Australian Government
Department of Health and Aged Care
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan (Consultation version) for

DIR-213

Clinical trial of a genetically modified human adenovirus for the treatment of melanoma

Applicant: Novotech (Australia) Pty Ltd

25 March 2025

This RARMP is open for consultation until 6 May 2025.

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

Via the consultation hub:	https://consultations.health.gov.au (search for DIR 213)
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 therapeutic **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-213

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a genetically modified organism (GMO). It qualifies as a Dealing involving the Intentional Release (DIR) of GMOs into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Novotech (Australia) Pty Ltd (Novotech), proposes to conduct a clinical trial to evaluate the safety and efficacy of a genetically modified (GM) human adenovirus for the treatment of Australian patients with metastatic melanoma.

Melanoma is the third most common cancer in Australia. In 2023 over 18,000 new cases of melanoma were diagnosed and an estimated 1,300 deaths were attributed to melanoma in Australia. Current treatment includes surgery to remove superficial melanoma, chemotherapy or immunotherapy.

The proposed GM adenovirus treatment has been designed to preferentially replicate in and kill cancer cells. The GM adenovirus would be manufactured overseas and imported into Australia. It would be administered by intra-tumoral injection in up to 30 patients with metastatic melanoma at clinical facilities and hospitals in Australia.

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 would also 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 would also require approval from the Department of Agriculture, Fisheries and Forestry (DAFF) for import of the GMO into Australia.

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

The application

Project Title	Clinical trial of a genetically modified human adenovirus for treatment of melanoma
Parent organism	Human adenovirus (HAdV-C6)
Genetic modifications	Modified human adenovirus: • Replacement of HAdV-C6 hexon hypervariable region (HVR) with HVR from HAdV-C57 (facilitates initial immune evasion) • Deletion within E1A protein (promotes viral replication in tumour cells and facilitates cellular antiviral responses) • Partial deletion of E3 gene replaced with human CD40L (enhances immune activation in target cells)

Principal purpose	The proposed trial is a Phase 1 study designed to evaluate the safety, tolerability and dose escalation study of genetically modified Adze 1.C, for the treatment of Australian patients with melanoma.
Previous clinical trials	None, this is a first in human clinical trial
Proposed limits and controls	
Proposed duration	3 years
Proposed release size	Up to 30 participants in Australia
Proposed locations	This clinical trial would be conducted within Australia at clinical trial sites and hospitals. The specific clinical trial sites are yet to be identified.
Proposed controls	• The GMO will be administered to trial participants within a suitable medical facility; • Staff handling the GMO will be trained and wear personal protective equipment; • Waste that may contain the GMO will be disposed of via the clinical waste stream; • At risk staff are excluded from handling the GMO; • The GMO will be transported and stored according to the Regulator's *Transport, Storage and Disposal Guidelines* appropriate for PC2 organisms

Risk assessment

The risk assessment concludes that the trial poses negligible risks to human health and safety and to the environment. No specific risk treatment measures are required to manage these negligible risks.

The risk assessment process considers how the genetic modification 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, taking into account information in the application (including proposed controls), relevant previous approvals and current scientific/technical knowledge. Both the short- and long-term risks are considered.

Credible pathways to potential harm that were considered include the potential exposure of people and animals to the GMO, the potential for the GMO to recombine with other similar viruses and the potential for the GMO to integrate into the host genome.

Important factors in reaching the conclusions of the risk assessment included that the GMO selectively replicates in cancer cells, unintended exposure to the GMO would be minimised by the proposed limits and controls outlined in the draft risk management plan and that the likelihood of complementation and recombination of the GMO with other adenoviruses is very low.

As risks to the health and safety of people, or the environment, from the proposed trial of the treatment with the GMO 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

AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
CDC	Centers for Disease Control and Prevention
DIR	Dealings Involving Intentional Release
DNA	Deoxyribonucleic acid
FSANZ	Food Standards Australia New Zealand
GTTAC	Gene Technology Technical Advisory Committee
GM	Genetically modified
GMO	Genetically modified organism
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
IBC	Institutional Biosafety Committee
ICH-GCP	*Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
mL	Millilitre
min	Minute
NHMRC	National Health and Medical Research Council
NPAAC	National Pathology Accreditation Advisory Council
NSQHS	National Safety and Quality Health Service Standards
OGTR	Office of the Gene Technology Regulator
PPE	Personal Protective Equipment
PFU	Plaque Forming Units
PCR	Polymerase chain reaction
RAF	Risk Analysis Framework
RARMP	Risk Assessment and Risk Management Plan
SOP	Standard Operating Procedure
SNV	Single nucleotide variation
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
TGA	Therapeutic Goods Administration
TSDs	The Regulator's *Guidelines for Transport, Storage and Disposal*
USA	United States of America
WHO	World Health Organization

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.

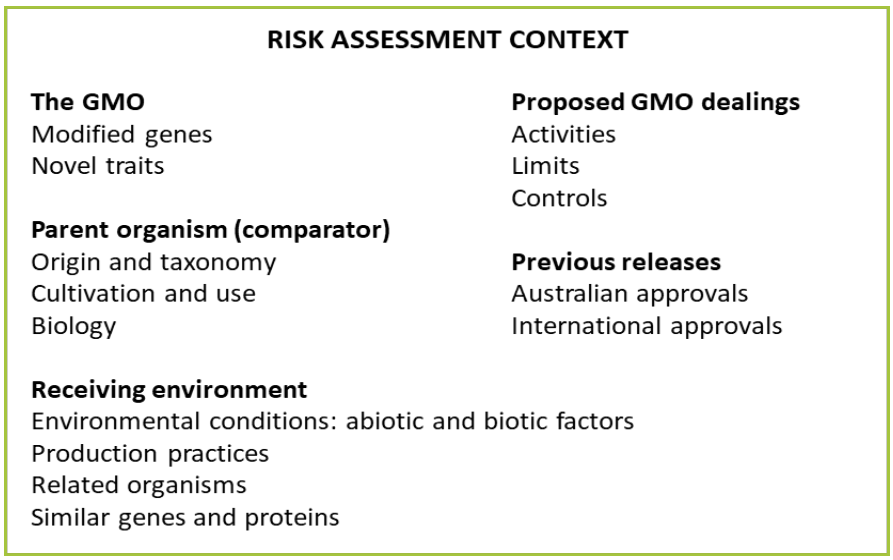

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

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 RARMP from the experts, agencies and authorities outlined above, as well as the public through a second round of consultation.

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, Fisheries and Forestry (DAFF).

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 virus, 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 GMO accounting and reconciliation.

14. DAFF 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 GMO).

15. 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, disease control (Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019) and handling of pathology samples (National Pathology Accreditation Advisory Council; NPAAC).

16. 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).

17. 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.

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. Novotech is seeking authorisation to carry out a Phase 1 clinical trial to assess the safety and efficacy of a genetically modified (GM) human adenovirus (HAdV) that preferentially replicates in cancer cells.

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

(a) Import the GMO;

(b) conduct the following experiments with the GMO:

i. prepare the GMO for administration to trial participants;

ii. administer the GMO to clinical trial participants by intra-tumoral (IT) injection;

iii. collect samples from trial participants;

iv. analyse the samples;

(c) transport the GMO;

(d) dispose of the GMO;

and the possession (including storage), supply and use of 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)

21. The clinical trial is proposed to take place over a three-year period from the date of issue of the licence. Up to 30 participants in Australia would receive 4-7 doses of the GMO via intra tumoral (IT) injection.

22. The clinical trial would take place at clinical trial sites and hospitals in Australia. These sites have not yet been identified.

23. Only trained and authorised staff would conduct dealings with the GMO. Administration of the GMO to trial participants would be conducted by highly trained staff.

2.2 The proposed controls to restrict the spread and persistence of the GMOs in the environment

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

- Only trained personnel would conduct dealings with the GMO. Staff preparing and administering the GMO would be experienced in the use and disposal of sharps.
- Staff considered to be at risk (see Paragraph 37) would be excluded from handling the GMO.
- Staff preparing or administering the GMO would be required to wear appropriate PPE (e.g. gown, gloves, and eye protection) during the procedures.
- Transport to and storage of the GMO at a clinical trial facility where it will be administered will be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs).
- Disinfecting surfaces and equipment that come into contact with the GMO using an effective disinfectant (including but not limited to 70% ethanol and 2% sodium hypochlorite).
- Providing patients with treatment instructions and providing instructions to decontaminate toilets with 10% bleach for 5 minutes after each use for the duration of the trial until 2 weeks after the final GMO administration.

2.3 Details of the proposed dealings

2.3.1 Manufacturing of the GMO

25. The GMO will be manufactured overseas in accordance with Good Manufacturing Practice (GMP) regulations and imported into Australia.

2.3.2 Transport and storage of the GMO

26. The GMO would be imported according to the packaging and labelling requirements of the International Air Transport Association (IATA) code UN3373.

27. Transport of the GMO from the Australian border would be directly to storage and distribution depots, then to clinical trial sites. Once at the depot or trial site, the GMO would be stored in a freezer with access restricted to appropriately trained personnel. The GMO will be contained within a sealed, unbreakable primary container and also be contained within a sealed unbreakable secondary container. The external surface of the primary and secondary container will be decontaminated before and after transport.

28. Procedures will be in place to ensure that all transported GMOs can be accounted for, and that a loss of GMOs during transport can be detected; and access to the GMOs will be restricted to authorised persons conducting dealings under the licence, who have been informed by the licence holder of any licence conditions that apply to them. This includes situations where containers are left for collection in a holding area.

29. The proposed method of supply and storage of the GMOs, as advised by the applicant, would be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSD).

2.3.3 Clinical trial sites

30. The clinical trial would be carried out at clinical trial facilities and hospitals, which are yet to be confirmed. Clinical trial sites would be assessed by the applicant for their ability to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practise (GCP) guidelines (ICH Guideline for Good Clinical Practice). Sites would also be selected based on their ability to comply with the TSDs and the licence conditions.

2.3.4 The clinical trial

31. The applicant proposes a Phase 1 open-label, dose escalation study, which is to be conducted at multiple locations in Australia (as noted in Section 2.3.3). The study aims to assess the safety profile of the GMO and determine the maximum tolerated dose (MTD) or maximum feasible dose (MFD) of the GMO administered by IT injection.

32. Participants will receive 4 doses of the GMO (week 1, week 4, week 6 and week 8) with a 2 week follow up period after each dose over 10 weeks. If no safety concerns are documented, participants may elect to receive an additional 3 doses at two-week intervals (week 10, 12 and 14). Patients will be monitored for up to 16 weeks.

33. Participants will be enrolled in 3 cohorts of escalating doses. The dose in each cohort will only be increased if the previous cohort demonstrates a good safety profile.

2.3.5 Selection of trial participants

34. Inclusion criteria proposed by the applicant relevant to this assessment include that trial participants must:

- be 18 years of age or older at screening.
- Have a diagnosis of Stage IIIb to IV metastatic melanoma.
- Have a negative serum pregnancy test prior to study entry, if female and of childbearing potential.
- Agree to use effective barrier contraceptives from screening until 30 days after the final administration of the GMO.

35. Relevant exclusion criteria include participants who:

- Are pregnant or lactating.

- Are ill with an active infection requiring systemic treatment within 5 days of screening.
- Are immunocompromised or known to be HIV positive.
- Have previously received adenovirus therapy.
- Have previously received any oncolytic virus within 2 months prior to screening.

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

2.3.6 Preparation of the GMO for administration

37. For the purposes of this RARMP, persons who are pregnant or have immunosuppressive disorders are considered persons at higher risk of a serious adverse event when exposed to the GMO. The applicant proposes that at risk persons will be excluded from preparing or administering the GMO.

38. The doses of the GMO for administration would be prepared in pharmacies within the clinical facilities by trained personnel. Access to the GMO would be restricted to the pharmacy personnel. Training would be provided by the licence holder in line with the licence conditions.

39. Dilutions of the GMO would be needed, the final volume after dilution of the original vial would be up to 10 ml in a dosing syringe. The preparation of the dose would be performed in a Class II Biosafety Cabinet (BSC-2). This would be carried out aseptically by drawing solution into dosing syringes from rubber stoppered vials. Sharps used for solution transfer would be discarded in clinical waste sharps bins. Therefore, there would not be open transfer of solutions outside the syringe or GMO vial as all solutions would be contained within the sealed primary vial or syringe. The filled capped syringe would be transported to the administration area as described in Section 2.3.2.

2.3.7 Intra-tumoral administration of the GMO

40. The GMO would be administered via IT injection at clinical trial sites. The IT administration would be carried out by study physicians who would be wearing appropriate PPE (face shield/safety glasses, face mask, disposable gown and disposable gloves).

41. Prior to administration, the filled syringe would be capped and transported to the clinic as described in Section 2.3.2.

42. The GMO would be administered directly into cutaneous or subcutaneous tumours up to a maximum volume of 10 mL per lesion. To minimise GMO leakage, doses would be administered using a fanning technique to evenly distribute the dose over lesions without removing the needle. The injection site would then be wiped with ethanol and covered with an occlusive dressing for at least one week. Participants would be required to stay in the trial site for at least 6 hours after the first and second administration, then 1 hour for subsequent administrations provided no adverse reactions occur during previous doses.

2.3.8 Decontamination and disposal of the GMO

43. 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, which can include high temperature incineration. Any unused vials of the GMO would be also disposed of using the same process. Disposal would be carried out by external service providers via the clinical waste stream.

44. Trained personnel would remove the occlusive dressing at the follow-up visit one week after administration, and would ensure disposal as part of the clinical waste stream.

45. Any equipment that is contaminated with the GMO would be cleaned with an appropriate disinfectant shown to be effective against the GMO.

2.3.9 Sample collection and analysis

46. Biological samples such as blood, urine, stool and saliva would be collected to evaluate viral shedding on dosing day and day 3 for the first 3 cycles (up to week 8) then only on dosing day 1 for further cycles of GMO administration. Samples taken on the dosing day 1 of cycles 4-6 will be taken pre-dose.

47. Blood samples would be collected by clinical site staff wearing appropriate PPE. Staff must ensure that the sample collection area is clean and sterile.

48. Urine, stool and saliva samples would be self-collected by trial participants within clinical settings during follow-up visits, or at home and returned to the clinical trial site. Appropriate instructions and training would be given to trial participants before sample collection.

49. After collection, clinical site staff may need to process the samples according to the study protocol. All sample processing steps would be performed following appropriate safety precautions and in compliance with standard clinical pathology procedures or other relevant guidelines.

50. Whilst some samples such as whole blood may be analysed at the site of collection, most would be transported to an independent laboratory in Australia or exported in accordance with IATA UN 3373 for analysis.

2.3.10 Personal protective clothing

51. Clinical trial staff involved in the preparation and administration of the GMO to trial participants and in the clean-up of spills would wear a disposable fluid-resistant gown, gloves, face mask and eye protection (safety glasses or face-shields).

2.3.11 Training

52. If the licence is issued, Novotech would have responsibility for ensuring training of personnel and compliance with licence conditions.

53. The applicant has indicated that appropriate training (e.g. training is all procedures specific to the GMO including preparation, handling, administration, spill procedures, containment and disposal etc.) materials would be provided to all personnel involved in the trial.

54. The doses of GMO would be prepared by trained pharmacists or pharmacy technicians in a BSC-2. Those staff would be trained on the preparation of the GMO and handling of sharps to minimise the likelihood of exposure.

2.3.12 Accountability and Monitoring

55. The applicant has proposed that trial participants would be instructed to monitor themselves for signs of infection or adverse reactions such as fever, flu-like symptoms or injection site reactions.

56. Any unintended exposure to the GMO through injury or direct contact would be reported to the Regulator.

2.3.13 Contingency plans

57. In the event of exposure of people to the GMO via sharps injury or contact with broken skin, the applicant proposes such persons would be instructed to:

(a) Implement institutional needlestick or exposure guidelines;

(b) Wash the area thoroughly with soap and water;

(c) Cover the area with a non-occlusive dressing for 7 days; and

(d) Report the incident to the licence holder, the institution's IBC and the trial sponsor.

58. In the event of unintentional release of the GMO due to spills, personnel would be instructed to follow spill management procedures, including that;

(a) The GMO will be contained to prevent further dispersal;

(b) Persons cleaning up the GMO will wear PPE including gloves, gown, mask (N95 or similar), and a face shield or safety glasses;

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

(d) Any material used to clean up the spill or PPE worn during the clean up will be decontaminated;

(e) Clinical trial staff will notify the licence holder as soon as reasonably practicable;

(f) The licence holder will notify the Regulator as soon as reasonably practicable.

Section 3 Parent organism

59. The GMO is derived from human adenovirus (HAdV) species C serotype 6 (HAdV-C6). It is a member of the genus *Mastadenovirus* in the *Adenoviridae* family. Adenoviruses (AdVs) are classified as Risk Group 2 microorganisms (Standards Australia/New Zealand, 2010). The characteristics of the parent organism provide a baseline for comparing the potential for harm from dealings with the GMO. As such, the relevant biological properties of HAdVs will be discussed here.

60. Human adenoviruses are categorised into seven species A to G based on their serology, sequence homology, serum neutralisation, hemagglutinin properties and genomic sequence (Lange et al., 2019; Bots and Hoeben, 2020; Leikas et al., 2023). HAdV-C6 belongs to species C with five serotypes (C1, C2, C5, C6 and C57) and is commonly associated with acute respiratory tract infections in children (Mennechet et al., 2019).

61. Despite the high prevalence of HAdV-C in the population, HAdV-C5 vectors have been frequently used in clinical trials as cancer therapies (Shaw and Suzuki, 2019; Sato-Dahlman et al., 2020; Leikas et al., 2023). The less prevalent HAdV-C6 has been proposed as a therapeutic candidate because it is likely to have similar biological characteristics to other HAdV-Cs such as HAdV-C5, with a lower risk of pre-existing immunity to the platform (Crosby and Barry, 2014; Crosby et al., 2015; Nguyen et al., 2018).

3.1 Pathology

62. Human adenoviruses are common human pathogens and cause a wide range of illnesses such as common cold; sore throat; bronchitis; pneumonia; diarrhoea; conjunctivitis; fever; inflammation of the stomach, intestine and bladder; and neurologic disease (conditions that affect the brain and spinal cord) (Public Health Agency of Canada, 2014; CDC, 2019a; Leikas et al., 2023).

63. Infections with HAdV are generally mild and self-limiting, but could be more severe or lethal in immunocompromised individuals or in the very young (Mennechet et al., 2019; Leikas et al., 2023). Overall, HAdV infections are responsible for about 2-5% of all respiratory infections in humans (Allard and Vantarakis, 2017) and are the most common cause of conjunctivitis in the world (Pihos, 2013).

64. Outbreaks of HAdVs-associated respiratory disease are more common in the late winter, spring and early summer, however infections can occur throughout the year. After natural HAdV infection, the incubation period of HAdVs ranges from 2 days to 2 weeks, depending on the viral species and serotype as well as the mechanism of acquisition (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017). For respiratory infections, the incubation period is generally 4-8 days, whereas it is 3-10 days for intestinal infections (Allard and Vantarakis, 2017). The symptoms of mild

infection usually last for a few days to a week but for the severe infections, symptoms may last longer.

65. The parental species, HAdV-C, has been mainly associated with acute respiratory tract infections in children and is the most common serotype reported in most populations, with anti-HAdV-C5 antibodies detected in almost 85% of the population (Mennechet et al., 2019; Leikas et al., 2023).

3.2 Structure and genomic organisation

66. Adenoviruses are non-enveloped, double-stranded DNA viruses with an icosahedral capsid comprising of major (hexon, penton base and fiber) and minor (protein IX, VIII, IIIa and VI) proteins; other proteins (V, VII, μ, Iva2, terminal protein and adenovirus protease); and a core that contains DNA (Robinson et al., 2011; Yu et al., 2017). The genome of AdVs is approximately 30-35 kilobases (kb) which includes 30-40 genes (Lasaro and Ertl, 2009; Charman et al., 2019). The genome is flanked by inverted terminal repeats (ITRs).

67. The HAdV genome consists of early and late genes, which are organised into transcription units (Figure 2). The early genes (E1, E2, E3 and E4) are involved in directly activating transcription of other viral regions, altering the host cellular environment to enhance viral replication, and co-ordination of viral DNA replication (Roy et al., 2004; Lasaro and Ertl, 2009; Afkhami et al., 2016; Saha and Parks, 2017). The late genes (L1 to L5) encode components of the viral shell and other proteins that are involved in assembly of the capsid and are essential for production of new virus particles.

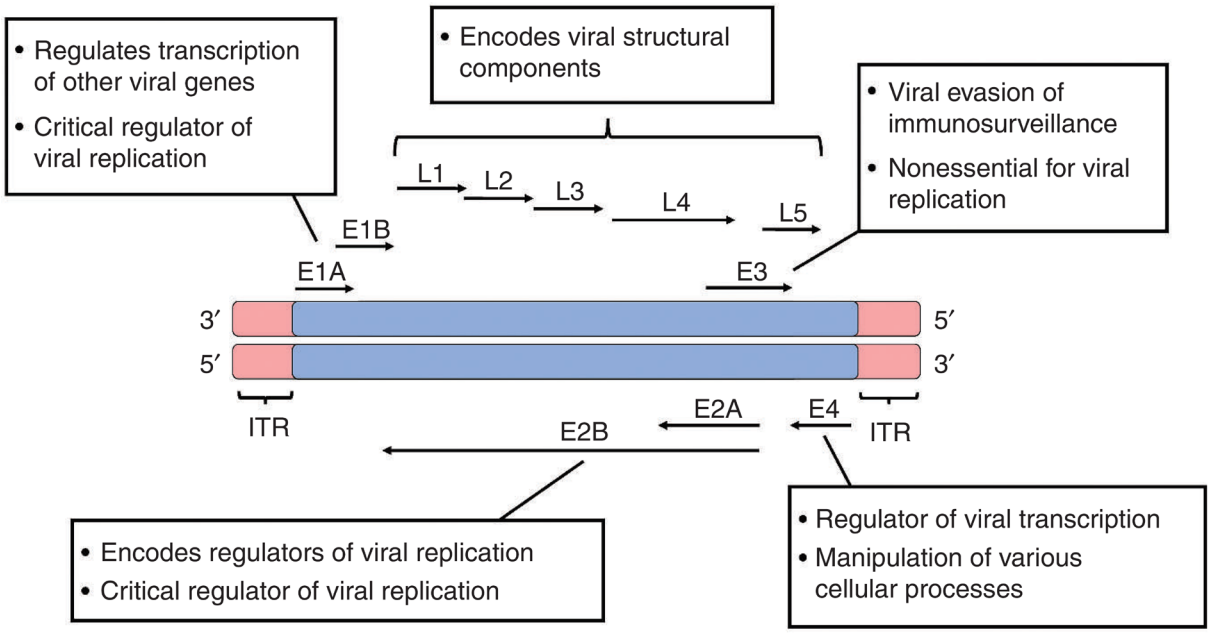

Figure 2: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).

68. The E1 gene is composed of E1A and E1B. The E1A gene controls transcription of viral genes and redirects host-cell gene expression machinery to enable virus replication. The proteins produced from the E1A genes are the first proteins expressed from the infecting virus, and are essential for the efficient expression of other viral genes (Roy et al., 2004; Saha and Parks, 2017). The E1B gene assists in viral replication and is mainly required for the export of viral late mRNA (L1 to L5) from the host-cell nucleus into the cytoplasm. Together, the E1A and E1B coding regions are essential for viral gene expression and replication (Roy et al., 2004; Saha and Parks, 2017).

69. The E2 gene consists of E2A and E2B, that encode E2 proteins. The E2 proteins are mainly involved in viral DNA replication and transcription of late genes (Roy et al., 2004; Saha and Parks, 2017). The E3 gene encodes viral proteins that aid the virus in evading the host immune response. The E4 gene modulates cellular function and assists with viral DNA replication and RNA processing.

70. Interactions of proteins encoded by the adenovirus genome are required to form a mature infectious particle. The 3 major proteins (hexon, penton and fiber) form the external capsid structure and "spikes" of the viral particle. The viral core proteins (V, VII and Mu) mediate the interactions between the core and the capsid, while the minor proteins (IIIa, VI, VIII and IX) contribute to the structure and stability of the virion by acting as cement proteins, connecting the major structural proteins with each other and with the viral core (see Figure 3) (Liu et al., 2010; Reddy et al., 2010; Reddy and Nemerow, 2014). These viral core and minor proteins are synthesised as precursors, then processed by adenovirus protease during assembly to form a mature infectious particle. The assembly of the final viral particle is thought to follow a sequential assembly pathway, whereby an empty capsid is formed prior to genome packaging (Ma and Hearing, 2011; San Martin, 2012; Mangel and San Martin, 2014; Ahi and Mittal, 2016).

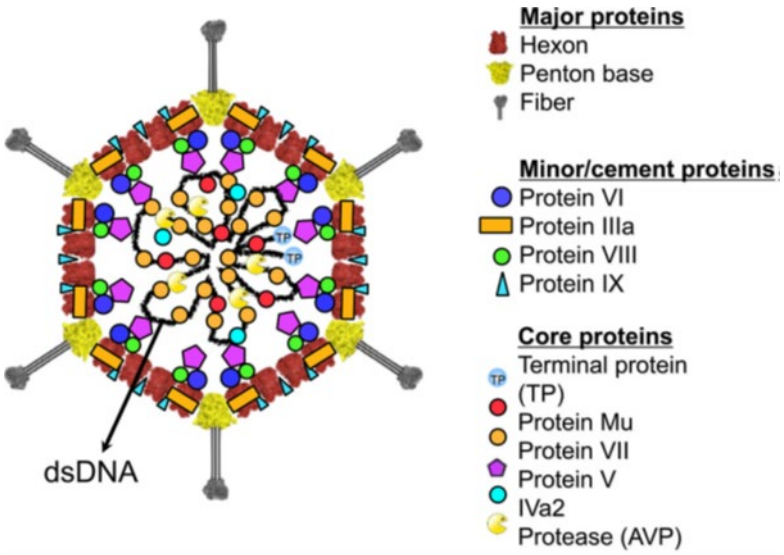

Figure 3: Structural model of human adenovirus (Benevento et al., 2014)

3.3 Viral infection and replication

71. Adenoviruses can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. AdVs most frequently infect epithelia of the upper or lower respiratory tract, eyes, gastrointestinal and urinary tract tissues. The tropism of AdVs is largely dependent on the species; species A, F and G infecting gastrointestinal cells, species C, E and some B species infecting the respiratory tract, the rest of species B infecting the urinary tract and species D infecting the conjunctiva (Leikas et al., 2023).

72. Human adenoviruses use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins, CD46, CD80, CD86 and sialic acid to enter the host cells (Zhang and Bergelson, 2005; Lion, 2019). *In vitro* studies with HAdV-C also showed that vitamin K-dependent blood factors including Factor X (FX) increases the binding efficiency of HAdV-C to hepatocytes (Weaver et al., 2011).

73. Replication of AdVs occurs in the nucleus of the host cell, using the host cell nuclear machinery to make copies of itself (Figure 4). Following attachment to cell membrane receptors (1-3), the AdV enters the host cell and is uncoated to release viral particles (4). The viral genome is transported into the nucleus (5) where the transcription occurs (6), described above in Section 3.2 (Charman et al.,

2019). Viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made and new virus particles are assembled (7-9). Finally, the host cell breaks apart releasing the viruses (10) (Waye and Sing, 2010b). Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes.

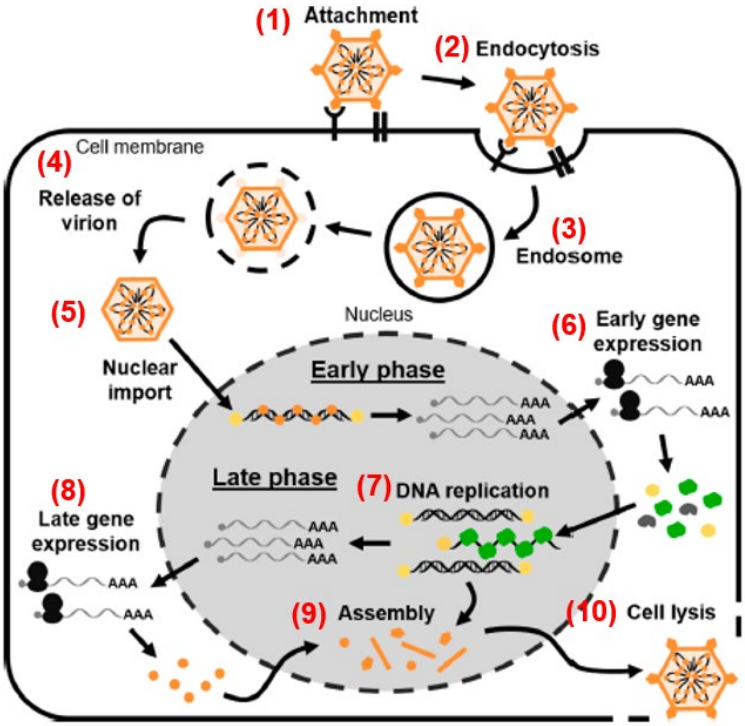

Figure 4: Overview of the adenovirus replication cycle (Charman et al., 2019). Virus entry and import of viral genomes into the nucleus lead to a program of early gene expression that includes the viral replication machinery. The onset of viral DNA replication marks progression from the early to the late phase of infection and is a prerequisite for both late gene expression and virion assembly.

3.4 Mutation and recombination of adenovirus

74. Adenovirus DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999) and AdVs do not have the machinery for efficient integration into the host genome. Instances of AdVs integration are considered rare, and random integration of virus DNA into the host genome has been observed only in very rare cases (Harui et al., 1999; Desfarges and Ciuffi, 2012; Hoppe et al., 2015; Dehghan et al., 2019).

75. Where a cell is infected by multiple AdVs at the same time, exchange of genetic material can occur, which promotes the molecular evolution of AdVs through homologous recombination. Homologous recombination appears to be restricted to members of the same species and occurs in the regions of high sequence homology (Lukashev et al., 2008).

76. Bioinformatic analysis of HAdV-C suggests that homologous recombination in the capsid (hexon, penton and fiber) and E3 genes were not common and were not major contributors to the diversity seen in HAdV-C (Dhingra et al., 2019). The hexon protein is a major constituent of the viral capsid and is suggested to be critical for the development of AdV vaccines or therapeutics by forming the serum neutralisation epitope; the penton and fiber proteins are responsible for host cell binding and internalisation; and the E3 proteins facilitate immune evasion by the virus (Robinson et al., 2011; Ismail et al., 2018). The lack of homologous recombination in these regions of HAdV-C reduces the likelihood of HAdV-C altering its cell tropism and of altering its ability to evade the immune system.

77. In addition, bioinformatic analysis also showed very low sequence diversity in the minor capsid proteins (IIIa, V, VI, VII, VIII and IX), suggesting that these proteins are well conserved between all HAdV-C serotypes (Dhingra et al., 2019). However, genome analysis of 51 circulating species HAdV-C revealed that the evolution of HAdV-C may be the result of recombination events in the early genes (e.g. E1 and E4) (Dhingra et al., 2019). Bioinformatics analysis also suggested that HAdV-E4, a species E AdV, was a result of a recombination event between species B and C (Gruber et al., 1993).

3.5 Epidemiology

3.5.1 Host range and transmissibility

78. Humans are the natural host for HAdVs (Custers, 2020). Experimentally, mice, cotton rats and rabbits have been infected with HAdVs to study AdV-induced disease, but HAdVs are unable to replicate in these animal models (Ismail et al., 2019) and no natural infections of non-human hosts have currently been described.

79. Transmission of HAdVs from an infected individual is primarily via direct contact with respiratory aerosols, conjunctival secretions or via the faecal-oral route (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Khanal et al., 2018; CDC, 2019b; Leikas et al., 2023). The virus can also be spread indirectly via contact with articles e.g. handkerchiefs, linens or utensils contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017).

3.5.2 Bio-distribution and shedding

80. The predominant natural tropism of HAdV-C is the respiratory tract and it causes a significant proportion of acute respiratory tract infections in children (Mennechet et al., 2019). Following natural HAdV infection, virus particles are shed via respiratory secretions or in the faeces. Respiratory infections generate the highest viral load early post-infection with residual virus remaining for up to 2 months post-infection (Huh et al., 2019). The ease of transmission of HAdV is thought to be facilitated by very high levels of viral particles shed into sputum or oral secretions of the infected person (Allard and Vantarakis, 2017).

81. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing the HAdV-E4 and HAdV-B7 serotypes. Over 50% of the vaccine recipients tested positive for AdV faecal shedding between 7-28 days following vaccination. No faecal shedding was detected after 28 days following vaccination or at any time point in throat swabs (Allard and Vantarakis, 2017).

3.5.3 Prevalence

82. An estimation of the seroprevalance of HAdV-E4, -C5, -D26 and -B35 (serotypes commonly tested in the clinics or used in clinical/pre-clinical trials) is shown in Figure 5, based on approximately 30 studies published over the past 20 years (Mennechet et al., 2019). HAdV-C5 is the most widely reported and has the highest seroprevalance globally. HAdV-C6, has a lower seroprevalence compared to HAdV-C2 and -C5 and is predominantly found in children (Mennechet et al., 2019).

83. In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health and Aged Care (1991-2000) showed an average of about 1400 reported cases of adenovirus infection per year over 10 years, of which only 48 reported cases were identified as HAdV-C6 infection (Spencer, 2002). It is important to note that the majority of reported AdV infections have not been serotyped and that testing for adenovirus infections may not be common in Australia. However, these numbers may indicate a low prevalence of adenovirus infections in Australia.

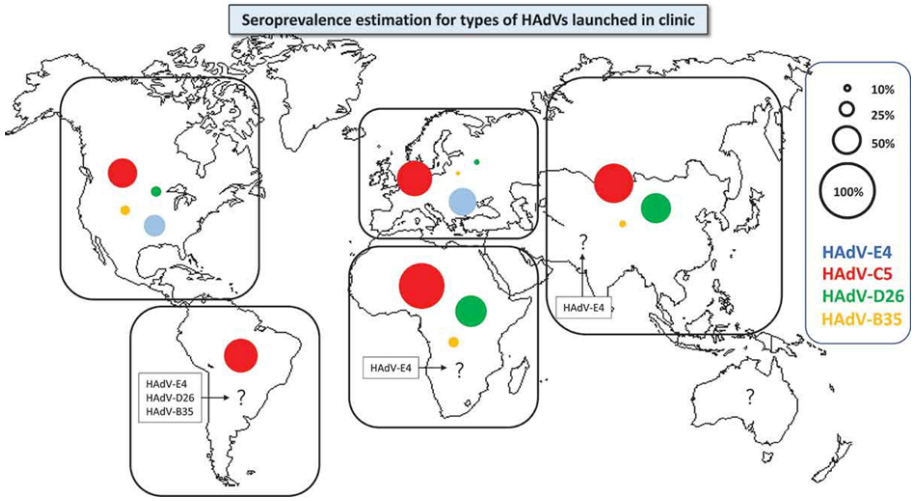

Figure 5: Seroprevalance for adenovirus types used in the clinic (Mennechet et al., 2019)

3.5.4 Control, environmental stability and decontamination methods

84. Infection with HAdV is generally asymptomatic or associated with mild disease in healthy adults and is generally managed through a combination of supportive care and enhanced personal hygiene measures to limit transmission. Antiviral drugs may be used in immunocompromised patients or those with severe disease. Antiviral agents such as Cidofovir and Ribavarin are commonly used as first line adenoviral therapies (Waye and Sing, 2010a; CDC, 2019a; Lion, 2019). There are currently no AdV-specific drugs to treat infection (Waye and Sing, 2010a; CDC, 2019a).

85. Adenoviruses are resistant to most chemical or physical decontamination processes and agents (including lipid-disrupting disinfectants) as well as high or low pH conditions (Rutala et al., 2006; Public Health Agency of Canada, 2014; Gray and Erdman, 2018). They are also resistant to UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003), thus supporting survival in treated wastewater and sewage, rivers, oceans, swimming pools water and drinking water (Public Health Agency of Canada, 2014).

86. Adenoviruses are very stable in the environment at pH 6-8 and below 40˚C (Rexroad et al., 2006) and can survive for long periods in liquid or on surfaces in a desiccated state. For example, HAdV can survive up to 10 days on paper under ambient conditions and for 3-8 weeks on environmental surfaces at room temperature (Public Health Agency of Canada, 2014). Therefore, AdVs survival time depends on the relative humidity, temperature and on the type of surface (Abad et al., 1994).

87. Worldwide, HAdVs have been detected in water samples of different kinds including wastewater, river water, drinking water, ocean and swimming pools (Allard and Vantarakis, 2017). They are often detected in high concentrations in domestic sewage and sludge in various countries and in some situations may be used in surveillance for faecal contamination (Allard and Vantarakis, 2017).

88. Adenoviruses are reported to be sensitive to 70% ethanol, 0.9% Virkon S (>5 min contact time), 0.2% chlorine, 0.55% ortho-phthalaldehyde and 2.4% glutaraldehyde (McCormick and Maheshwari, 2004; Rutala et al., 2006). In addition, AdVs can be inactivated by heat e.g. heating to 56°C for 30 minutes or 60°C for 2 minutes or autoclaving (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017; Gray and Erdman, 2018).

Section 4 The GMO - nature and effect of the genetic modification

89. The GMO (Adze 1.C) is based on HAdV-C6 and has been genetically modified to render it oncolytic - to preferentially replicate in and kill tumour cells. The GMO is designed to treat melanoma in patients with diagnosed metastatic tumours.

4.1 The genetic modifications and their effects

90. Adze 1.C has 3 modifications that render it oncolytic (Figure 6). First, the backbone vector is based on HAdV-C657, where the hexon hypervariable region (HVR) from HAdV-C6 has been replaced with the hexon HVR from HAdV-C57 allowing the GMO to evade any pre-existing immunity (Nguyen et al., 2018). Second, the E1A gene has 2 point-mutations (deletions) referred to as d1101 and d1107, that promote the replication of the GMO in tumour cells. The final modification is a partial deletion of E3 which is replaced by human CD40L under control of a constitutive CMV promoter and enhances the immune activation in infected cells. The overall effect of these modifications is that the GMO preferentially replicates in and kills tumour cells. More detail is given following Figure 6.

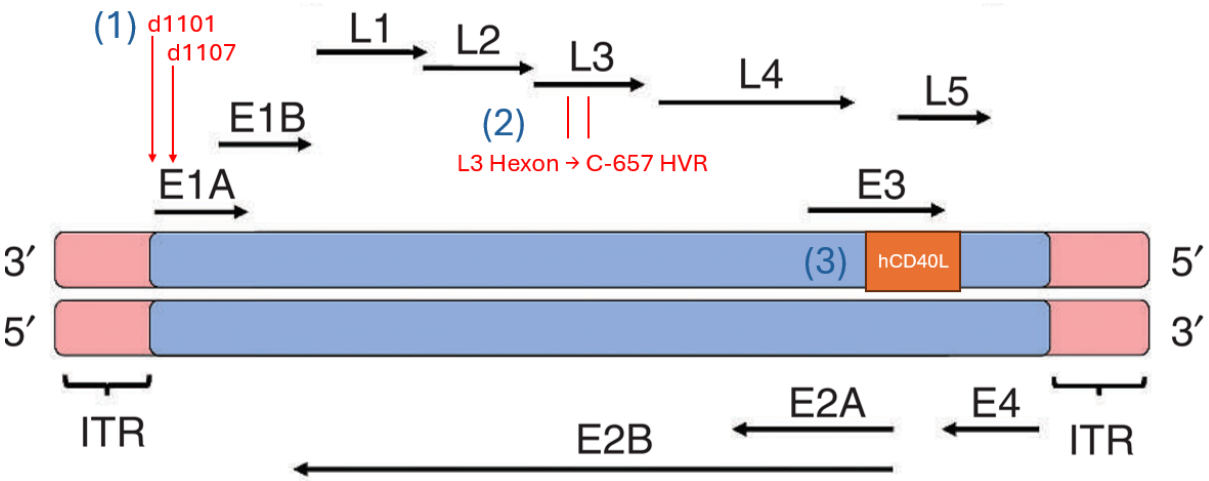

Figure 6: Adze1.C structure with (1) two deletions in E1A, (2) Hexon variable region (HVR) replaced with HAdV-C657 HVR and (3) deletion in E3 replaced with human CD40L gene (modified from Afkhami et al., 2016)

91. The GMO was produced using homologous recombination and bacteriophage lambda red recombination to introduce the targeted modifications (Campos and Barry, 2004).

92. The hexon HVR of the GMO is HAdV-C657 resulting from the replacement of the HAdV-C6 hexon HVR with that of HAdV-C57 (Nguyen et al., 2018). The modified hexon HVR has reduced serological cross-reactivity with HAdV-C1, C2 and C5 and requires sera with much higher anti-HAdV-C6 titre to be neutralised (Nguyen et al., 2018). This modification allows the GMO to evade any pre-existing immunity to HAdV-C6 in patients that would otherwise make the GMO less effective.

93. The E1A protein recruits several nuclear proteins to facilitate DNA synthesis and viral replication. The deletions in E1A are expected to facilitate targeted replication of the GMO in tumour cells, by exploiting oncogenic mutations in regulatory genes of these cells. Deletion d1101 prevents E1A binding to p300, a transcriptional coactivator which is thought to act as a tumour suppressor in healthy cells (Santer et al., 2011) and which is recruited to facilitate viral replication (Miao et al., 2024). In tumour cells, p300 is often mutated and the mutated protein is strongly oncogenic (Santer et al., 2011). Deletion in E1A is theorised to prevent binding to p300 in healthy cells while allowing binding, and therefore viral replication, in tumours cells.

94. The retinoblastoma protein pRB acts as a negative regulator of transcription factors that drive cellular proliferation. In tumour cells, the pRB pathway is often defective, allowing cellular

proliferation and promoting tumour growth (Cascallo et al., 2007; Miao et al., 2024). Deletion d1107 prevents E1A binding to pRB (Cascallo et al., 2007; Miao et al., 2024), preventing the activation of cellular transcription factors that allow viral replication (Cascallo et al., 2007; Laborda et al., 2014). Therefore, the deletion d1107 is expected to prevent replication of the GMO in healthy cells but allow replication in tumour cells in which the pRB pathway is defective.

95. Part of the gene encoding E3, which is not required for viral replication, is deleted and replaced with human CD40L under control of a constitutive CMV promoter. CD40L is the ligand for CD40, a member of the tumour necrosis factor family of proteins, that activates B cells and antibody production. CD40L has been used in oncolytic therapies to amplify immune responses against infected tumour cells (Lu et al., 2022).

96. As a result of these genetic modifications, the GMO is expected to replicate preferentially in tumour cells and kill them, while having limited or no effects on healthy cells.

4.2 Characterisation of the GMO

97. Data obtained from pre-clinical trials using the proposed GMO and from other pre-clinical and clinical trials using similar oncolytic HAdVs for a range of diseases has been used to characterise the GMO.

4.2.1 Genetic stability and molecular characterisation

98. Oncolytic viruses, like live attenuated viruses, have the potential to regain their pathogenic properties over the course of multiple replication cycles. Reversion to virulence of oncolytic HAdVs has not been observed or reported in either pre-clinical or Phase I-III clinical trials that have been performed over the past 20 years (Buijs et al., 2015)

99. Adenovirus vectors are considered non-integrating vectors and do not have a tendency to integrate or reactivate in a host (EMEA, 2007; FDA, 2020). The viral DNA is maintained as multiple episomal copies in the infected nuclei. However, some studies in cell lines and mice have suggested plausible integration of AdV vectors into host genomes at very low frequencies (Hillgenberg et al., 2001; Stephen et al., 2010). A study on cell lines from human, hamster, monkey and mice calculated the integration frequency of approximately one in every 10^3 to 10^5 transduced cells (Harui et al., 1999). However, no clinical or human studies have shown integration of AdV vectors into the host genome.

4.2.2 Stability in the environment and decontamination

100. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Methods of decontamination effective against the parent organism, HAdV-C6, are expected to be equally effective against the GMO (see Chapter 1, Section 3.5.4).

4.2.3 Pre-clinical studies using the GMO (Adze1.C) and other oncolytic HAdVs

101. Pre-clinical studies in mice, comparing a single administration of HAdV-C5, HAdV-C6 or HAdV-C657, showed that mice receiving HAdV-C6 and HAdV-C657 had significantly improved survival compared to those receiving wild type HAdV-C5. Mice given multiple administrations of an oncolytic HAdV-657 virus with CD40L modifications showed no changes in body weight (Lu et al., 2022).

102. Pre-clinical studies assessed the biodistribution of Adze1.C in healthy Syrian hamsters, as there are no suitable melanoma models in hamsters. Syrian hamsters were injected with the GMO by subcutaneous injection at a higher dose than that proposed for the human clinical trial (dose $1x10^{10}$ viral particles [vp] /0.5 mL) and assessed for biodistribution and shedding on days 2, 4, 8, 15 and 30. No shedding of the GMO was detected in urine, blood or saliva at any of the time points assessed. GMO DNA was detected in faeces on Day 8 in one of 6 samples and at no other time point. GMO DNA was detected in skeletal muscle and the skin at the injection site up to Day 30.

103. Toxicology studies in Syrian Hamsters using ONCOS-102, an oncolytic HAdV-C5 with similar E1A deletions to the GMO, showed no adverse events or effects on body weight, behaviour or liver enzymes (Kuryk et al., 2017). Studies using Adze1.C administered subcutaneously showed no adverse effects.

4.2.4 Clinical trials using other oncolytic adenovirus vectors

104. As of January 2025, 74 clinical trials were listed on www.clinicaltrials.gov using oncolytic adenoviral therapies.

105. A Phase I/II trial using LOAd703 (maximum dose $5x10^{11}$vp) for the treatment of pancreatic and ovarian cancer used a similar dose escalation protocol to that proposed by the applicant for this clinical trial. The most frequent adverse events reported were fever (82%), chills (54%) and fatigue (43%) with no serious adverse events reported (Hahn et al., 2023).

106. Phase I/II trials of ONCOS-102 (based on HAdV-C5) for the treatment of melanoma assessed the safety and efficacy of multiple IT injections in conjunction with intravenous administration (maximum dose $3x10^{11}$ vp). Biodistribution analysis found significantly elevated levels of ONCOS-102 in tumours through to Day 64 relative to non-tumour tissue, including non-injected tumours. The most reported adverse events were pyrexia (48%), chills (43%), and hypertension (43%) (Shoushtari et al., 2022). Biodistribution studies using the same GMO found that the GMO was shed in urine and saliva for up to 3 days post administration (Ranki et al., 2016) when simultaneously administered intravenously and intratumorally. GMO DNA was not detected in samples from subjects administered solely by IT administration (Ranki et al. 2016).

107. A Phase I study of NG-350A, an oncolytic HAdV with enhanced CD40 response, assessed IT (up to $1x10^{12}$ vp) versus intravenous administration (up to $6x10^{12}$ vp). Both methods demonstrated limited viral shedding and strong localising of vector DNA to tumours for up to 7 weeks post dosing. No treatment related serious adverse events or dose limiting toxicities were reported (Patel et al., 2023).

Section 5 The receiving environment

108. The receiving environment forms part of the context for assessing risks associated with dealings with the GMO (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 administration

109. The intended primary receiving environment will be cutaneous and subcutaneous lesions of the clinical trial recipient as the GMO will be delivered via the IT administration using a syringe.

110. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and waste disposed of, however none of the procedures are expected to generate aerosols. 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 the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

111. The principal route by which the GMO may enter the wider environment following administration is via shedding. Based on data provided by the applicant in animal studies and shedding analysis of other oncolytic HAdVs, the GMO may be shed in minimal quantities in urine or faeces after the administration of the GMO for up to 8 days. Further, GMO may also enter the environment via accidental spills of unused GMO.

5.2 Presence of related viral species in the receiving environment

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

113. AdVs belong to five genera: *Aviadenoviruses* (infecting birds), *Mastadenovirus* (infecting mammals), *Atadenovirus* (infecting a broad range of hosts including reptiles, lizards and some mammals), *Siadenovirus* (infecting one species of frog and one species of tortoise and multiple species of domestic, wild and captive birds) and *Ichtadenovirus* (infecting fish) (Tong et al., 2010; Lange et al., 2019; Vaz et al., 2020). As such, they are a common cause of infection in humans and animals, and can be found in all environments where humans or animals congregate in groups (Usman and Suarez, 2020). A more detailed description of AdVs presence in the environment is in Section 3.5.4.

114. The prevalance of HAdVs in Australia based on the reported cases and seroprevalance is low, as mentioned in Section 3.5.3.

5.3 Presence of similar genetic material in the environment

115. The balance of a system could be perturbed by the introduction of new genetic material through horizontal gene transfer 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

116. The modified hexon HVR region is derived from HAdV-C5 and HAdV-C6, both of which already circulated in the Australian environment.

Section 6 Previous authorisations

117. This GMO has not been previously authorised for clinical trials or commercial supply in any region or country. This is a first in human clinical trial.

Chapter 2 Risk assessment

Section 1 Introduction

118. 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 7). 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.

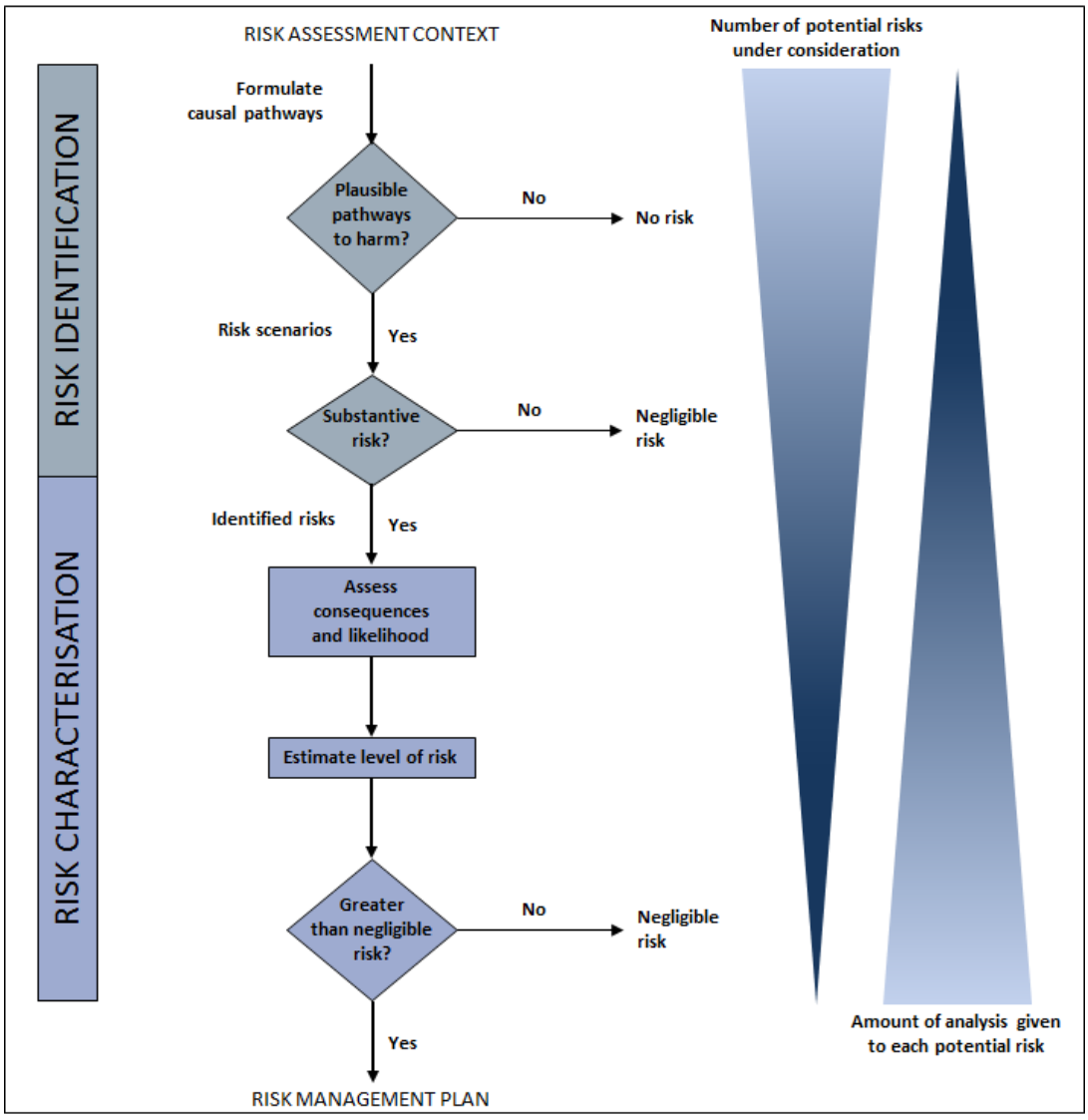

Figure 7: The risk assessment process

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

120. 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.

121. 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 8), i.e. the risk is considered no greater than negligible.

122. 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

123. Postulated risk scenarios are comprised of three components (Figure 8):

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.

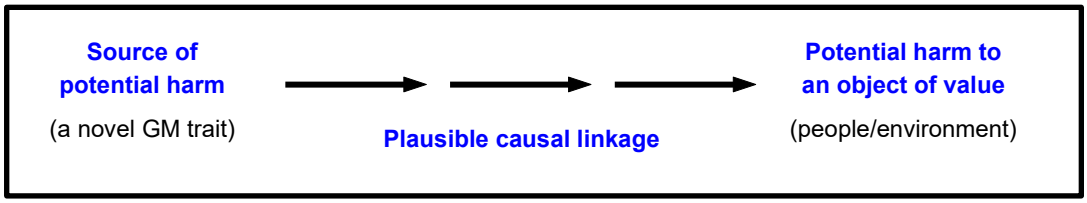

Figure 8: Components of a risk scenario

124. 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

125. The parent organism is a human adenovirus serotype 6 (HAdV-C6). Details of the pathogenicity and transmissibility of HAdV is discussed in Chapter 1. Infection is generally the result of inhalation of aerosolised droplets excreted from respiratory or ocular secretions containing the virus or mucosal exposure to the virus or via faecal-oral transmission. HAdV infects humans and causes common cold-like symptoms, eye infections or diarrhoea.

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

127. 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 horizontal gene transfer (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. HGT commonly occurs from cells to viruses but rarely occurs from viruses to their

host cells, with the exception of retroviruses and some DNA viruses. This pathway is further considered as a potential source of risk.

128. As discussed in Chapter 1, Section 4.1, the GMO has been modified by replacing the hexon variable region with that of HAdV-C657; deleting two amine acids from E1A; partial deletion of E3; and by insertion of a gene encoding human CD40L. These introduced genes and their encoded proteins are considered further as a potential source of risk.

2.2 Causal pathway

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

- the proposed dealings, which are import, transport or disposal of the GMO and possession (including storage) in the course of any of these 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 horizontal gene transfer;
- unauthorised activities; and
- practices before and after administration of the GMO.

130. 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 GMO recipient, and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO.

131. 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.

132. As mentioned in Chapter 1, Section 3.4, adenoviruses remain episomal throughout the infection and do not integrate into the host DNA. Similarly, the vectors derived from these adenoviruses are considered as non-integrating vectors which do not have a propensity to integrate or reactivate following latency in a host (EMEA, 2007; FDA, 2020). Further, adenoviral vectors (such as HAdV-C5, which is the same species as HAdV-C6) have been used extensively in clinical studies as a vaccine and as a gene therapy for almost 30 years (Crystal, 2014) and there is no evidence of

integration of viral DNA into the host genome. Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

133. Recombination between different GMOs using adenovirus platforms is highly unlikely because it is improbable that two or more adenovirus-based therapies are administered at the same time with the same route (IT) and the lack of homology between adenoviral vectors further reduces the possibility of recombination. Thus, the potential of recombination between adenoviral vectored vaccines or therapies will not be further discussed.

2.3 Potential harms

134. 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 virus that could cause harm to people or the environment

2.4 Postulated risk scenarios

135. Three risk scenarios were postulated and screened to identify substantive risks. These hypothetical scenarios are summarised in Table 1 and discussed in depth in Sections 2.4.1-2.4.3 (this chapter).

136. In the context of the activities proposed by the applicant and considering both the short and long term, none of the 3 risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 1 Summary of hypothetical risk scenarios from dealings with the GMO

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events: (a) Preparation and administration of the GMO (b) During import, transport or storage of the GMO (c) Disposal of the GMO (d) Shedding of the GMO ⬇ Transduction of cells by GMO ⬇	Adverse immune reactions (e.g., cytokine storm); illness, local inflammation, flu-like symptoms	No	• Import and transport of the GMO would be in accordance with IATA 3373 and/or the Regulator's *Guidelines for Transport, Storage and Disposal of GMOs* • Only trained and experienced personnel would conduct dealings with the GMO, using personal protective equipment to minimise potential exposure • GMO and contaminated waste would be double contained and disposed of as infectious clinical waste • The dose received through accidental exposure during preparation or administration would be substantially less than that

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		Post infection immune response due to the presence of the virus and/or Expression of CD40L and infection in Rb- and p300- defective cells			administered to trial participants and would not be sufficient to result in a serious adverse reaction in exposed persons • At risk people (i.e. immunosuppressed or pregnant) would be excluded from handling the GMO • The GMO has limited replication in healthy cells • People are regularly exposed to HAdVs and the genetic modifications do not confer any pathogenic advantage over the wild type • Most of the population has pre-existing immunity to HAdVs • The immune system is expected to clear the GMO quickly
2	GMO	Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ⬇ (a) Complementation by AdV (b) Homologous recombination with AdV ⬇ Production of other recombinant GMOs	Adverse immune reactions (e.g., cytokine storm) Disease in people or animals	No	As for risk scenario 1 and: • Participants will consent to adequate hygiene and protective practices. • Viral titres shed by trial participants are likely to decrease over time due to a smaller number of GMO permissive cells and immune response. • Low reported HAdV infection rates (including HAdV-C) in Australia. • There is only a short temporal window when co-infection could occur and the same cell has to be infected with both viruses at the same time. • Recombination among adenoviruses is usually restricted to the same species and are very rare events. • Homologous recombination in regions with high homology, which are

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
					involved in virus tropism (capsid proteins) or immune-evasion (E3) are not common in HAdV-C. • Homologous recombination at E1 and E4 could plausibly occur in HAdV-C, however this would not alter the viral tropism and immune evasion properties of the GMO. • Multiple recombinations are required to produce a HAdV with altered tropism and immune evasion properties.
3	GMO	GMO release into the environment (e.g. sewerage, spills) ⬇ Exposure to people or animals ⬇ As per scenario 1-2	Adverse immune reactions (e.g. cytokine storm); Disease in people or animals	No	• As discussed in Risk Scenario 1 and 2. • GMO not known to naturally infect non-human hosts and does not infect aquatic species. • There are a large number of HAdVs in the sewage or water systems. • The GMO does not replicate outside a host.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events: (a) Preparation and administration of the GMO (b) During import, transport or storage of the GMO (c) Disposal of the GMO (d) Shedding of the GMO ⬇ Transduction of cells by GMO ⬇ Post infection immune response due to the presence of the virus and/or Expression of CD40L and infection in Rb- and p300- defective cells
Potential harm	Adverse immune reactions (e.g. cytokine storm); illness, local inflammation, flu-like symptoms

Risk source

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

Causal Pathway

138. People (other than the intended recipient) and animals could be directly or indirectly exposed to the GMO in a number of ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO or during preparation of the GMO. It could also be transmitted during administration by needlestick injury. It is also likely that the GMO will be shed in urine and faeces from participants for up to 8 days post administration, potentially contaminating toilet facilities and exposing non-participants. This exposure could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

139. As discussed in Chapter 1, Section 2.1, preparation and administration of the GMO will be carried out in clinical trial sites. There is the potential for exposure of people involved in the preparation of the GMO by needle stick/sharps injury, preparation and/or due to breakage/spillage of GMO onto surfaces during preparation and administration; or through shedding of the GMO in urine or faeces following administration. The GMO will be prepared and administered by authorised, experienced and trained health professionals. All personnel working in settings where healthcare is provided, including clinical trial 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.*

140. The trial participants are expected to shed the GMO for up to 8 days post administration in urine and faeces. Trial participants would be instructed to follow good hand hygiene practices to limit surface contamination.

141. Caregivers and healthcare personnel who are in close contact with people treated with the GMO may be inadvertently exposed to the GMO during administration via spillage or after patient use of bathrooms. Caregivers and others exposed to the GMO in this way will only be expected to be exposed to low levels of the GMO. Furthermore, rare accidental exposures to oncolytic viruses in healthcare personnel during preparation, administration or care, have not resulted in illness (Kaufman et al., 2015).

142. For a productive infection to occur, individuals must be exposed to an infectious dose. Residual liquid in used vials and used syringes would not contain a sufficient titre to cause a productive infection. The same would apply to secondary waste such as gloves that may be contaminated with the GMO. Thus, the dose received through accidental exposure would be far smaller than that administered during the clinical trial and lower than that required for productive infection. Therefore, even if an individual or animal is inadvertently exposed to the GMOs, they are unlikely to develop an adverse immune reaction.

143. The compliance with the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and the *Australian Immunisation Handbook* and existing work practices will minimise the potential exposure of people to the GMOs during preparation and administration of the GMO.

Exposure during import, transport and storage of the GMO

144. If the GMO was spilled during import, transport or storage, this could result in exposure to people or animals in the area via aerosol or liquid contact with eyes, mucous membranes or skin. Further, people or animals could be inadvertently exposed to the GMO via contact with materials or surfaces contaminated with the GMO and subsequent hand to mouth transmission.

145. The GMO will be imported, stored, handled and transported according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs) (Chapter 1, Section 2.1). In addition, biological samples that may contain GMO will be handled in the same manner. These practices will lower the likelihood of unintended dispersal of the GMOs.

146. Antiviral disinfectants would be used for decontamination and disinfection after administration of the GMO or in the case of accidental spills during the supply of the GMO.

147. The import, transport and storage procedures discussed above would mitigate exposure occurring as a result of spills of the GMO during these dealings.

Exposure during disposal of the GMO

148. 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 GMO are stored;
- locations where the GMO is administered.

149. As discussed in Chapter 1, Section 2.1, 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 Environmental Protection Agency or Health Department in the relevant State or Territory (TAS, 2007; NT, 2014; WA, 2016; ACT, 2017; NSW, 2018; QLD, 2019; SA, 2020; VIC, 2020). Adherence to these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

150. 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

151. If people or animals are exposed to the GMOs, they could develop flu-like symptoms, eye infections or local inflammation for a short period of time before the virus is cleared by the immune system. It is plausible that exposed people or animals could experience an adverse immune response or disease.

152. The GMO is unlikely to replicate in non-tumour cells to produce further viral particles which are required to sustain an infection. In addition, any reactions to CD40L would be transient and the GMO would be cleared by the immune system. The minimal exposure and transient nature of infection would be expected to result in very mild or negligible symptoms and would also minimise the potential for an adverse immune response to the GMO. Therefore, exposure to the GMO is not expected to result in an infection and would not result in an increased disease burden in humans or animals.

153. Increased CD40L in the host is highly unlikely to result in the production of novel toxic or allergenic compounds. The genome of the GMO including the introduced genes has been fully sequenced. The introduced gene is expected to facilitate clearance of the GMO.

154. The GMO encodes human CD40L which is already present in the human population. Transfer of this genetic material into wild HAdVs would be expected to enhance an immune response against the HAdV and allow for more rapid clearance by the immune system.

155. The modifications to E1A affect the ability of E1A to recruit the host cell replication machinery, therefore this genetic material is not expected to confer a selection advantage to wild type HAdVs

Conclusion

156. The potential for an unintentional exposure of people and animals to the GMO to cause harm via a serious adverse immune reaction in humans and animals is not identified as a risk that could be greater than negligible. The main reasons are that that the GMO is not expected to infect or replicate in healthy people or animals, and any infection resulting from potential exposure is expected to be

rapidly cleared and unlikely to cause disease. Therefore, this risk scenario does not warrant further detailed assessment.

2.4.2 Risk Scenario 2

Risk source	GMO
Causal pathway	Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ↙ ↘ Complementation by AdV Homologous recombination with AdV ↘ ↙ Production of other recombinant GMOs
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk source

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

Causal Pathway

158. Transmission of GMO can occur by the pathways mentioned in Risk Scenario 1 which could potentially result in transduction of host cells. If the person or animal exposed to the GMO has an existing infection of AdVs at the same time as exposure to the GMO or acquired an AdV infection while the GMO is present, this co-infection could potentially result in complementation and recombination of the GMO with wild-type AdVs and cause adverse immune reactions and/or disease in people or animals.

Complementation of E1A, HVR or E3 by AdV

159. As mentioned in Section 3.5.3, there is a high prevalence of HAdV-C globally, especially HAdV-C5 (Weaver et al., 2011; Mennechet et al., 2019). Although the prevalence of HAdV-C6, the vector used to construct this GMO, is reportedly much lower, it is plausible that the *E1A, HVR* or *E3* genes could be provided in *trans* from a pre-existing or acquired HAdV infection in people accidentally exposed to the GMO if a co-infection in the same cell occurs. This could result in complementation by the HAdV leading to the GMOs being able to replicate in any infected cell in the host; a GMO with transient immune evasion properties; or a GMO with less viral replication capacity.

160. The reported prevalence of HAdVs in Australia is very low (Spencer, 2002). In addition, HAdV infections are self-limiting, which decreases the probability of continuous complementation of GMO by HAdV (Knight et al., 1962; Lichtenstein and Wold, 2004). Thus, the likelihood that a person has a HAdV-C infection that could continuously complement the modified *E1A*, *HVR* or *E3* genes in the GMO is very low.

161. Multiple copies of the proteins (E1A or E3) would be required to allow replication in healthy cells (Liu et al., 2010; Reddy et al., 2010; Reddy and Nemerow, 2014). As complementation would likely be provided by WT AdV, there would also be direct competition with WT AdV to form a mature viral particle, which would limit the chances of complementation by these proteins enabling the GMO to replicate in healthy cells.

162. As mentioned in Chapter 1, Section 3.5.1, HAdVs are unable to replicate in animal models (Ismail et al., 2019) and no natural infections of non-human hosts have currently been described.

Therefore, the likelihood that the GMO could replicate in animals as a result of complementation is highly unlikely.

Homologous recombination with AdV

163. Recombination is common among circulating wild-type adenoviruses in nature. It is seen as a key driver for adenoviral evolution. Similar to complementation, homologous recombination requires the person or animals exposed to the GMO to be infected with a wild-type AdV at the same time. Adenoviruses are prevalent in respiratory, gastrointestinal or ocular tissue. Therefore, it is plausible that a person or animal exposed to the GMO is co-infected with AdV. Co-infection could also occur from contact with GMO contaminated surfaces or spills. Licence conditions will be in place to limit and control the exposure of the GMO to people or animals via inhalation or contact with mucus tissue via requirements to use PPE and though transport and disposal procedures.

164. As mentioned in Chapter 1, Section 3.4, homologous recombination is restricted to members of the same species. However, homologous recombination with closely related adenoviruses species has been observed where high sequence homology occurs (Hoppe et al., 2015; Dehghan et al., 2019). The DNA homology between HAdV species is less than 20% (Ghebremedhin, 2014). There is a potential for homologous recombination between the GMO and HAdV-C as they belong to the same species. If it was to occur, co-infection and recombination processes could potentially result in the generation of different GM recombinants, as described in Table 2.

Table 2 Theoretical recombinants of GMO and wild-type (WT) Human Adenoviruses

Recombinant region	Resultant recombinant	Outcome	Likelihood
E3/CD40L between • GMO • WT HAdV	• Conditionally replicating GMO with intact E3 region • Replication-competent HAdV without the E3 region and CD40L transgene	• GMO with restored immune-evasion properties. However, replication would remain restricted to tumour cells. • Replication-competent HAdV without immune evasion properties and increased immune clearance	Unlikely
E1A between • GMO • WT HAdV	• Replication-competent GMO with intact E1A region • Conditionally replicating HAdV	• Replication-competent GMO expected to be cleared similarly to WT • HAdV with decreased replication capability in healthy cells	Unlikely
HVR between • GMO • WT HAdV	• GMO with WT HVR • WT HAdV with HAdV-C657 HVR	• Conditionally replicating GMO with increased susceptibility to pre-existing antibodies • HAdV with reduced susceptibility to pre-existing antibodies	Unlikely

165. The GMO could theoretically have the partial E3 deletion restored through recombination with WT AdV and regain some immune evasion properties while losing the enhanced immune targeting from the CD40L. However, the resulting recombinant GMO would retain the E1A deletions that restrict viral replication to cells with disrupted p300 and pRB pathways and would not be expected to replicate in healthy cells.

166. The GMO could regain a WT E1A gene without deletions and have unrestricted replication capability. However, the partial E3 deletion and CD40L would still be expected to facilitate immune clearance and the GMO would be expected to be cleared in a similar manner to WT HAdV.

167. In order for a full reversion of the GMO into a wild-type virus, multiple recombination events would need to occur and this is highly unlikely.

168. Homologous recombination could potentially occur at the hexon, resulting in the GMO with a restored susceptibility to pre-existing antibodies against the HAdV-C5 or C6 hexon, or a WT HAdV with reduced susceptibility to pre-existing antibodies. However, homologous recombination in the hexon, penton and fiber regions is not common in HAdV-C.

Potential harm

169. If complementation were to occur, the GMOs produced in the host cells may be able to infect cells other that tumour cells and possibly increase the persistence of the GMO in the host. Homologous recombination could have a similar effect. The exposed individuals may generate a stronger antibody response and also develop T-cell responses. These are not expected to cause harm to affected individuals. If a person exhibits any symptoms of adenoviral infection, effective antiviral treatments can be used to treat the infection.

170. A person exposed to recombinant GMO could potentially experience mild respiratory or eye infections depending on the route of exposure as described in Chapter 1, Section 3.1. These infections are self-limiting and rarely need medical intervention. If needed, first line adenoviral antiviral therapies could be used. Theoretically, if homologous recombination in the major capsid proteins or other AdV regions with high homology occurs, it could alter the tropism and host range of the virus. However, the risk of increased harm is negligible as adenoviruses do not typically cause severe disease and the resultant recombinants would be less pathogenic than the wild-type virus.

Conclusion

171. The exposure of people to a GMO or other recombinant viruses resulting in adverse immune responses or disease in people or animals is not identified as a risk that could be greater than negligible. The reasons for this are that the GMO is highly unlikely to be present in the same cell as another AdV, and resulting strains from any recombination will not produce disease more severe than wild type AdV. Therefore, this risk scenario does not warrant further assessment.

2.4.3 Risk scenario 3

Risk source	GMO
Causal pathway	Release of GMO into the environment via accidental spill/unused residues (e.g. sewerage, spills) ⬇ Exposure of people or animals ⬇ As per scenario 1-2
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk Source

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

Causal Pathway

173. The GMO could be released into the environment through a spill during transport, storage, or disposal or via shedding from trial participants. This could result in exposure of people and animals (including marine or aquatic animals) to the GMO and could potentially result in adverse immune reactions and/or disease in people and animals.

174. As discussed in Risk Scenario 1, accidental spills associated with import, transport, storage, disposal and shedding from participants have been considered, including the range of measures that are in place that would reduce the chances of GMO being released into the environment.

175. Accidental spills or unused vials, if not decontaminated appropriately, could result in the survival of the GMO and its presence in the sewerage and subsequently GMO dispersal in the aquatic environment. Without correct decontamination with suitable disinfectants, the GMO could potentially persist on surfaces for more than 12 weeks at low humidity (see Chapter 1, Section 3.5.4). In cold water or dark sediments, survival could be up to a few months (see Chapter 1, Section 3.5.4 and Section 4.3.2). As AdVs are resistant to UV treatment in wastewater and can survive for a long time, this could lead to the persistence of the GMO and/or recombinant adenoviruses in the environment. However, due to its conditionally replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods and is unlikely to spread and would eventually degrade.

176. In the event that the GMO is released into sewage water, it would be markedly diluted due to the small quantity of GMO present in a large volume of liquid waste or water. Water quality studies have shown that sewerage treatment does not kill adenovirus (Fong et al., 2010), however the GMO is unlikely to be able to replicate and would be unlikely to be present in high enough amounts for an infectious dose. Therefore, it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source.

177. As mentioned in Chapter 1, Section 3 and 5.2, HAdV-C6 is a member of the genus *Mastadenovirus* which infects a wide range of mammals including non-human primates, bats, felines, swine, canine, ovine and caprine (Roy et al., 2004; Borkenhagen et al., 2019). Therefore, hypothetically the GMO could infect other mammals including non-human primates. However, given that the GMO is unlikely to replicate in healthy cells and is not known to infect and replicate in animals or animal models, the likelihood of infecting other mammals from exposure to the GMO is very low.

178. As mentioned above, HAdV infection is limited to mammals only and is not known to infect insects, birds and other non-mammalian aquatic organisms. Therefore, the likelihood of HAdVs infecting other species in the Australian environment in highly unlikely.

Potential harm

179. Potential harms in this risk scenario would be the same as considered in risk scenarios 1 and 2.

Conclusion

180. The potential for the GMO to be released into the environment and result in adverse immune reactions or disease in people or other animals is not identified as a risk that could be greater than negligible. This is for the reasons described in Risk Scenario 1 and 2. Therefore, this risk scenario does not warrant further assessment.

Section 3 Uncertainty

181. Uncertainty is an intrinsic part of risk analysis[1]. 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.

182. 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
  - perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

183. 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.

184. As this is a first in human clinical trial, there is no available clinical bio-distribution and shedding data for this GMO. Pre-clinical data using the GMO and clinical data from similar GMOs have been taken into account in this assessment.

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

[1] 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.

Section 4 Risk evaluation

186. 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.

187. 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.

188. Three 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 complementation and recombination of the GMO with other adenoviruses. The potential for GMO to be released into the environment and its effects was also considered.

189. 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.

190. 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 unable to form mature viral particles in healthy cells, which will prevent it from multiplying in non-tumour cells;
- the GMO is unlikely to be shed from recipients except in faeces;
- the likelihood of accidental exposure to the GMO in people not being treated or animals would be minimised due to well-established import, transport, storage and disposal procedures; and
- complementation and recombination of GMO with other adenoviruses is highly unlikely to lead to adverse effects; and
- survival and persistence of the small amount of GMO in the Australian aquatic and terrestrial environment is highly unlikely.

191. 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.[2]

[2] 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

192. 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.

193. 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.

194. All licences are subject to 3 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.

195. 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

196. 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 2.1), the proposed controls (Chapter 1, Section 2.2), 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

197. 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

198. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Novotech. Many of these are discussed in the 3 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 proposed by Novotech

199. The proposed clinical trial would involve a maximum of 30 participants within Australia, and dealings with the GMOs would take place in medical facilities such as clinical trial facilities or hospitals. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMOs. The applicant has proposed to complete dealings with the GMO within 3 years of commencement. A proposed licence condition limits the period when the GMO may be administered under the licence to 3 years from the date of issue of the licence. Other conditions maintaining the risk context and proposed limits of the trial such as a maximum of 30 trial participants and requirements for dealings related to preparation and administration of the GMO to be conducted at a clinical trial site have been included in the draft licence.

200. The applicant advised that import and transport of the GMO and waste containing the GMO would be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. 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 GMO for analysis. These measures would limit the exposure of people and the environment to the GMOs.

201. There are proposed inclusion and exclusion criteria for both trial participants and staff as listed in Chapter 1, Section 2.3.5. 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.

202. The relevant inclusion criteria proposed by the applicant include that the trial participants must:

- agree to use an acceptable method of effective contraception for 90 days after the last treatment with the GMO;
- agree to abstain from donating blood, sperm, ova or organs for 90 days after the last treatment with the GMO.

203. The relevant exclusion criteria proposed by the applicant include pregnant and breastfeeding women.

204. As stated in Chapter 1, Section 3.5.2 , shedding of live adenoviruses can last for two months in respiratory samples and for 28 days in faeces. Shedding of infectious viral particles from trial participants who have received oncolytic adenovirus is expected to be minimal and occur for at most 8 days. Shedding in semen has not been assessed for this GMO. Due to the IT mode of administration and the conditionally replicative nature of the GMO, sexual transmission of the GMO from the trial participants is unlikely. Using the conservative timeframe of 60 days, as is standard in similar clinical trial licences, the use of effective barrier contraception and abstinence from blood, gamete or organ donation would further minimise the potential for transmission of infectious viral particles. Therefore, the criteria included in the draft licence are that the licence holder must obtain written agreement from the trial participant that for the duration of the trial and 60 days after the last dose of the GMO they will not donate blood or organs and will use effective barrier contraception.

205. The GMO may be shed in faeces or urine for up to 8 days. The applicant proposed requiring trial participants to dose toilets with 10% bleach after use and leave the bleach to sit for at least 10 minutes before flushing. This was for the duration of the trial and for two weeks after the final administration of the GMO. However, as shedding of the GMO is expected to be minimal in urine and faeces, and the GMO will be diluted in a large volume of water, this requirement is not conditioned by the licence.

206. While recombination with other adenoviruses is considered unlikely to occur, a precautionary condition is included in the licence to exclude participants who have recently received a different adenovirus based oncolytic therapy or are currently infected with an adenovirus.

207. The risk context is maintained provided the GMO can be cleared by the immune system, therefore a precautionary condition is included in the licence to exclude participants with an immunosuppressive disorder or an illness that impairs immune function.

208. The potential transmission to babies via breastfeeding and to foetuses if pregnant women are included in the trial is minimal. However, this risk would be minimised further by excluding breastfeeding and pregnant women and a condition to exclude pregnant and breastfeeding women from the clinical trial has been included in the draft licence.

209. The clinical staff handling the GMO would wear PPE including 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.

210. For the context of this RARMP, persons who have immunosuppressive disorders or who are pregnant are considered persons at higher risk of a serious adverse event when exposed to the GMO. To manage risk and to maintain the context of the risk assessment, a condition in the draft licence requires that immunosuppressed persons must be made aware of the risks of preparing, handling or administering the GMO.

211. 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.

212. 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). The clinical waste stream typically involves destruction of infectious waste by incineration or autoclaving, which are considered appropriate for disposal of the GMO. Given that AdV can persist in the environment, disposal measures such as burial or maceration would not ensure containment. Therefore, the draft licence requires waste disposal by external service providers to be by autoclaving or high-temperature incineration. These measures would limit the exposure of people or other animals to the GMOs.

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

214. Other standard conditions included in the draft licence 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.

215. Further conditions to be implemented in the draft licence is 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

216. 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 30 trial participants;
- the trial must be conducted at suitable clinical trial sites;
- limit the time when the GMO can be administered to 3 years from issue of the licence;
- 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 appropriate decontamination of the GMO and materials and equipment that have been in contact with the GMO;
- transport and store the GMO and samples from GMO-treated participants in accordance with IATA shipping classification UN 3373 [Category B] and/or the minimum requirements for packaging, and labelling as detailed in the draft licence;
- clinical waste stream to be used by external service providers to destroy untreated GMO and GMO-related waste.

3.2 Other risk management considerations

217. 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

218. 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.

219. 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.

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

3.2.2 Contingency plans

221. 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

222. 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

223. 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.

224. 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

225. 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.

226. 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.

227. 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

228. 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 biodistribution and shedding of the GMOs in trial participants at the trial sites.

Section 5 Conclusions of the consultation RARMP

229. 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.

230. 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 in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;

    (b) words importing a gender include every other gender;

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

    (d) expressions used to denote persons generally (such as “person”, “party”, “someone”, “anyone”, “no one”, “one”, “another” and “whoever”), include a body politic or corporate as well as an individual;

    (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 particular meaning, other grammatical forms of that word or phrase have corresponding meanings;

    (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.

‘GM’ means genetically modified.

‘*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.

‘OGTR’ means the Office of the Gene Technology Regulator

'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 a treated trial participant for analysis as part of the trial.

'Storage facility' means a third-party facility offering logistical services and distribution of clinical supplies.

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:

(a) the licence holder, and any employees, agents or External service providers engaged by the licence holder; and

(b) the project supervisor(s); and

(c) 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 with the GMO as described in **Attachment A** 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 licence authorises specific dealings in respect of the GMO identified and described in **Attachment A**.

Dealings authorised by this licence

11. The licence holder and persons covered by this licence may conduct the following dealings with the GMO:

(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 intra-tumoral 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 to any other 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 12 does not apply to trial participants.

Monitoring and audits (section 64)

14. If a person is authorised by this licence to deal with the GMO 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 they become 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 they were reckless as to whether such information existed; and

(b) The licence holder is taken to have become aware of contraventions, or unintended effects, if they were 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.

Note 4: As example of informing immediately is contact made at the time of the incident via the OGTR free call phone number 1800 181 030.

Informing the Regulator of any material changes of circumstance

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

(d) 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 an External service provider covered by this licence, the licence holder must not permit that person to conduct any dealings unless the person has been informed of the condition, including any variation to it.

Note: Information required under Condition 17 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 35(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 sub-condition 18(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 30 trial participants.

23. The preparation and administration of the GMO must be completed within 3 years from the date of issuing of the licence.

Preparation and administration of the GMO

24. Administration of the GMO to 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 41(a).

Conditions relating to 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 exclusion criteria in selecting trial participants include (though are not limited to):

(a) pregnant and breastfeeding women;

(b) any people suffering from an active infection or any immunosuppressive disorder;

(c) those having received a prior treatment with an oncolytic virus;

(d) those intending to become pregnant during the trial or during the first 60 days following each treatment with the GMO.

28. Before inoculating any trial participant with the GMO, the licence holder must obtain written agreement from the trial participant that they would:

(a) Use barrier contraception for the duration of the trial and for 60 days following each administration of the GMO; and

(b) not donate blood, sperm, ova, tissues or organs while participating in the trial and for 60 days after the final 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.

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

(b) 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 who are required to adhere to appropriate standards and guidelines. For example, standards developed by the National Pathology Accreditation Advisory Council for pathology practices, the Australian Guidelines for the Prevention and Control of Infection in Healthcare, Guidelines for Good Clinical Practice and 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 the Regulator on request.

Work practices at Clinical trial sites

32. For the purposes of Condition 29, the work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) immunosuppressed persons must not prepare, handle or administer the GMO.

(b) preparation of the GMO must be conducted in a Class II biosafety cabinet (Class II BSC), or alternative containment equipment approved in writing by the Regulator;

(c) persons preparing the GMO must wear personal protective equipment (PPE), including gowns, gloves and eye protection;

(d) persons administering the GMO must wear PPE including gowns, gloves, eye protection and an N95 or equivalent facemask;

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

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

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

(h) the infusion site(s) must be covered with an occlusive dressing following administration of the GMO;

(i) the dressing applied to the administration site/s must be removed and disposed of via the clinical waste stream.

Transport, storage and disposal of the GMOs

33. Unless covered by an NLRD, the licence holder must ensure that transport of the GMOs is conducted only for the purposes of, or in the course of, another dealing permitted by this licence.

34. For the purposes of import, transport between the border and either a Storage facility or a Clinical trial site, the licence holder must ensure the GMO is packaged, labelled, stored and transported consistent with International Air Transport Association (IATA) shipping classification UN 3245 or UN 3373.

35. Transport between a Storage facility and the Clinical trial site can also be done consistent with IATA shipping classification UN 3245 or UN 3373 if the GMO is not repackaged at the Storage facility.

36. The licence holder must ensure that transport and storage of the GMO, unless conducted according to Condition 33 or 34, follows these sub-conditions:

(a) The GMO must be contained within sealed, unbreakable primary and secondary containers, with the outer packaging labelled to indicate at least:

i) that it contains GMOs; and

ii) that it contains biohazardous material as designated by a biohazard label; and

iii) the contact details for the licence holder; and

iv) instructions to notify the licence holder in case of loss or spill of the GMOs; and

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

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

(d) access to the GMO is restricted to authorised persons for whom Condition 17 or Condition 18 has been met (i.e. the GMO is 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; and

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; and

(g) for the purposes of transport entirely within a building, where the GMO is accompanied by an authorised person for whom Condition 18 has been met, Conditions 35(a)iii), 35(a)iv) and 35(c) do not apply.

37. The licence holder must ensure that all GMOs and waste reasonably expected to contain the GMOs 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, or exported; and

(c) By autoclaving, chemical treatment, high-temperature incineration or any other method approved in writing by the Regulator.

38. Where transport is conducted by External service providers for the purposes 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 by an External service provider, compliance with relevant State or Territory legislation and regulations to manage clinical or biohazardous spills is sufficient.

Contingency plans

39. 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.

40. If there is a spill or an unintentional release of GMO at a Storage facility or 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 appropriate PPE; 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 PPE 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 by email to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at ***Attachment B****.*

41. The licence holder must notify the Regulator, in writing, of the name and address of each storage facility commencement of dealings at that location.

42. At least 14 days prior to first administering the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator, 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 role and contact details for 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 and have been consulted regarding site specific procedures;

(d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Condition 14, 15, 42 and 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 29 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.

43. For each Clinical trial site, the licence holder must notify the Regulator, in writing, of the end of the clinical trial, no later than 30 days:

(a) The final dose being administered; or

(b) The decision that no further participants will be treated at the site.;

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

(a) in the event of a loss or spill of the GMO;

(b) in the event of the exposure of a person other than a trial participant to the GMO; and

(c) if a trial participant has not followed the procedures described in the instructions provided by the licence holder.

45. 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: 213

Full Title: Clinical trial with a genetically modified human adenovirus for the treatment of melanoma

Organisation Details

Postal address: Novotech (Australia) Pty Ltd
Level 2, 15-31 Pelham Street
Carlton,
Victoria, 3053

GMO Description

GMOs covered by this licence:

Human adenovirus C serotype 6 modified by replacement of the hexon variable region (HVR) with the HVR from HAdV-C657, deletion within E1A to prevent replication in healthy cells and partial deletion of E3 replaced with human CD40L

Parent Organisms:

Common Name: *Human adenovirus*

Scientific Name: *Human adenovirus C serotype 6 (HAdV-6 Strain Tonsil 99)*

Modified traits:

Categories: Human therapeutic

Description: The GMO is an attenuated human adenovirus derived from species C serotype 6. It has been modified to preferentially replicate in tumour cells. The E1A contains two deletions that impair binding to p300 and pRB viral replication pathways in healthy cells. The HVR has been replaced with the HVR from HAdV-C657. E3 has been partially deleted and replaced with human CD40L under control of a CMV promoter to increase T-cell responses against infected tumour cells. Modified genes and regulatory sequences are listed in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Identity and modifications	Insert of a transgenic cassette containing: • Cytomegalovirus (CMV) enhancer/promoter • Human CD40L Deletion of: • E3 region • Single site deletions in E1A at positions 1101 and 1107 Replacement of HadV-C6 HVR with HadV-C657 HVR
Function	• CMV – Activates transgene expression • CD40L – immunomodulatory – enhances T-cell response against cells producing CD40L • E3 – deletion reduces immune evasion • E1A – deletions prevent binding to viral replication pathways (p300 and pRB) in healthy cells; while allowing viral replication in tumour cells • C657 HVR – limits effects of pre-existing immunity to HAdV-C6 or HAdV-C5

Purpose of the dealings with the GMOs:

To conduct a Phase I clinical trial assessing the safety, tolerability, and efficacy of a genetically modified human adenovirus based therapeutic to treat melanoma.

Trial participants and route of administration of the GMO

Intra-tumoral injection to adult humans with melanoma.

Attachment B

Prior to the commencement of the trial	Condition	Timeframe for reporting
A written Compliance Management Plan for each Clinical trial site: • the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; • the role and contact details for key persons responsible for the management of the trial at the site; • that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures; • the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events; • 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 29 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO	40	At least 14 days prior to the first administration of the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator
Information to be provided at any time during the Clinical trial		
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	14(a), (c)	Immediately
Information related to any contravention of the licence by a person covered by the licence	14(b)	Immediately
Any relevant conviction of the licence holder	15(d)	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	15(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	15(c)	Immediately
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	43(b), (c)	As soon as reasonably possible
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	43(d)	As soon as reasonably possible
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	16	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	44	Within a timeframe stipulated by the Regulator

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