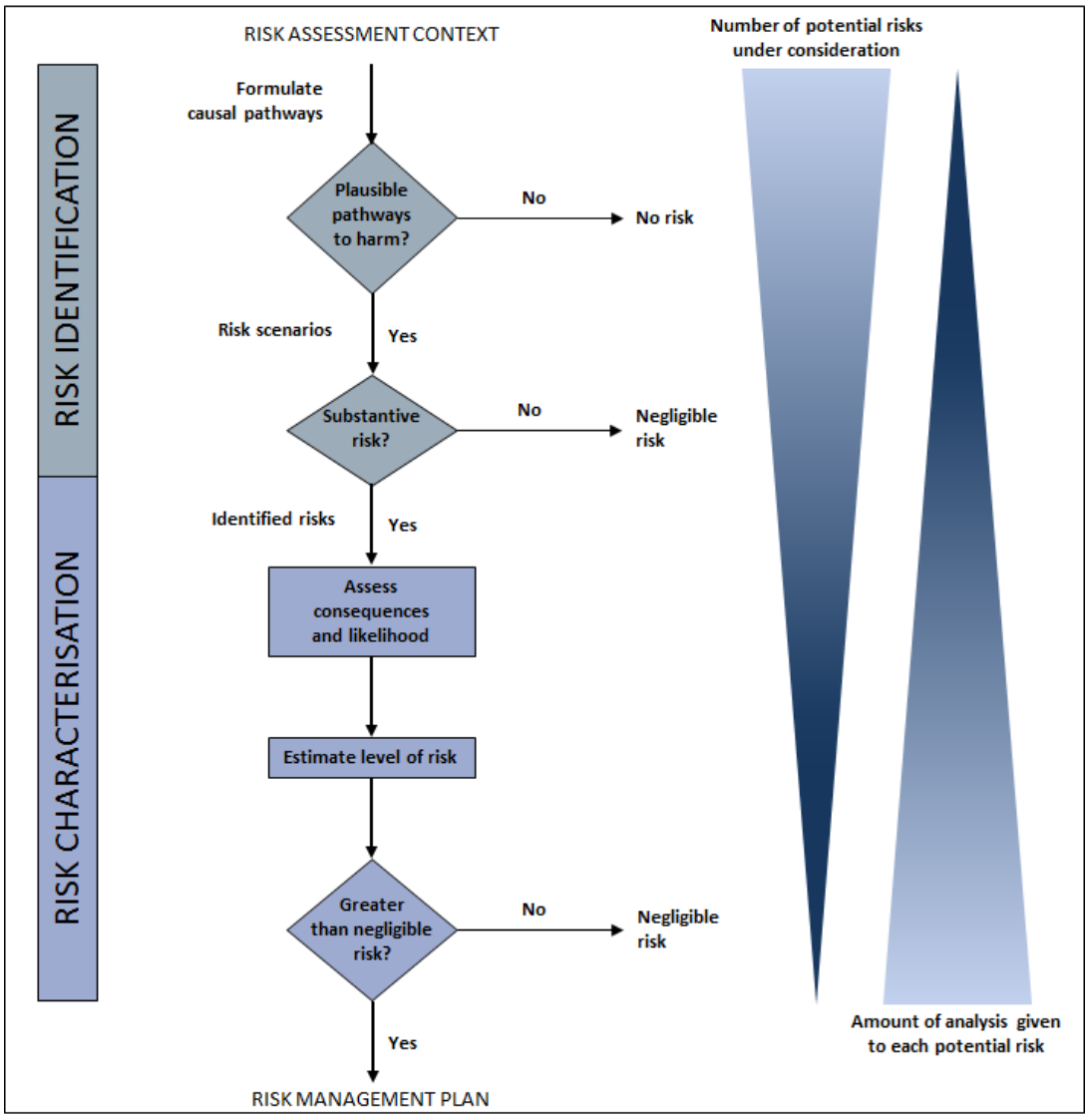

Figure 2: The risk assessment process

122. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013).

123. Risk identification first considers a wide range of circumstances in which the GMO, or the introduced genetic material, could come into contact with people or the environment. This leads to postulating causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are called risk scenarios.

124. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the short and long term, do not advance in the risk assessment process (Figure 2), i.e. the risk is considered no greater than negligible.

125. Risk scenarios identified as substantive risks are further characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The consequence and likelihood assessments are combined to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk identification

126. Postulated risk scenarios are comprised of three components (Figure 3):

i. The source of potential harm (risk source)

ii. A plausible causal linkage to potential harm (causal pathway), and

iii. Potential harm to people or the environment.

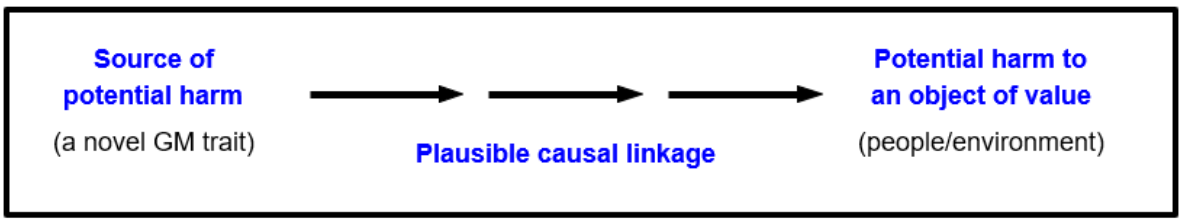

Figure 3: Components of a risk scenario

127. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Chapter 1:

- the proposed dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO and
- the characteristics of the parent organism(s).

2.1 Risk source

128. The parent organism is *Bordetella pertussis* (Tohama I strain). Details of the pathogenicity and transmissibility of *B. pertussis* is discussed in Chapter 1. Infection is generally the result of inhalation of aerosolised droplets excreted from respiratory secretions containing the bacteria. *B. pertussis* infects humans and causes the disease commonly known as whooping cough.

129. Toxicity and allergenicity of the introduced genes and their protein products have not been directly considered but are considered in the context of their contribution to ill health.

130. Potential sources of harm can be due to the intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology. Unintended effects can arise through HGT, which is the stable transfer of genetic material from one organism to another without sexual reproduction. All genes within an organism, including those introduced by gene technology, can be transferred to another organism by HGT. A gene transferred through HGT could confer a novel trait to the recipient organism. The novel trait may result in negative, neutral or positive effects on the fitness of the recipient organism. This pathway is further considered as a potential source of risk.

131. As discussed in Chapter 1, Section 4.1, the GMO has been modified by the modification of the *ptx* gene; replacement of the *B. pertussis ampG* gene with the *E. coli ampG* gene; and the deletion of the *dnt* gene. These modified genes and their encoded proteins are considered further as a potential source of risk.

132. The current assessment focusses on risks posed to people or the environment, including long term persistence of the GMOs, which might arise from the import, transport, storage or disposal of BPZE1.

2.2 Causal pathway

133. The following factors are taken into account when postulating plausible causal pathways to potential harm:

- the proposed dealings;
- restrictions placed on the import, transport or disposal of the GMO by other regulatory agencies, the States and Territories;
- characteristics of the parent organism;
- routes of exposure to the GMOs, the introduced gene(s) and gene product(s);
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism;
- potential exposure of other organisms to the introduced gene(s) and gene product(s) from other sources in the environment;
- potential exposure of other organisms to the GMOs in the environment;
- the release environment;
- spread and persistence of the GMOs (e.g. dispersal pathways and establishment potential);
- environmental stability of the organism (tolerance to temperature, UV irradiation and humidity);
- gene transfer by HGT;
- unauthorised activities; and
- practices before and after administration of the GMO.

134. As discussed in Chapter 1 Section 1.1, the TGA, the trial sponsor, the Investigators and HREC all have roles in ensuring the safety of trial participants under the *Therapeutic Goods Act 1989*, and human clinical trials must be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council et al., 2018). Therefore, risk scenarios in the current assessment focus primarily on risks posed to people other than the intended vaccine recipient, and to the environment.

135. The Act provides for substantial penalties for unauthorised dealings with GMOs or non-compliance with licence conditions, and also requires the Regulator to have regard to the suitability of an applicant to hold a licence prior to the issuing of the licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities. Therefore, unauthorised activities will not be considered further.

136. As mentioned in Chapter 1, Section 3, there is no evidence that *B. pertussis* can integrate into the host DNA. *B. pertussis* is also not known to harbour any plasmids. Thus, the consequences of integration of bacterial DNA into a host cell genome will not be further discussed.

137. As discussed in Chapter 1, Section 4.2.2, the GMO is unable persist in the environment due to fastidious growth requirements. In addition, the GMO is unable to grow in highly acidic environments such as the digestive tract. Therefore, the ingestion of the GMO during administration is unlikely to result in the persistence of the GMO in the gut resulting in any gastrointestinal shedding of the GMO.

Therefore, the consequence of genes being shed from the gut of trial participants will not be considered further.

138. Recombination between different *B. pertussis* vaccines is highly unlikely because it is improbable that two or more vaccines are administered at the same time using the same route of administration (IN). In addition, currently Australia only uses acellular vaccines for pertussis, which only contains *B. pertussis* proteins and not the whole bacteria. Thus, the potential of recombination between pertussis vaccines will not be further discussed.

2.3 Potential harms

139. The following factors are taken into account when postulating relevant risk scenarios for this licence application:

- harm to the health of people or desirable organisms, including disease in humans or animals or adverse immune response to the GMO
- the potential for establishment of a novel bacteria that could cause harm to people or the environment

2.4 Postulated risk scenarios

140. Three risk scenarios were postulated and screened to identify substantive risk. These hypothetical scenarios are summarised in Table 1 and discussed in depth in Sections 2.4.1-2.4.2 (this chapter).

141. In the context of the activities proposed by the applicant and considering both the short and long term, none of the two risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 1 Summary of hypothetical risk scenarios from dealings with GM vaccine

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people or animals to the GMO via aerosols, needle stick or mucous membranes during the: (a) Preparation and administration of the GMO (b) Shedding of the GMO (e.g. coughing, sneezing, runny nose) (c) Import, transport, storage of the GMO (d) Disposal of the GMO ⬇ Colonisation of the GMO in the respiratory tract or entering the blood stream ⬇	Pertussis infection, Ill health	No	• The GMO has been attenuated and unable to cause disease. • The dose from accidental exposure would be far smaller than administered GMO. • The GMO is not known to replicate in the blood stream. • Treatment with antibiotics are available in the case of accidental exposure. • Protection against disease from previous pertussis vaccination. • Import would be in accordance with IATA 3245. • Transport, storage and disposal of the GMO would

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		Infection of host cells			be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.
2	GMO	Exposure of other people or animals to the GMO as mentioned in Risk Scenario 1 ⬇ Colonisation of the GMO in the respiratory tract ⬇ (a) Reversion of the GMO to the toxigenic phenotype (b) Transfer of genetic material to or from the GMO ⬇ Production of bacteria with toxigenic phenotype ⬇ Infection of host cells	Pertussis infection, ill health	No	• Very little evidence of HGT in *B. pertussis*. • The GMO has been safely used in several Phase 1 and 2 clinical trials. • Passive surveillance of staff involved with the trials and close contacts of participants did not document any transmission or unsolicited adverse events. • The genetic stability of the GMO has been investigated in several different studies and was found to be stable. • Reversion of the GM bacteria to the toxigenic phenotype would not increase the pathogenicity of the microorganism above the parent strain.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of other people or animals to the GMO via aerosols, needle stick or mucous membranes during the: (a) Preparation and administration of the GMO (b) Shedding of the GMO (c) Import, transport or storage of the GMO (d) Disposal of the GMO ⬇ Colonisation of the GMO in the respiratory tract ⬇ Infection
Potential harm	Pertussis infection, ill health

Risk source

142. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

143. People (person handling the GMO, household contacts including people at risk and pregnant women) could be directly or indirectly exposed to the GMO in several ways. This exposure could result in colonisation of the GMO in the upper respiratory tract and subsequently cause infection that could lead to ill health.

Exposure during preparation and administration of the GMO

144. There is potential for exposure of people other than the trial participant to the GMO during the preparation or administration of the GMO via inhalation of aerosols via breakage/spillage, needle stick injury and discharge (e.g. sneezing) of the initial inoculum containing the GMO following administration.

145. As discussed in Chapter 1, Section 2.1, the preparation and administration of the GMO will be carried out in clinical trial sites by authorised, experienced, and trained health professionals. All personnel working in settings where healthcare is provided, including vaccination services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and the *Australian Immunisation Handbook.* The compliance with the guidelines*;* existing work practices; and advice to trial participants will minimise the potential exposure of people to the GMOs during preparation and administration of the vaccine.

146. The potential for production of aerosol during the preparation of the GMO is highly unlikely because there would be no open transfer of the GMO during preparation. Similarly, while administering the GMOs, clinical trial staff would be wearing PPE and administration of the GMO is directly into the nose of participants. This significantly reduces the likelihood of exposure to the GMO from aerosols. In the event of an exposure, carers and clinical staff are unlikely to develop disease as they would only be exposed to a small quantity of GMOs.

147. The dose received through the pathways described above would be far smaller than that administered during vaccination. In addition, clinical trials have shown no serious adverse effects using the full dose of the GMO. Therefore, even if an individual is inadvertently exposed to the GMO, they are unlikely to develop an adverse immune reaction, particularly given they are likely to have been vaccinated against *B. pertussis*.

Exposure due to shedding of the GMO from trial participants

148. There is potential that the participants could shed the GMO (e.g. coughing, sneezing, runny nose) to close contacts or people at risk (e.g. immunocompromised, unvaccinated individuals) after they leave the clinical trial site. However, there has not been any reported shedding or transmission of the GMO in pre-clinical and clinical studies with the GMO. Also, shedding was not observed in a controlled study where vaccinated participants were infected with *B. pertussis*. The discharge of the initial inoculum is likely to contain the highest GMO concentration following administration leading to exposure to health care personnel and caregivers (if present). Experiments using radio-labelled albumin as a vaccine surrogate to investigate the absorption of IN delivered vaccines demonstrated that the nasal spray was absorbed with halftimes of clearance ranging from 40-60 minutes, with a mean time of 50 minutes in adults (Bryant et al., 1999). To minimise the discharge of concentrated dose of the GMO, trial participants would be advised to use tissue to collect any nasal discharge (e.g. sneezing) immediately after administration and appropriately dispose the tissues used.

149. For a productive infection to occur, individuals must be exposed to an infectious dose. Initial Phase 1 clinical trials showed that the GMO has a reduced capacity to colonise the upper-respiratory tract of participants at low doses of the vaccine (10^3 and 10^5 CFU; 1 out of 12 participants). The administration dose used in this clinical trial is 10^9 CFU, so it would be unlikely for close contacts to be exposed to an infective dose.

Exposure during import, transport and storage of the GMO

150. If the GMO was unintentionally/accidentally spilled during import, transport or storage, this could result in exposure to people or animals in the area via the inhalation or contact of mucous membranes from the generation of aerosols.

151. The GMO will be imported, stored, handled and transported in accordance to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs) (Chapter 1, Section 2.2.2). In addition, biological samples that may contain GMO will also be handled in the same manner. These practices will lower the likelihood of dispersal and exposure to the GMOs.

152. The likelihood of exposure to the GMO - animals is highly unlikely because the GMO is unable to replicate and persist outside the human host. In addition, *B. pertussis* is a strict human pathogen and no natural infections of non-human hosts have been described. Further, the presence of animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

153. Decontamination and disinfection measures appropriate for the GMO will be carried out after administration of the vaccine or in the case of accidental spills during the supply of the GMO.

154. The import, transport and storage procedures discussed above would mitigate exposure due to spills of the GMO during these dealings.

Exposure during disposal of the GMO

155. Individuals may be inadvertently exposed to GMOs while disposing of used, expired, or unused vials of the GMO. The two locations where this is most likely to occur are at:

- locations where stocks of the GMOs are held;
- locations where the GMO is administered.

156. As discussed in Chapter 1, Section 2.2.8, unused and expired vials of the GMO as well as the vials with residual GMO, syringes and waste contaminated with the GMO would be treated as clinical/medical waste and disposed of in accordance with the waste disposal methods approved by the relevant State and Territory legislated procedures for clinical/medical waste disposal. Adherence with these procedures would reduce the likelihood of accidental exposure to aerosolised GMOs of people or animals to the GMO.

157. Taken together, the disposal and decontamination procedures discussed above would minimise likelihood of exposure that could be associated with conducting these dealings with the GMOs.

Potential harm

158. If people are exposed to the GMOs, they could develop minor symptoms like runny nose, mild symptoms of fever, sneezing and cough, as observed in the participants in the clinical trials. These symptoms are short-lasting. It is plausible that exposed people could experience similar adverse events. However, exposure is unlikely to cause any negative effects of ill-health because:

- The GMO is attenuated and has not been shown to cause severe disease in clinical trials.
- Pre-clinical studies with the GMO in immunocompromised mice did not cause severe disease.
- The GMO requires very specific conditions for growth as mentioned in Chapter 1, Section 3.3.5 and is not known to replicate in the human blood stream.
- Australia has a high rate of pertussis vaccination (above 92% average), limiting the potential harm caused by the GMO.
- Availability of antibiotic treatments in the event of accidental exposure.

159. As mentioned previously, *B. pertussis* is a strict human pathogen and no natural infections of non-human hosts have been described. Therefore, the potential harm to animals is highly unlikely.

Conclusion

160. The potential for an unintentional exposure of people and animals to the GMO resulting in ill health in humans and animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

2.4.2 Risk Scenario 2

Risk source	GMO
Causal pathway	Exposure of other people or animals to the GMO as mentioned in Risk Scenario 1 ⬇ Colonisation of the GMO in the respiratory tract ⬇ (a) Reversion of the GMO to the toxigenic phenotype (b) Transfer of genetic material to or from the GMO ⬇ Production of bacteria with toxigenic phenotype ⬇ Infection of host cells
Potential harm	Pertussis infection, ill health

Risk source

161. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

162. The transmission of GMO can occur by the pathways mentioned in Risk Scenario 1 which could potentially result in a transient colonisation of the GMO in the respiratory tract. This could potentially result in the reversion of the GMO to the toxigenic phenotype and/or the transfer of genetic material to or from the GMO to other bacteria colonising the respiratory tract.

Reversion of the GMO to the toxigenic phenotype

163. As mentioned in Chapter 1, Section 4.1, mutations were carried out in in two key residues in subunit A of PT involved in the substrate binding (Arg-9 with Lys) and enzyme activity (Glu-129 with Gly) of the GMO respectively. A mutation that counteracts the effects of the initial mutation could plausibly occur allowing the GMO to regain the functions of PT. A reversion of both the mutated residues (substrate binding and enzyme activity) is required for the restoration of a functional PT as one mutation was sufficient to inactivate the toxin. Therefore, further decreasing the likelihood of a revertant GMO. As mentioned in Chapter 1, Section 4.2.1, the GMO was shown to be genetically stable after serial propagation in cells and mice. Phase 1 and 2 clinical trials with the GMO demonstrated a good safety profile with no reported vaccine related serious events and no symptoms of whooping cough were observed suggesting no reversion of the GMO to its toxigenic phenotype.

164. As mentioned in Chapter 1, Section 3.3.1, *B. pertussis* is a strict human pathogen and is unable to naturally infect non-human hosts. Therefore, the likelihood that the GMO can infect animals, resulting in the reversion of the GMO to wild type is highly unlikely.

Homologous recombination with Bordetella pertussis and E. coli

165. The GMO could potentially recover its toxigenic phenotype by regaining the genes via homologous recombination with wild-type *B. pertussis* to produce a functional pertussis toxin (PT) and dermonecrotic toxin (DNT). The GMO would also need to lose the ability to internalise tracheal cytotoxin (TCT) by regaining the *B. pertussis ampG* gene and losing the *E. coli ampG* gene. For Risk

scenario 2 to occur, the GMO has to first colonise the respiratory tract of the person that was exposed to the GMO as mentioned in Risk scenario 1. In addition, the GMO, the wild-type *B. pertussis* and/or *E. coli* have to be present simultaneously in the respiratory tract of the person exposed. As mentioned in Risk scenario 1, the likelihood that a person would be exposed to enough GMO to effectively colonise the respiratory tract is very low. All three bacteria would also need to infect the same cell long enough for any homologous recombination to happen, which is highly unlikely to occur.

166. As mentioned in Chapter 1, Section 3.3.6, there is very little evidence of HGT in *B. pertussis* and studies of a large number of clinical strains from several countries showed that the genome of *B. pertussis* is very stable and gene acquisition is rare. To revert to its toxigenic phenotype, multiple recombination events of the GMO would need to occur to acquire three different genes from wild type *B. pertussis* and *E. coli* (*ptx, B. pertussis ampG and dnt*) and this is highly unlikely.

Potential harm

167. In the unlikely event that the GMO reverts to the wild type phenotype by mutation or homologous recombination, it could cause a similar disease to the wild type strain. As with pertussis infection, this disease would be more serious to unvaccinated and immunocompromised individuals. However, as mentioned in Chapter 1, Section 3.3.4, majority of the Australian population is vaccinated. This is not expected to increase the disease burden and can be readily treated by antibiotics available in Australia.

168. As mentioned in Risk Scenario 1, *B. pertussis* is a human pathogen and is unlikely to cause harm in animals.

Conclusion

169. The exposure of people to a GMO which has reverted to the wild type phenotype resulting in ill-health or disease in people or animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

Section 3 Uncertainty

170. Uncertainty is an intrinsic part of risk analysis[2]. There can be uncertainty in identifying the risk source, the causal linkage to harm, the type and degree of harm, the likelihood of harm or the level of risk. In relation to risk management, there can be uncertainty about the effectiveness, efficiency and practicality of controls.

171. There are several types of uncertainty in risk analysis (Clark and Brinkley, 2001; Hayes, 2004; Bammer and Smithson, 2008). These include:

- uncertainty about facts:
  - knowledge – data gaps, errors, small sample size, use of surrogate data
  - variability – inherent fluctuations or differences over time, space or group, associated with diversity and heterogeneity
- uncertainty about ideas:
  - description – expression of ideas with symbols, language or models can be subject to vagueness, ambiguity, context dependence, indeterminacy or under-specificity

[2] A more detailed discussion is contained in the Regulator's *Risk Analysis Framework* available from the OGTR website or via Free call 1800 181 030.

- perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

172. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk, the Regulator will take this uncertainty into account in making decisions.

173. Although there were no reported shedding or transmission of the GMO from patients to staff involved in the clinical trial and no documented adverse events on staff and clinicians handling/administrating the GMO from passive surveillance, there is no actual shedding data for this GMO available. However, as assessed in Chapter 2, even if there was shedding of the GMO, the risk from shedding is considered negligible.

174. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

Section 4 Risk evaluation

175. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

176. Factors used to determine which risks need treatment may include:

- risk criteria,
- level of risk,
- uncertainty associated with risk characterisation, and
- interactions between substantive risks.

177. Two risk scenarios were identified whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people and animals can be exposed to the GMO while conducting the dealings and whether there is a potential for the GMO to revert to its wild type phenotype through mutation and homologous recombination. The potential for GMO to be released into the environment and its effects was also considered.

178. A risk is substantive only when the risk scenario may, because of gene technology, have some chance of causing harm. Risk scenarios that do not lead to harm, or could not reasonably occur, do not represent an identified risk and do not advance in the risk assessment process.

179. In the context of the range of measures already in place, including the operating guidelines and requirements of the other regulatory agencies, and considering both the short and long term, none of these scenarios was identified as representing a substantive risk requiring further assessment. The principal reasons for this include:

- the GMO is modified so that it is unable to produce toxins that cause the disease;
- reversion of the GMO to its wild-type phenotype is highly unlikely;
- the GMO is a human pathogen and highly unlikely to cause disease in animals;
- the likelihood of accidental exposure to the GMO in people not being vaccinated (vaccinees) or animals would be minimised due to well-established import, transport, storage and disposal procedures;
- the likelihood of that exposure of the GMO to individuals in contact with vaccinees through shedding will cause harm is unlikely; and

- survival and persistence the GMO in the Australian environment is highly unlikely.

Therefore, any risks to the health and safety of people, or the environment, from the proposed clinical trial using the GMO are considered to be negligible. The *Risk Analysis Framework* (OGTR 2013), which guides the risk assessment and risk management process, defines negligible risks as insubstantial with no present need to invoke actions for their mitigation. No controls are required to treat these negligible risks. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment[3]

[3] As none of the proposed dealings are considered to pose a significant risk to people or the environment, Section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP.

Chapter 3 Risk management plan

Section 1 Background

180. 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 addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through proposed licence conditions.

181. Under section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

182. All licences are subject to three conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings: Section 64 requires the licence holder to provide access to premises to OGTR inspectors and Section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder are also required to be reported to the Regulator.

183. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in Section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under Section 152 of the Act.

Section 2 Risk treatment measures for substantive risks

184. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed clinical trial with the GMO. These risk scenarios were considered in the context of the scale of the proposed clinical trial (Chapter 1, Section 2.2.4), the proposed controls (Chapter 1, Section 2.1), the proposed receiving environment (Chapter 1, Section 5), and considering both the short and long term effects of the GMO. Limits and controls proposed by the applicant and other general risk management measures are discussed below.

Section 3 General risk management

185. The limits and controls proposed in the application were important in establishing the context for the risk assessment and in reaching the conclusion that the risks posed to people and the environment are negligible. Therefore, to maintain the risk context, draft licence conditions have been imposed to limit the number of trial participants, location limited to hospitals and clinical trial sites, limits on the duration of the trial, as well as a range of controls to restrict the spread and persistence of the GMOs and their genetic material in the environment. The conditions are discussed and summarised in this Chapter and listed in detail in the draft licence.

3.1 Limits and controls on the clinical trial

186. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Novotech. Many of these are discussed in the 2 risk scenarios considered in Chapter 2. The appropriateness of the limits and controls is considered further in the following sections.

3.1.1 Consideration of limits and controls

187. The proposed clinical trial would involve a maximum of 300 participants within Australia, and most dealings with the GMOs would take place in medical facilities such as clinical trial units and hospitals. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMOs. The applicant has proposed that the trial will be completed within 5 years of commencement. Conditions maintaining the risk context and proposed limits of the trial such as the maximum number of trial participants and duration of the study and have been included in the draft licence.

188. The applicant proposed that import and transport of the GMO and waste containing the GMO would be in accordance with IATA and the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* respectively. These are standard protocols for the handling and minimising exposure to the GMOs. Once at the clinical trial site, access to the GMO would be restricted to appropriately trained personnel. These proposed transport conditions are suitable for the GMO. Therefore, the draft licence details the minimum requirements for packaging and labelling the GMO and waste contaminated with the GMO for transport and storage within a clinical trial site, as well as transport of the samples that may contain the GMO for analysis. These measures would limit the exposure of people and the environment to the GMOs.

189. As mentioned in Chapter 1, Section 2.2.9, nasal swabs, blood and urine samples would be collected as part of the clinical trial. Nasal swabs would be expected to contain the GMO and would be conditioned in the draft licence. However, as blood and urine samples are not reasonably expected to contain the GMO due to the expected biodistribution of the GMO, these samples are not included in the draft licence.

190. There are proposed inclusion and exclusion criteria for both trial participants and staff as listed in Chapter 1, Section 2.2.5. The inclusion and exclusion criteria for trial participants would be subject to approval by a HREC, who would consider the safety of the individuals involved in the trial. There have not been any adverse effects seen with the GMO in pre-clinical and clinical studies; pertussis vaccines have been recommended even for HIV positive infants; and there has not been any reported transmission of the GMO to staff or close contacts or participants. However, as mentioned in risk scenario 2 and Chapter 1, Section 3.1, the people most at risk are immunocompromised individuals and unvaccinated infants. Therefore, to further minimise any chance of risk of adverse effects to these individuals, the draft licence would require excluding people who:

- have routine and/repeated contact with, or are currently living in a household with, an immunocompromised individual; and
- reside or may reside with an infant less than 6 months of age.

191. When the GMO is administered via the IN route, there is potential for the inoculum to be sneezed out during administration. In addition, the GMO is found to colonise the upper respiratory tract of participants for up to 28 days with the highest percentage of bacteria observed at day 4 and day 7 post-inoculation (Chapter 1, Section 4.2.4). Risk scenario 1 has not identified any risk associated with the exposure of carers and staff to the GMO as they are unlikely to be exposed to a sufficient amount of GMO to colonise the respiratory tract. Therefore, the requirements for trial participants to remain at the clinical trial site for a period after administration is not included in the licence. However, draft licence conditions would include, instructions to dispose the tissues used in the case of accidental sneezing or coughing during the administration of the GMO within the clinical trial site, as it may contain the highest amount of GMO.

192. Although the risk of exposure to high enough concentrations of GMO is very low, the risk from exposure to the GMO would be highest during the administration of the GMO. The clinical staff handling the GMO would wear PPE including disposable gown, gloves, mask and eye protection/face shield. These practices would minimise exposure of people handling and administering the GMOs

(Risk scenario 1) and have been included in the draft licence conditions. In addition, draft licence would include that carers of participants who may be present during the administration be wearing masks.

193. Conditions are included in the draft licence requiring the licence holder to ensure that all GMOs, including material or waste that has been in contact with the GMO, within the clinical trial site, are decontaminated by autoclaving, chemical treatment or by high-temperature incineration. Draft licence conditions require that the licence holder must ensure that the GMO, or material or waste that has been in contact with the GMO, that is to be destroyed by external service providers, is through a clinical waste stream. This is considered satisfactory, provided that the licence holder is only permitted to engage persons who can adhere to appropriate standards to conduct the dealings, as described in Paragraph 195.

194. The Industry Code of Practice for the Management of Clinical and Related Wastes details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability (Biohazard Waste Industry, 2010).

195. A standard condition is included in the draft licence requiring the licence holder to ensure that dealings are conducted to ensure containment of the GMO, not compromise the health and safety of people and minimise unintentional exposure to the GMO. A note written under the condition explains that compliance may be achieved by only engaging persons who are required to adhere to appropriate standards to conduct the dealings.

196. Other conditions included in the draft licence are standard conditions that state that only people authorised by the licence holder are covered by the licence, and that the licence holder must inform all people dealing with the GMOs, other than external service providers, of applicable licence conditions.

197. Further conditions to be implemented in the draft licence are to ensure that a compliance management plan is in place for each clinical trial site before administration of the GMOs commences at that site. The compliance management plan must detail how the licence holder intends to comply with the licence conditions, including listing persons responsible for site management, proposed reporting structures, staff training procedures and transport and disposal processes.

3.1.2 Summary of licence conditions to be implemented to limit and control the clinical trial

198. A number of licence conditions have been drafted to limit and control the proposed clinical trial, based on the above considerations. These include requirements to:

- limit the trial to 300 trial participants, which are to be conducted at clinical trial sites;
- restrict access to the GMO;
- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements;
- ensure appropriate PPE is used;
- restrict personnel permitted to administer the GMO;
- requiring decontamination of the GMO and materials and equipment that have been in contact with the GMO at clinical trial sites using effective disinfectants or disposal using a certified waste contractor in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation;
- transport and storage of the GMO and samples from GMO-treated participants in accordance with the minimum requirements for packaging, and labelling as detailed in the draft licence and import in accordance with IATA shipping classification UN 3245 and/or;
- clinical waste stream to be used by external service providers to destroy untreated GMO and GMO-related waste.

3.2 Other risk management considerations

199. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- contingency plans
- identification of the persons or classes of persons covered by the licence
- reporting requirements
- access for the purpose of monitoring for compliance.

3.2.1 Applicant suitability

200. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under Section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country
- the capacity of the applicant to meet the conditions of the licence.

201. If a licence were issued, the conditions would include a requirement for the licence holder to inform the Regulator of any information that would affect their suitability.

202. In addition, the applicant organisation must have access to an IBC and be an accredited organisation under the Act.

3.2.2 Contingency plans

203. Should a licence be issued, Novotech is required to submit a contingency plan to the Regulator before commencing dealings with the GMOs. This plan will detail measures to be undertaken in the event of:

- the unintended release of the GMOs, including spills
- exposure of, or transmission to persons other than trial participants
- a person exposed to the GMOs developing a serious adverse response.

3.2.3 Identification of the persons or classes of persons covered by the licence

204. If issued, the persons covered by the licence would be the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by the licence. Prior to dealings with the GMOs, Novotech is required to provide a list of people and organisations that are covered by the licence, or the function or position where names are not known at the time.

3.2.4 Reporting requirements

205. If issued, the licence would require the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the clinical trial.

206. A number of written notices are also required under the licence regarding dealings with the GMO, to assist the Regulator in designing and implementing a monitoring program for all licensed dealings. The notices include:

- identification of the clinical trial sites where administration of the GMO to trial participants would take place
- expected date of administration with the GMOs for each clinical trial site
- cease of administration with the GMOs for each clinical trial site

3.2.5 Monitoring for compliance

207. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow inspectors and other persons authorised by the Regulator to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

208. If monitoring activities identify changes in the risks associated with the authorised dealings, the Regulator may also vary licence conditions, or if necessary, suspend or cancel the licence.

209. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Issues to be addressed for future releases

210. Additional information has been identified that may be required to assess an application for a commercial release of the GMO, or to justify a reduction in limits and controls. This includes:

- information and data that would address the uncertainties noted in Chapter 2, Section 3. Specifically, information obtained on the shedding of the GMOs in nasal secretions following vaccination of trial participants.

Section 5 Conclusions of the consultation RARMP

211. The risk assessment concludes that the proposed clinical trial of the GMOs poses negligible risks to the health and safety of people or the environment as a result of gene technology. These negligible risks do not require specific risk treatment measures.

212. If a licence is issued, conditions are imposed to limit the trial to the proposed scale, location and duration, and to restrict the spread and persistence of the GMOs and its genetic material in the environment, as these were important considerations in establishing the context for assessing the risks.

Chapter 4 Draft licence conditions

1. In this licence:

    (a) unless defined otherwise, words and phrases used in this licence have the same meaning as they do in the Act and the Regulations;

    (b) words denoting a gender include any other gender;

    (c) words in the singular include the plural and words in the plural include the singular;

    (d) words denoting persons include a partnership and a body whether corporate or otherwise;

    (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

    (f) where any word or phrase is given a defined meaning, any other part of speech or other grammatical form in respect of that word has a corresponding meaning;

    (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

'Act' means the *Gene Technology Act 2000* (Commonwealth) or the corresponding State Law under which this licence is issued.

'Analytical facility' means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC).

'Clinical trial site' means a medical facility in Australia such as a clinical trial facility and associated pharmacy, which are notified in writing to the Regulator for the purposes of conducting this clinical trial.

'Decontaminate' (or ***'Decontamination'***) means, as the case requires, kill the GMOs by one or more of the following methods:

    (a) chemical treatment;

    (b) autoclaving;

    (c) high-temperature incineration; or

    (d) a method approved in writing by the Regulator.

Note: 'As the case requires' has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.

'External service provider' means a person engaged by the licence holder solely in relation to transport, storage and/or disposal of the GMOs, or Sample analysis other than at a Clinical trial site, and who is not undertaking any dealings with the GMOs that are not for those purposes.

'*GMO'* means the genetically modified organisms that are the subject of the dealings authorised by this licence.

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

'Personal information' has the same meaning as in the *Privacy Act 1988*. Personal information means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

(a) whether the information or opinion is true or not; and

(b) whether the information or opinion is recorded in a material form or not.

'Pharmacy' means a location within the Clinical trial site, where authorised staff stores, prepares, and dispenses medications in a medical environment.

'*Regulations*' means the *Gene Technology Regulations 2001* (Commonwealth) or the corresponding State Law under which this licence is issued.

'Regulator' means the Gene Technology Regulator.

'Sample' means any biological material collected from trial participants for subsequent analysis.

'Serious adverse event' means any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

Holder of licence

3. The licence holder is Novotech (Australia) Pty Ltd.

Remaining an Accredited Organisation

4. The licence holder must, at all times, remain an accredited organisation.

Validity of licence

5. This licence remains in force until it is suspended, cancelled, or surrendered. No dealings with the GMO are authorised during any period of suspension, or after the licence has been cancelled or surrendered.

Note: Although this licence has no expiry date, the duration of preparation and administration of the GMOs is restricted in accordance with Condition 23.

Persons covered by this licence

6. The persons covered by this licence are the licence holder, and any employees, agents or External service providers of the licence holder, or the project supervisor(s), or other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.

7. To the extent that any activity by a trial participant may be considered to be a dealing for purposes of the Act, that dealing is authorised by this licence.

8. The licence holder must keep a record of all persons covered by this licence and must keep a record of the contact details of the project supervisor(s) for the licence.

Note: Where External service providers are used, it is sufficient to record the company name and the position or job title of the person(s) conducting the dealing.

9. The licence holder must provide information related to the persons covered by the licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Description of GMOs covered

10. The dealings authorised by this licence are only permitted to be conducted in respect of the GMOs identified and described in **Attachment A**.

Dealings authorised by this licence

11. The dealings authorised by this licence are to:

(a) import the GMO;

(b) conduct the following experiments with the GMOs:

i) prepare the GMO for administration;

ii) administer the GMO to clinical trial participants by intranasal administration;

iii) collect samples from trial participants;

iv) analyse the samples described in 11(b)iii);

(c) transport the GMO; and

(d) dispose of the GMOs;

and may possess, supply, use or store the GMO for the purposes of, or in the course of, any of these dealings.

12. Supply of the GMOs for the purposes of dealings by a person or organisation not covered by this licence is only authorised by this licence if the Regulator provides prior written approval to the licence holder.

Note: For approval to be granted, the receiving person or organisation must have an appropriate authorisation to conduct dealings with the GMOs. This is likely to be an NLRD or a licence issued by the Regulator.

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

13. The licence holder must inform any person covered by the licence, to whom a particular condition of the licence applies, of the following:

(a) the particular condition, including any variations of it; and

(b) the cancellation or suspension of the licence; and

(c) the surrender of the licence.

Note: No particular conditions of this licence apply to trial participants; therefore, Condition 13 does not apply to trial participants.

Monitoring and audits (section 64)

14. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Additional information to be given to the Regulator (section 65)

15. The licence holder must inform the Regulator if he or she becomes aware of:

(a) additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

(b) any contraventions of the licence by a person covered by the licence; or

(c) any unintended effects of the dealings authorised by the licence.

Note 1: For the purposes of this Condition:

(a) The licence holder is taken to have become aware of additional information if he or she was reckless as to whether such information existed; and

(b) The licence holder is taken to have become aware of contraventions, or unintended effects, if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

Note 2: Contraventions of the licence may occur through the action or inaction of a person.

Note 3: Additional information includes any changes at a Clinical trial site, which might increase the likelihood of unintentional exposure of people or release of the GMO into the environment.

Informing the Regulator of any material changes of circumstance

16. The licence holder must immediately, by notice in writing, inform the Regulator of:

(a) any relevant conviction of the licence holder occurring after the commencement of this licence;

(b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State, or a foreign country, being a law relating to the health and safety of people or the environment;

(c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

17. The licence holder must provide information related to the licence holder's ongoing suitability to hold a licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Further conditions with respect to informing persons covered by the licence

18. If a particular condition, including any variation of it, applies to a person with respect to any dealing, the licence holder must not permit a person covered by this licence to conduct that dealing unless the person has been informed of the condition, including any variation of it.

Note: Information required under Condition 18 may be provided to External service providers who are engaged solely for storage and transport of the GMO through labelling of the outermost container of the GMOs in accordance with Condition (c)(a).

19. If a particular condition, including any variation of it, applies to a person with respect to any dealing, other than to an External service provider, the licence holder must not permit a person covered by this licence to conduct that dealing unless:

(a) the licence holder has obtained from the person a signed and dated statement that the person:

i) has been informed by the licence holder of the condition and, when applicable, its variation; and

ii) has understood and agreed to be bound by the condition, or its variation; and

iii) has been trained in accordance with paragraph (b) below; and

(b) the licence holder has trained that person in a manner which enables them to conduct the dealings in accordance with the conditions of this licence.

20. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

21. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence, other than External service providers, who are conducting dealings with the GMO.

Note: The licence may be made available electronically.

Limits on clinical trials conducted under this licence

22. The GMO may be administered to a maximum of 300 trial participants.

23. The preparation and administration of the GMO must be completed within 5 years from the date of issuing of the licence.

Preparation and administration of the GMOs and collection of samples

24. Administration of the GMOs into human trial participants must not commence prior to approval by a Human Research Ethics Committee.

25. The following activities must occur within a Clinical trial site:

(a) preparation of the GMO for administration to trial participants; and

(b) administration of the GMO to trial participants.

Note: Before any of these activities take place, the details of each Clinical trial site must have been notified to the Regulator in accordance with Condition 40(a).

Conditions about trial participants

26. The licence holder must notify each trial participant, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

27. The licence holder must ensure that persons that:

(a) have routine and/repeated contact with or are currently living in a household with an immunocompromised individual; and

(b) reside or may reside with an infant less than 6 months of age;

are excluded from being selected as trial participants.

28. The licence holder must ensure surgical facemasks are worn by people present during the administration of the GMO.

Conditions related to the conduct of the dealings

29. Conditions that apply to dealings with GMOs do not apply to samples collected from trial participants, or other materials or waste, that are reasonably expected not to contain the GMO. The licence holder must provide to the Regulator upon request, a written justification for this expectation.

Note: Example of samples that may reasonably not contain the GMO would include urine and blood.

30. The licence holder must ensure that dealings are only conducted in a manner which:

(a) does not compromise the health and safety of people; and

(a) minimises the exposure of persons conducting the dealings to the GMO, other than intended exposure of trial participants.

Note: The licence holder may do this by only engaging or otherwise authorising persons to conduct dealings at facilities which adhere to appropriate standards and guidelines, e.g. those developed by the National Pathology Accreditation Advisory Council for pathology practices, or the National Safety and Quality Health Service (NSQHS) Standards.

31. The licence holder must ensure that procedures are in place to account for the GMO from import to destruction/export, and records must be made available to the Regulator on request.

32. For the purposes of Condition 30, the work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) persons conducting dealings with the GMOs must wear personal protective equipment (PPE), including gowns, gloves and, unless working in a negatively pressured pharmaceutical isolator or a biological safety cabinet, eye protection and a surgical facemask;

(b) all work surfaces must be decontaminated before and after they have been used for conducting dealings authorised by this licence;

(c) equipment used for dealings with the GMOs must be decontaminated after use;

(d) preparation and administration of the GMO must be conducted by suitably qualified and trained staff;

(e) Any tissues used by the trial participant immediately post-administration of the GMO must be disposed of via the clinical waste stream prior to the trial participant leaving the Clinical trial site.

Transport, storage and disposal of the GMOs

33. The licence holder must ensure that transport of the GMOs must only be for the purposes of, or in the course of, another dealing permitted by this licence, or for supply in accordance with Condition 12.

34. For the purposes of import and transport between the border and either a storage facility, the licence holder must ensure the GMO is packaged, labelled, stored and transported consistent with IATA shipping classification UN 3245.

35. The licence holder must ensure that transport and storage of the GMOs and Samples within the Clinical trial site and within the Australian border, follows these sub-conditions:

(a) GMOs are contained within sealed, unbreakable primary container, with the outer packaging labelled to indicate at least:

i) that it contains GMOs; and

ii) the contact details for the licence holder; and

iii) instructions to notify the licence holder in case of loss or spill of the GMOs.

(b) the external surface of the primary containers must be decontaminated prior to and after transport; and

(c) procedures must be in place to ensure that GMOs can be accounted for and that a loss of GMOs during transport or failure of delivery can be detected; and

(d) access to the GMOs is restricted to authorised persons for whom Condition 18 has been met (i.e. the GMOs are within a locked unit or an area which has restricted access). This includes situations where containers are left for collection in a holding area, or left unattended prior to decontamination;

Note: All stored GMOs remain the responsibility of the licence holder.

(e) if the GMO is being transported or stored with a coolant (e.g. dry ice, liquid nitrogen or any other coolant) which will release a gas, a mechanism to allow the escape of the gas must be included. If water ice is used as a coolant then the outer packaging should be constructed so as to prevent any leakage. All containers must be able to withstand the temperatures to which they will be subjected; and

Note: When transporting and storing with coolants, it is preferable for coolants to be used outside of the secondary container.

(f) a consolidated record of all GMOs being stored under this condition is maintained and made available to the Regulator upon request.

(g) For the purposes of transport entirely within a building, where the GMOs are accompanied by authorised persons for whom Condition 18 has been met, Conditions 35(a)ii), 35(a)iii) and 35(c) do not apply.

36. The licence holder must ensure that all GMOs and all waste reasonably expected to contain the GMO are decontaminated:

(a) prior to disposal, unless the method of disposal is also a method of decontamination; and

(b) before or upon suspension, cancellation or surrender of the licence, unless covered by another authorisation under the Act; and

(c) by autoclaving, chemical treatment, or high-temperature incineration; and

37. Where transport is conducted by External service providers for the purpose of destruction, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, enters the clinical waste stream for decontamination via autoclaving or high-temperature incineration.

Note: In the event of a spill during transport for the purpose of disposal by an External service provider, compliance with relevant State or Territory legislation and regulations to manage clinical or biohazardous spills is sufficient.

Contingency plans

38. The licence holder must ensure that any person (other than a trial participant) exposed to the GMOs is offered prompt medical advice. The clinician must be provided with any relevant information about the GMO, including any drugs to which it may be resistant.

39. If there is a spill or an unintentional release of GMO at the Clinical trial site, the following measures must be implemented:

(a) the GMOs must be contained to prevent further dispersal; and

(b) persons cleaning up the GMO must wear protective clothing; and

(c) the exposed area must be decontaminated with an appropriate chemical disinfectant effective against the GMO; and

(d) any material used to clean up the spill or personal protective clothing worn during clean-up of the spill must be decontaminated; and

(e) the licence holder must be notified as soon as reasonably possible.

Notification and reporting

Note: The following licence conditions are imposed to demonstrate compliance with other conditions and facilitate monitoring of compliance by staff of the OGTR. Notices and reports may be emailed to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at ***Attachment B****.*

40. At least 14 days prior to first administering the GMO at each Clinical trial site, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

(a) the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities;

(b) the key persons responsible for the management of the trial at the site;

(c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial;

(d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Conditions 42;

(e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;

(f) the person(s) or class of persons administering the GMO;

(g) where, within the site, the GMO is expected to be administered;

(h) the expected date of first administration; and

(i) how compliance with Condition 30 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.

Note: For the purpose of finding out whether the Act has been complied with, an OGTR inspector may, if entry is at a reasonable time, enter a facility occupied by the licence holder or a person covered by the licence and exercise monitoring powers.

41. The licence holder must notify the Regulator, in writing, of the final inoculation of the last trial participant at each Clinical trial site, within 30 days of the decision to cease inoculations.

42. The licence holder must inform the Regulator as soon as reasonably possible:

(a) in the event of a trial participant experiencing a *Serious adverse event* which may be related to the GMO;

(b) if they are notified of, or otherwise become aware of, a loss or spill of the GMO;

(c) if they are notified of, or otherwise become aware of, the exposure of a person other than a trial participant to the GMO; and

(d) if they become aware that a trial participant has not followed the procedures described in the instructions provided by the licence holder.

43. Upon request from the Regulator, the licence holder must provide any signed records or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.

Attachment A

DIR No: 185

Full Title: Clinical trial with genetically modified *Bordetella pertussis* for the prevention of whooping cough

Organisation Details

Postal address: Novotech (Australia) Pty Ltd
Level 3, 235 Pyrmont St
Pyrmont,
New South Wales, 2009

Phone No: (08) 8569 1400

GMO Description

GMOs covered by this licence:

Bordetella pertussis (Tohama I strain) attenuated by inactivation of pertussis toxin gene, replacement of *B .pertussis ampG* gene with *E. coli ampG* gene and deletion of *dnt* gene.

Common Name: *Bordetella pertussis / Whooping cough*

Scientific Name: *Bordetella pertussis* (Tohama 1 strain)

Modified traits:

Categories: Vaccine

Description: The GMO, is an attenuated *B. pertussis* derived from the Tohama I strain. It has attenuated to remove properties that cause disease. Modified bacteria will stimulate the immune response when administered as a vaccine. Modified and deleted genes sequences are listed in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Identity and modifications	• Modification in 2 residues of pertussis toxin (PT) • Replacement of *B. pertussis ampG* gene with *E. Coli ampG* gene. • Deletion of *dnt* gene
Function	• PT modification - inactivates the function and binding of PT. • *E. coli ampG* gene - replacement reduces activity of Tracheal Cytotoxin (TCT) • *dnt* gene - deletion results in no production of dermonecrotic toxin (DNT)

Purpose of the dealings with the GMOs:

To conduct clinical trials assessing the safety, tolerability, immunogenicity, and efficacy of a genetically modified *B. pertussis* vaccine to prevent whooping cough.

Attachment B

Prior to the commencement of the trial	Condition	Timeframe for reporting
A written Compliance Management Plan for each trial site, including: • the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; • the key persons responsible for the management of the trial at the site; • the IBC associated with the site (if any) that has been notified of the trial; • the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Condition 42(b), (c); • details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; • the person(s) or class of persons administering the GMO; • where, within the site, the GMO is expected to be administered; • expected date of first administration; and • how compliance with Condition 30 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO	40	Prior to the first administration of the GMO at the Clinical trial site
Information to be provided at any time during the Clinical trial		
Changes to any of the contact details of the contact person(s) for the licence or project supervisor(s) from that notified in the licence application or subsequently		As soon as reasonably possible
Any additional information related to the health and safety of people and the environment associated with the dealing covered by the licence, or any unintended effect of the dealing authorised by the licence	15(a), (c)	As soon as the licence holder becomes aware
Information related to any contravention of the licence by a person covered by the licence	15(b)	As soon as the licence holder becomes aware
Any relevant conviction of the licence holder	16(a)	Immediately
Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	16(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately
Provide notification to the Regulator, in writing, of the final GMO administration of the last trial participant at each Clinical trial site	41	Within 30 days of the decision to cease GMO administration at that particular Clinical trial site.

Any Serious adverse event which may be related to the GMO	42(a)	As soon as reasonably possible
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	42(b), (c)	As soon as reasonably possible after becoming aware of the event
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	42(d)	As soon as reasonably possible after becoming aware of the event
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	43	Within a timeframe stipulated by the Regulator

***** Notifications and documents to be sent to OGTR.M&C@health.gov.au

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