DIR-184 – Attachment 1

Available on request under Section 54 of the *Gene Technology Act 2000*.

- **Australian Government**

  Department of Healtb
  Office of the Gene Techno lo gy Regulator

Application for a licence

for dealings with a non-plant GMO involving intentional release of the GMO into the environment (DIR)

Title of the project:	Clinical development of an Adenovirus Vector SARS-CoV-2 vaccine (SC-Ad6-1-002) given by Intranasal Administration to prevent COVID-19
Applicant organisation name:	Avance Clinical Pty Ltd
Accreditation number: (If the organisation is accredited by the Gene Technobgy Regulator)	Accreditation pending

Is this application accompanied by an application for a declaration that certain information be treated as Confidential Commercial Information (CCI)?

Yes ☐No

If the CCI is covered by previous CCI application(s), please provide the CCI or DIR application number(s) here:

the relevant CCI application number(s): Enter numbers

and the DIR application number(s): Enter number

If any information provided is covered by previous CCI declaration(s) and can now be made available to the public, please contact the Office of the Gene Technology Regulator to have the declaration revoked.

Time taken to complete this form: Enter hours Enter minutes

Information for applicants

We encourage prospective applicants to contact the Office of the Gene Technology Regulator (OGTR) before submitting an application to advise you in selecting the appropriate application form and discuss information requirements. **This is particularly important if the parent organism is not present in the Australian environment.** You can call (1800 181 030) or email.

What is this application form for?

This form must be used for applications for a licence for dealings (activities) with a GMO involving intentional release (DIR) of the GMO into the environment under the *Gene Technology Act 2000* (the Act). There are separate forms if you wish to apply for a licence to conduct dealings involving GM plants.

What information do you need to provide?

This application for a licence must contain correct and adequate answers. You must answer each question unless otherwise instructed.

The Regulator is not required to consider applications for a licence which do not contain the information specified.

If you wish to protect any information on this form from public disclosure, you must also fill out an *Application for Declaration that specified information is Confidential Commercial Information (CCI)*. Please submit it together with this DIR licence application form. Further explanatory material with respect to the information requirements associated with a CCI application is provided on the *Application for Declaration that specified information is CCI* form.

What will we use the information provided in this form for?

We will use the information in the application to prepare a Risk Assessment and Risk Management Plan (RARMP) in relation to the proposed activities. The Regulator's decision whether or not to issue a licence, and conditions to impose if a licence is issued, is based upon the RARMP.

Information in this application, including all attachments, may be released to the public (refer to section below 'What else do you need to know?' for further information).

What is the application fee for a DIR licence application?

There is currently no application fee.

How should you fill out this form?

- We prefer you sending your application electronically in a searchable format.
- Ensure you answer each relevant question in sufficient detail. Not providing the required information could delay a decision, or the Regulator may not consider your application (section 43 of the Act).
- Ensure you answer each question to the best of your knowledge. Deliberately providing false or misleading information is a punishable offence (section 192 of the Act).
- Ensure you answer each question with adequate supporting material. Scientific information should be comprehensive and supported by whatever data and references are available. We may ask you to provide electronic or hard copies of journal publications and unpublished information.
- Do not repeat information. If necessary, refer to your answer to other questions.
- Contact us if you have any questions or would like our comments on a draft application.

How can you submit this form?

Once you have obtained the relevant signatures, you can submit a hard copy or an electronic copy by:

- **email** to: ogtr.applications@health.gov.au
- **by mail** to: Office of the Gene Technology Regulator, MDP 54, GPO Box 9848, Canberra, ACT, 2601.

Please keep a copy of the application for your records.

You should note that if you email an application containing sensitive information (such as CCI), it will be transmitted via an unclassified internet connection and will not be protected in the process. Within a

reasonable time of receipt of the application, staff in the OGTR will securely store the sensitive information as appropriate. If you wish to make alternative arrangements to securely transmit CCI information, please contact this office.

What will happen after you have submitted the application?

We will acknowledge receipt of the application by email and assign it an OGTR reference number. Please cite this reference number whenever you contact us regarding the application.

Please contact us if we have not confirmed receipt within two weeks of submission.

We will notify the public about the application and then prepare a RARMP, including proposed licence conditions. This document will be released for expert and public consultation. You will also be invited to comment, particularly on whether you would be able to comply with the proposed licence. We will finalise the RARMP considering the comments received. It then forms an important part for the basis on which the Regulator will decide whether or not to issue a licence. Once issued, a licence is a legally binding instrument and penalties may apply for breaches of conditions.

Please refer to the fact sheet 'Application assessment process for dealings involving intentional release (DIR) of a GMO into the environment' for more information.

How long will it take the Regulator to decide whether or not to issue a licence?

The Regulator must make a decision to issue, or to refuse to issue, a licence for a limited and controlled release application under Section 50A of the Act within 150 working days, or 170 working days if significant risk is identified (weekends and ACT public holidays are excluded). The Regulator must make a decision for all other DIR applications within 255 working days.

We may ask you for additional information in relation to your application. Any days on which the Regulator cannot proceed with decision making while awaiting requested information do not count for purposes of determining the end of the decision-making period. The Regulator may cease to consider your application if you fail to provide requested information within the specified timeframe.

Will the Regulator need additional information after deciding to issue a licence?

Licence conditions require a licence holder to:

- provide details of any adverse or unintended effect that becomes evident during the release
- supply a contingency plan to be implemented in the event that the GMO is found outside of permitted areas
- detail a detection method specific for the GMO and introduced genetic modification and
- report annually in relation to permitted activities.

What else do you need to know?

The Regulator must provide a copy of a submitted DIR application to anyone requesting it (see section 54 of the Act). Any information in your application, including personal information in Parts 1, 2, 5 and 6, may be made public, except:

- information declared or under consideration as confidential commercial information (CCI) by the Regulator (see section 185 of the Act)
- information in the application about relevant convictions (see section 58 of the Act)
- information subject to the Privacy Act 1988.

Part 1:Contact Details for the Application

Details of the person the OGTR can contact regarding this application.

Personal title, e.g. Ms/Mr/Dr:	[redacted]
Surname :	[redacted]
First name:	[redacted]
Phone number:	[redacted]
Mobile number:	[redacted]
Fax number:	Enter fax number
Email address:	[redacted]
Job title:	[redacted]
Street number and name:	[redacted]
Town/city/locality:	[redacted]
State/territory:	[redacted]
Postcode:	[redacted]
Country:	[redacted]
Postal address, if different:	Enter postal address

Part 2:Project Supervisor

Personal title, e.g. Ms/Mr/Dr:	[redacted]
Surname:	[redacted]
First name:	[redacted]
Preferred first name, if different:	Enter preferred first name
Phone number:	[redacted]
Mobile number:	[redacted]
Fax number:	n/a
Email address:	[redacted]
Job title:	[redacted]
Street number and name:	[redacted]
Town/city/locality:	[redacted]
State/territory:	[redacted]
Postcode:	[redacted]
Country:	[redacted]
Postal address, if different:	Enter postal address
Relevant qualifications and skills:	[redacted]

Part 3:Applicant Organisation type

3.1 This application is being made by:

☐ a natural person, or

☒ an organisation

3.2 Information about the applicant organisation type

If the application is by an organisation, indicate below which of the following best describes your organisation. You may need to tick more than one box.

Note: Your response to this question is necessary to determine whether the Regulator will issue the licence under Commonwealth legislation or under corresponding State law. If unsure you should seek legal or other advice which will accurately identify the legal status of the organisation.

a. For an organisation which is a constitutional corporation, ie a trading, foreign or financial corporation within the meaning of paragraph 51(xx) of the Constitution, is the organisation a:

☐ Higher Education Institution

☐ Hospital

☐ Research Institute or similar

☐ Commonwealth Authority which is a body corporate established under an Act and/or a company in which a controlling interest is held by the Commonwealth or a Commonwealth authority

☐ State instrumentality which is a body corporate established under an Act and/or a company in which a controlling interest is held by that State or by a State instrumentality

☒ Corporation which is none of the above? Please provide details.

Australian Private Company

b. For an organisation which is NOT a constitutional corporation, is the organisation a:

☐ Higher Education Institution

☐ Hospital

☐ Research Institute or similar

☐ Commonwealth Department

☐ State Government Department

☒ Organisation which is none of the above? Please provide details.

Proprietary Limited Company

Part 4:Suitability of the applicant

4.1 Has the applicant been convicted of an offence against a law of the Commonwealth, a State[1] or a foreign country which relates to the health and safety of people or the environment where the offence was committed within a period of ten years immediately before the making of the application for this licence and which was punishable on conviction by a fine of $5000 or more, or by a term of imprisonment of one year or more?

[redacted]

4.2 If the applicant answered Yes to the preceding question and is a body corporate:

[redacted]

b. Was any person who is currently an officer or shareholder of the applicant, in a position to influence the management of the applicant, also such an officer or shareholder at the time that the offence was committed?

[redacted]

[1] 'State' includes the Australian Capital Territory and the Northern Territory (Section 10 of the Act).

4.3 Has the applicant had a licence or permit (however described) revoked or suspended 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?

[redacted]

4.4 To the best of the applicant's knowledge, will the applicant be financially viable for the proposed duration of the licence?

☒Yes ☐No

If No, justify why the Regulator should consider the applicant suitable to hold a licence.

Enter details

4.5 What is the date of the applicant's latest financial statement?

30/06/2020

4.6 Attach copies of the applicant's latest financial statement and either the audit findings or a statement from a director of the company (or a person otherwise authorised to make the statement) that the financial statement provided presents a true and fair view, in all material aspects, of the affairs of the applicant for the period covered by the statement.

The Regulator will not consider an application unless it is accompanied by the required financial information. If available, an electronic copy of the financial statement can be provided, eg by providing the URL for the statement on the internet.

The financial statements were submitted to OGTR by the Chief Financial Officer or delegate to ogtr@health.gov.au as part of the DNIR application "Clinical development of an Adenovirus Vector SARS-CoV-2 vaccine (SCAd6-1-002) given by Intramuscular injection".

4.7 What is the expected date of the applicant's next financial statement?

If the applicant's next financial statement is prepared prior to the Regulator reaching a decision on this application a copy of the financial statement must be sent to the OGTR as soon as it is available.

30/06/2021

4.8 Is there any other information relevant to the above questions that may assist the Regulator in making a decision about the suitability of the applicant for a licence?

☐ Yes ☒No

If yes, provide details.

Enter details

Part 5:Supporting Information from the Institutional Biosafety Committee (IBC)

This part must be completed by the IBC responsible for the Applicant Organisation.

Name of IBC:	[redacted]
Name of IBC Chair:	[redacted]
Phone number of the IBC: Chair	[redacted]
Fax number of the IBC: Chair	n/a
Email address of the IBC Chair::	[redacted]
Date of IBC evaluation of this application	4/03/2021

Name of IBC Primary Contact:	[redacted]
Phone number of the IBC Primary Contact:	[redacted]
Fax number of the IBC primary Contact:	n/a
Email address of the IBC primary Contact:	[redacted]

5.1 Has the information contained in this form been checked by the IBC and found to be complete?

Yes ☐No

Provide more detail, where appropriate.

Enter information

5.2 Does the IBC consider that the personnel intended to be involved in dealing(s) with the GMO(s) to have adequate training and experiencefor the task?

Yes ☐No

Provide more detail, where appropriate.

Enter information

5.3 When considering the information contained in this application, was the IBC constituted in **accordance with the relevant provisions of the Regulator's *Guidelines for the Accreditation of Organisations?***

Yes ☐No

Provide more detail, where appropriate.

Enter information

Part 6:Declarations

Part s 5 an d 6 mus t be completed after the applicant has completed all other Parts.

I DECLARE THAT:

- I am duly authorised to sign this declaration;and
- to the best of my knowledge, the information supplied on this form and any attachment(s) is not false or misleading.

CEO (or Delegate with Authority to Sign) of the Applicant Organisation

Print name:	[redacted]
Signature:	[redacted]
Job title:	[redacted]
Date:	Select date

Project Supervisor

Print name:	[redacted]
Signature:	[redacted]
Job title:	[redacted]
Date:	Select date

IBC Chair

Print name:	[redacted]
Signature:	[redacted]
Job title:	[redacted]
Date:	12/03/2021

Part 7:About the dealings with the GMO(s)

Before answering this Part the applicant is encouraged to familiarise themselves with 50A of the Act. Questions in Part 7 and 12 of this form that appear in ***italics and bold*** are the most important questions that relate to any proposed limits and controls for this application. Answers to these questions will be taken into account by the Regulator for purposes of deciding whether section 50A of the Act can apply to this application.

Title of project:	Clinical development of an Adenovirus Vector SARS-CoV-2 vaccine (SC-Ad6-1-002) given by Intranasal Administration to prevent COVID-19
Proposed date of commencement:	1/06/2021
Proposed date of completion:	1/06/2026
Description of proposed dealing(s) with the GMO(s), including a description of the proposed intentional release into the environment:	To Assess the Safety, Reactogenicity, Immunogenicity and Protective Efficacy of Adenovirus Vector SARS-CoV-2 vaccine SC-Ad6-1 given via Intranasal (IN) route in Healthy Subjects as part of human clinical trials
Specify person, persons or class of persons intended to be authorised to undertake dealing(s) with the GMO(s):	Registered Medical Practitioners, Registered Nurses and Registered Pharmacists, laboratory staff, specialist vendors involved in transport, storage and disposal of the GMO vaccine.
Description of purposes and aims of the proposed dealing(s): **Note:** The answer to this question is important for the Regulator to determine whether the principle purpose of the application is to conduct experiments. Please provide details of any proposed dealings for testing hypotheses, gaining scientific or technical knowledge or gaining data for regulatory purposes, or for product development or marketing.	Clinical trial program to assess the safety, reactogenicity, immunogenicity and protective efficacy of the SC-Ad6-1 vaccine given intra-nasally. Dealings include importation, transport, disposal and possession , supply or use of the GMO.

7.1 Will any of the proposed dealing(s) involve the intentional release of GMO(s) into the environment?

☐Yes No

7.2 Is it the intention of the applicant that the dealing(s) to be undertaken will involve a limited and controlled release pursuant to section 50A of the Act?

Yes ☐No

7.3 Will any of the proposed dealings with **GMOs** involve the use of nanotechnology*, or inclusion or production of engineered nanomaterials**?

☐Yes No

* **Nanotechnology** is engineering at the atomic or molecular level, involving the manipulation of matter at the nanoscale (generally accepted as 100 nanometres or less) to create new materials, structures and devices. For the purpose of this question, nanotechnology does not include standard techniques of molecular biology/gene technology.

** **Engineered nanomaterials** are materials designed at the molecular level to take advantage of novel properties which are generally not seen in their conventional counterparts.

The Australian Government has committed to taking a proactive approach in monitoring developments in nanotechnology so as to ensure the regulatory frameworks charged with protecting public health, safety and the environment keep pace with these changes.

Information about the dealings with the GMO(s)		**Attachment Number**
7.4	Details of: (i) the number of sites for proposed release; and (ii) the area of land to be used (if applicable); and (iii) the location of the proposed release(s), including identification of the local government area(s) in which any release will take place and the geographical location, grid references and GPS coordinates of the site(s)	Attachment #1
7.5	Details of the reasons for the choice of location(s) for the release(s)	Attachment #1
7.6	Details of the number of different types (events, lines, species, etc) of GMO(s) that will be released	Attachment #1
7.7	Details of how the GMO(s) will be released	Attachment #1
7.8	Details of the methods to be used to test for batch to batch consistency, if large scale production is required to produce the GMO(s) for release	Attachment #1
7.9	Details of the measures that have been taken, or will be taken, in the production process to ensure quality and purity of the GMO(s) intended to be released	Attachment #1
7.10	Details of the arrangements for conducting any other dealing(s) in association with the proposed release(s), such as importation of a GMO(s) and transportation of a GMO(s), to or from a release site(s)	Attachment #1
7.11	Details of proposed uses of the GMO(s), or of things derived or produced from the GMO(s), following release into the environment	Attachment #1

Part 8:Description of the GMO(s)

Information		Attachment Number
8.1	Details of the modified trait(s) and how the modification will change the phenotype of the organism(s) to be released, including information to demonstrate the effects of the modification(s)	Attachment #1
8.2	Identity of the gene(s) responsible for the modified trait(s), including a description of gene combinations in the GMO(s) (if any)	Attachment #1
8.3	Details of the origin(s) of the DNA to be inserted	Attachment #1
8.4	If the inserted DNA will come from an organism that causes disease or other ill-health in humans, animals, plants or fungi, details of the effects	Attachment #1
8.5	Details of the genetic modification(s) that have been or will be made, including details of the steps involved in its construction	Attachment #1
8.6	Details of the stability of the genotype(s) of the GMO(s), including a statement on whether it has a potentially unstable genotype	Attachment #1
8.7	Details of the extent to which the genetic modification(s) has been characterised (that is, the DNA sequenced, and the potential gene products understood)	Attachment #1
8.8	Details of the location of the inserted DNA and the number of copies that will be present in the final construct	Attachment #1
8.9	Is the site of integration of the inserted DNA, within the host genome, known?	Attachment #1
8.10	Details of the markers or sequences that will enable the GMO(s) to be identified in the laboratory and under field conditions	Attachment #1
8.11	Details of the type of vector used in the transfer (including a description of the vector), showing the position of the inserted DNA and any other control sequences or markers in the vector	Attachment #1
8.12	Details of whether the vector has the ability to transfer to other hosts and, if so, details of the host range	Attachment #1
8.13	Details of whether the recombinant vector will be present in the final construct and if not, how it will be removed	Attachment #1
8.14	If no vector will be involved, details of how the DNA will be introduced and how many copies of the gene will be inserted	Attachment #1
8.15	Details of secondary genetic effects that may be anticipated	Attachment #1
8.16	Details of the intrinsic genetic features, if any, of the GMO(s) that will regulate survival in the environment, including a statement on how stable those features are	Attachment #1
8.17	Details of the genetic changes, if any, that will be included in the GMO(s) to limit or eliminate any capacity to reproduce or transfer genes to other organisms	Attachment #1

Part 9:Risk assessment information – the parent organism(s)

Information		Attachment Number
9.1	Details of the common name of the parent organism(s)	Attachment #1
9.2	Details of the scientific name of the parent organism(s). If a GMO(s) is the result of a crossing event between more than one species, please include relevant information	Attachment #1
9.3	Details of the strain(s), cultivar(s) etc to be released. If a GMO(s) is the result of a crossing event between more than one strain, cultivar etc, please include all relevant information	Attachment #1
9.4	Details of whether the parent organism(s) has an extended history of safe use in agriculture or other industries	Attachment #1
9.5	Details of whether the parent organism(s) is capable of causing disease or other ill-health in people, plants or animals and, if so, the possible effects	Attachment #1
9.6	Details of the natural habitat of the parent organism(s), and its range	Attachment #1
9.7	Details of the location where the parent organism(s) was originally isolated for the purpose of the proposed dealing(s)	Attachment #1
9.8	Details of the distribution of the parent organism(s), and closely related organism(s), in Australia and in particular its distribution at or near the site of proposed release, including details if the parent organism(s) is exotic to Australia	Attachment #1
9.9	Details of any known predators, parasites, pests or diseases of the parent organism(s) in Australia	Attachment #1

Part 10: Risk assessment information – interaction between the GMO(s) and the environment

Information		Attachment Number
10.1	Details on whether the proposed release of the GMO(s) could prejudice any beneficial function of the parent organism(s) in the environment	Attachment #1
10.2	On the basis of contained experiments, details of: (i) the survival times of the GMO(s) in habitats relevant to the release; and (ii) the growth rate (or generation time) of the parent organism(s) and GMO(s) in the ranges of environmental conditions characteristic for the place and date of release; and (iii) the frequency of reversion or loss of the genetic change	Attachment #1
10.3	Details of the capability of the GMO(s) to disperse from the release area(s), and, if any, the dispersal mechanism	Attachment #1
10.4	Is the GMO(s) likely to be able to establish in the environment outside the release site(s)? If so please provide details	Attachment #1
10.5	Is the GMO(s) able to form long-term survival structures, such as spores? If so please provide details	Attachment #1
10.6	Details of whether the inserted genetic trait(s) will be able to be transferred to other organism(s) found at the release site and surrounding environment and, if so: (i) the organism(s) the trait(s) can be transferred to and the frequencies at which it can be transferred, including information about the species that have been tested for transfer and the rationale for selecting the test species; and (ii) the transfer mechanisms involved; and (iii) the techniques that have been used to demonstrate transfer; and (iv) any possible adverse effects of the transfer including: (a) any advantage that affected organism(s) are likely to have over members of the species that do not contain the transgene(s); and (b) environmental risks posed by such an advantage	Attachment #1
10.7	Details of whether interactions between pathogens and the transgene(s) are possible (for example, gene silencing) and, if so: (i) the incidence and distribution of relevant pathogens; and (ii) possible effects of interaction	Attachment #1

Part 11: Risk assessment information – risks GMO(s) may pose to the health and safety of people

Information		Attachment Number
11.1	Details of any allergens or toxins that may be expressed by the proposed GMO(s) that are not found in the parent organism(s)	Attachment #1
11.2	Details of any pathogenic properties in the GMO(s) that are not found in the parent organism(s)	Attachment #1
11.3	Details of any occupational health and safety risks to personnel dealing with the GMO(s) and safety risks to the wider community	Attachment #1

Part 12: Risk management information

Information		Attachment Number
12.1	***Details of measures proposed for restricting the dissemination or persistence of the GMO(s), or its genetic material, in the environment, including details of proposed measures for disposing of the GMO(s) when the release is complete and any waste deriving from the GMO(s)***	Attachment #1
12.2	***Details of measures proposed for monitoring the release including monitoring for:*** ***(i) the survival or presence of the GMO(s), or transferred genetic material, beyond the proposed release site(s), including specificity, sensitivity and reliability of detection methods; and*** ***(ii) impacts on the characteristics, or abundance, of other species; and*** ***(iii) transfer of the introduced gene(s) to other species; and*** ***(iv) any other hazards or deleterious effects*** ***the survival or presence of the GMO(s) after the release is completed***	Attachment #1
12.3	Details of the methods that will be used to minimise the effects of any transfer of the modified genetic trait(s) to other organisms	Attachment #1
12.4	Details of the specific experimental methods proposed for detecting the presence of the GMO(s), or transferred genetic material, in the recipient organism(s)	Attachment #1
12.5	Details of proposed release site supervision procedures and, if necessary, any relevant safety procedures designed to protect staff, including a description of procedures for on-site supervision of the release if the release site(s) is located at some distance from the location of the applicant	Attachment #1
12.6	Details of measures proposed for: (i) informing persons covered by the licence of any licence conditions; and (ii) informing the public about the proposed dealing(s)	Attachment #1
12.7	Details of proposed procedures for auditing, monitoring and reporting on compliance with any conditions imposed by the Regulator	Attachment #1
12.8	Details of any contingency measures that will be in place to rectify any unintended consequence if an adverse effect becomes evident during the course of the release(s)	Attachment #1

Part 13: Information about current and previous assessments or approvals

Information		Attachment Number
13.1	Details of any related current application under consideration by a Commonwealth, State or overseas government authority or regulator	Attachment #1
13.2	Details of results of any applications made for approval or use of the GMO(s), or any derived GM products, by any other regulator in Australia or overseas, including information about whether the application was successful or unsuccessful and details of conditions (if any) attached to the approval	Attachment #1
13.3	Details of any previous applications (whether successful or unsuccessful) under the Act, or to the Genetic Manipulation Advisory Committee, for a dealing with the GMO(s), or of a notification of a dealing under the Act, from which the work in the present application has developed	Attachment #1
13.4	If the GMO(s) has been previously released in Australia or overseas, details of any adverse consequences of the release, including identifying references and reports of assessments	Attachment #1
13.5	A list of Commonwealth and State government authorities that have been consulted about the proposed dealings with the GMO(s)	Attachment #1
13.6	For an imported GMO(s) – the date of importation or intended importation, including, if possible, a copy of documentation of clearance or assessment from the Australian Quarantine and Inspection Service (AQIS)	Attachment #1

Part 14: Additional Information - GM plant(s)

This part has been removed due to the development of specific forms for GM plants.

Not applicable.

Part 15: Additional information – GM micro-organism(s) not living in or on animals and not a live vaccine

Information about GMO(s) associated with plants		**Attachment Number**
15.1	Details of any partner species of plant, including information about the specificity of the interaction and the range of plant species with which the parent organism(s) can interact	n/a
15.2	Details of the effects of the GMO(s) on the partner plant species, and details of how it will be monitored	n/a
15.3	Details of any secondary effects that the GMO(s) might have on the partner plant species	n/a
15.4	Details of whether the modification(s) is likely to cause any change to the range of host plant species susceptible to infection by the organism(s)	n/a
15.5	Details of the effect, if any, of the GMO(s) on the distribution and abundance of host plant species or other species with which the GMO(s) can interact	n/a
15.6	Details of the effect the GMO(s) might have on insects, birds, animals or humans that may eat the plant	n/a
Information if the GMO(s) is associated with plant species that are food crops		
15.7	Details of whether the GMO(s) could affect the suitability of the resultant produce for consumption by animals or human beings and, if so, the effect	n/a
Information about the impact of the GMO(s) on soil and water		
15.8	Details of the expected effects of the GMO(s) on local soil chemistry (for example, pH, mineral leaching and nutrient levels)	n/a
15.9	Details of the possible effects of the GMO(s) on local water quality	n/a
15.10	Details of the effects the GMO(s) might have on soil organisms that are known to be beneficial to plants (for example, *Rhizobium, Azospirillum, Frankia* and mycorrhizal fungi) and that are likely to be in a release site(s)	n/a
Information about any interactions between GMO(s) and closely related micro-organisms		**Attachment Number**
15.11	Details of any known interaction between the GMO(s) and closely related micro-organisms in any partner plant (if applicable) and in the environment of the release site(s)	n/a
Information about known genetic exchange between parent organism(s) and plant pathogens		
15.12	Details of any known exchange of genetic material between the parent organism(s) and plant pathogens	n/a
Other information		
15.13	Information about the expected survival and dispersal of the GMO(s), including dispersal in natural waters, soil and on other natural surfaces	n/a
15.14	Details of whether the GMO(s) will be resistant to desiccation	n/a
15.15	A list of sterilising and anti-microbial agents (if any) that are expected to be active against the GMO(s)	n/a

15.16	Details of whether the GMO(s) will be susceptible to ultraviolet or ionising radiation	n/a

Part 16: Additional information – GM micro-organisms that live in or on animals

You must only respond to this Part if you are proposing to deal with a **GMO(s) that is (are) a micro-organism(s) that live(s) in or on animals** (for example, gut biota living in larger hosts and bacteria applied externally to an animal to prevent foot rot).

Information about the impact of the GMO(s) on the host		**Attachment Number**
16.1	Identification of the animal host species	n/a
16.2	Details of any new capacity the GMO(s) will provide for the host species (for example, ability to degrade plant or pasture toxins)	n/a
16.3	Details of whether the competitive advantage, ecological fitness, biology or distribution, of the host will be altered, and relevant data (if any) on the subject	n/a
16.4	Details of any secondary effects expected to result from the introduction of the GMO(s) into or onto the host (for example, information about any possibility of the genetic insert being transferred to other organisms in the host, or to host cells)	n/a
Information about the impact of the GMO(s) on the environment (particularly the impact on other animals, plants, soil and water)		
16.5	Any evidence that the GMO(s) might be capable of establishing in, or on, other animals, including feral animals	n/a
16.6	Any evidence of other likely effects (including secondary effects) on other plants or animals in the agricultural and natural environments	n/a
16.7	If the proposed GMO(s) will establish in an animal, information about whether the GMO(s) will be excreted or otherwise leave the animal and, if so, the time period that it is expected the GMO(s) can survive outside the animal	n/a
16.8	Details of the possible effects of the GMO(s) on local water quality	n/a
Other information		
16.9	Details about whether the GMO(s) will be resistant to desiccation	n/a
16.10	A list of sterilising and anti-microbial agents (if any) that are expected to be active against the proposed GMO(s)	n/a
16.11	Details of whether the proposed GMO(s) will be susceptible to ultraviolet or ionising radiation	n/a

Part 17: Additional information – live GM vaccine for use in animals or humans

You must only respond to this Part if you are proposing to deal with a **GMO that is a live vaccine for use in animals or humans.**

Information about the purpose of the vaccine		**Attachment Number**
17.1	Identification of the disease to be treated, or prevented, by use of the vaccine	Attachment #1
17.2	Identification of the host species on which the vaccine is to be used	Attachment #1
17.3	Details of the host range of the parent organism from which the vaccine is constructed	Attachment #1
17.4	Details of the level, and duration, of immunity produced in the host species after administration of the vaccine	Attachment #1
Information about the vaccine		
17.5	Details of the potential for the generic material of the vaccine GMO to become incorporated in whole, or in part, into the genome of any cells of the vaccinated host	Attachment #1
17.6	Details of the period over which the vaccine GMO will be detectable in a test animal/person, or its excretions or secretions	Attachment #1
17.7	If the GMO is a viral vaccine, information about the potential for the nucleic acid of the virus in the vaccine to be rescued, or to be restored to wild type, by recombination or complementation with intracellular viruses	Attachment #1
17.8	Details of any deleterious effects the vaccine GMO may have on a pregnant animal/person	Attachment #1
17.9	Details on whether the vaccine GMO has a teratogenic effect on a foetus at any stage of gestation	Attachment #1
17.10	Details on whether the use of the vaccine GMO is likely to: (i) preclude its use for vaccination against other diseases subsequently; or (ii) affect its usefulness for other vaccinations	Attachment #1
17.11	Details on whether the vaccine GMO is resistant to desiccation	Attachment #1
17.12	A list of sterilising and anti-microbial agents (if any) that are active against the GMO	Attachment #1
17.13	Details on whether the vaccine GMO is susceptible to ultraviolet or ionising radiation	Attachment #1

Information about the effect of the GMO on the environment		**Attachment Number**
17.14	Details of: (i) the potential for the vaccine GMO to spread from vaccinated to unvaccinated animals or people (of the same or other species including human beings); and (ii) if the potential exists, the likely mechanism and frequency of such spread	Attachment #1
17.15	Details of whether the susceptibility of the host to the vaccine GMO could be affected by: (i) the state of the host at the time of vaccination (for example, immunosuppression, or superimposition of other disease); or (ii) other treatments, such as drugs	Attachment #1
17.16	Details of proposed methods for disposing of waste containing the vaccine GMO	Attachment #1
17.17	Details of the intended fate of vaccinated animals at the end of the trial	Attachment #1
17.18	Information about whether the live vaccine GMO will be carried by an animal or person at the end of the trial and, if so: (i) the potential for dissemination of the live GMO vaccine through the person or animal's family contact, or to the general population of the species; and (ii) measures intended to be taken to minimise the potential for dissemination; and (iii) the potential for the GMO to cross the placenta of a pregnant animal/person	Attachment #1

Part 18: Additional information – GM vertebrate animal

You must only respond to this Part if you are proposing to deal with a **GMO that is a vertebrate animal (other than aquatic organisms)**.

Information about the effects of the GMO(s) on the environment		**Attachment Number**
18.1	Information about the likelihood of any unintended effect on other animals resulting from the release of the GMO	n/a
18.2	Information about any intended gains that are directly linked to changes in other characteristics of the subject species	n/a
Information about feral populations of subject species, if any, that exist in Australia or that may be established		
18.3	Details of: (i) the likelihood of the introduced trait(s) enhancing the ability of the species to establish feral populations; and (ii) if there is a likelihood, the arrangements in place to prevent this from occurring	n/a
18.4	Details of any agricultural, environmental or disease-control problems caused by feral populations of the subject species	n/a
18.5	Details of any experimental work that has been done on expression of the novel genetic material in feral animals (such as cross-breeding of GMO(s) with captive feral animals), and the results of such work	n/a
18.6	Details of the likelihood of the novel genetic material entering the feral gene pool (for example, by interbreeding with modified farm animals)	n/a
18.7	Details of the effect that the entry of the novel genetic material into a feral gene pool might have: (i) on the distribution and abundance of the feral population; or (ii) on the ability of the feral population to cause agricultural or environmental problems; or (iii) in contributing to the spread of infectious disease	n/a
Information about the capacity of the GMO(s) to interbreed		
18.8	Details of the capacity of the GMO(s) to interbreed with any species native to, or currently present in, Australia	n/a
Information about requirements for optimal expression of the introduced trait		
18.9	Details of the management procedures and environmental factors, if any, that would be required for optimal expression of the introduced trait(s)	n/a

Information about future dealings with the GMO(s)		Attachment Number
18.10	Details of whether an animal in the experiment is intended to be allowed to breed and, if not, whether breeding is planned in the future	n/a
18.11	Details of whether the proposed arrangements for handling any offspring are the same as those for the experimental animal(s), and, if not, the proposed different arrangements	n/a
18.12	Has the proposed work been reviewed by the Institutional Animal Ethics Committee? Please provide details	n/a
18.13	Does the proposed work meet the requirements of relevant State animal welfare legislation? Please provide details	n/a

Note: All work involving animals should be conducted according to the NHMRC *Australian Code of Practice for the Care and Use of Animals for Scientific Purposes*, which requires review by an Institutional Animal Ethics Committee and by the relevant Authority administering State animal welfare legislation.

Part 19: Additional information – GM aquatic organism

You must only respond to this Part if you are proposing to deal with a **GMO that is an aquatic organism**, for example fish, crustaceans and molluscs.

Information about the impact of the GMO(s) on the environment		**Attachment Number**
19.1	Details of whether the GMO(s) could produce any novel metabolites, or toxins, that are likely to have deleterious effects on parasites, pests or predators and, if so, the likely effect	n/a
19.2	Details of any unintended effects that may result from the release	n/a
19.3	Details of whether the expression of the modified gene is expected to be directly linked to undesirable changes in other characteristics of the subject organisms (for example, a decrease in nutritional value)	n/a
19.4	Information about: (i) whether the modified genetic material can be transmitted to any other species; and (ii) if so, the expected mechanism of transfer, the likely affected species and any likely consequences	n/a
Information about any impact on populations		
19.5	Information about whether populations of the parental organism, or a closely related species, exist in Australia (including in rivers, lakes, dams or coastal waters) and, if so, details about any problems the existing populations cause other organisms or the environment	n/a
19.6	Information about the potential for the modified trait(s) to enhance the ability of the species to establish populations in aquatic habitats	n/a
19.7	Information about the results of any experimental work that has been done on phenotypic expression of the modified genetic material in naturally occurring organisms (such as cross-breeding of GMO(s) with wild or farmed stocks)	n/a
19.8	Details of the likelihood of the modified genetic material entering the gene pool of established populations	n/a
19.9	Information about any impact the entry of the modified genetic material into the gene pool of an organism could have on: (i) the distribution and abundance of the organism; or (ii) associated aquatic farms; or (iii) the environment; or (iv) public health	n/a
19.10	Information about mechanisms intended to be used to prevent dispersal of the GMO(s) in the environment	n/a
Information about future dealings with the GMO(s)		
19.11	Details of whether an organism in the experiment is intended to be allowed to breed and, if not, whether breeding is planned in the future	n/a
19.12	Details of whether the proposed arrangements for handling any offspring are the same as those for the experimental organisms and, if not, the proposed different arrangements	n/a

Part 20: Additional information – GM invertebrate animal

You must only respond to this Part if you are proposing to deal with a **GMO that is an invertebrate animal other than aquatic invertebrates.**

Information about the GMO(s)		**Attachment Number**
20.1	Information about the effect the GMO(s) might have on the food chain	n/a
20.2	Information about the potential for the GMO(s) to produce any novel metabolites, or toxins, that are likely to have deleterious effects on parasites or predators	n/a
20.3	Information about other unintended effects that may result from the release	n/a
20.4	Details of whether the GMO(s) will be fertile and, if not, whether it is intended to use fertile organisms in later releases	n/a
20.5	Information about whether populations of the parental organism, or a closely related species, exist in Australia and, if so, any environmental or public health problems, or benefits, caused by the populations	n/a
20.6	Information about: (i) whether the modified genetic material can be transmitted by means other than by reproduction normal for the species; and (ii) if so, the likelihood of that genetic material entering gene pools of natural populations	n/a
20.7	Information about: (i) whether the modified genetic material can be transmitted to any other species; and (ii) if so, the expected mechanism of transfer, and the likely affected species	n/a
20.8	Information about any experimental work that has been done on the phenotypic expression of the novel genetic material in other genetic backgrounds (such as cross-breeding of modified strains with wild or caught stock)	n/a
20.9	Information about the effect, on the distribution and abundance of populations of the organism, of the entry of the novel genetic material into the gene pool of those populations	n/a
20.10	Details of the mechanisms proposed to be used to prevent dispersal of the GMO(s) in the environment	n/a

Part 21: Additional information – GMO(s) for biological control

You must only respond to this Part if you are proposing to deal with a **GMO(s) that is (are) to be used for biological control.**

Information about the expected interaction between the GMO(s) and the species targeted for biological control		**Attachment Number**
21.1	The name of the species targeted for biological control	n/a
21.2	Details of any direct effects the parent organism(s) has on the target species	n/a
21.3	Details of any direct effects the GMO(s) is expected to have on the target species	n/a
21.4	Details of how the GMO(s) is intended to be transferred from one target organism to another, and what factors affect the transferability	n/a
21.5	Details of the genetic response(s) that may be invoked in populations of the target organism as a result of the use of the GMO(s) (for example, increased resistance to the modified organism(s)), and the expected evidence for the response	n/a
Information on the possible effects of the GMO(s) on non-target organisms		
21.6	Details of the host range of the GMO(s), and of any difference from the host range of the parent organism(s)	n/a
21.7	A list of the non-target organisms that have been tested for susceptibility to the GMO(s), and the rationale for the choice of species tested	n/a
21.8	If the modified trait(s) can be transmitted to other organisms that are likely to be in the environment of the release site, details of any effects those other organisms are likely to have on non-target species	n/a
Information on other possible effects of the GMO(s) on the environment		
21.9	Details of the secondary effects that can be envisaged on competitors, predators, prey or parasites of the target species	n/a
21.10	Details of the consequence of the removal, or reduction, of the target species on the management of agriculturally significant plants or farm animals	n/a
21.11	Details of any predicted change in the ecosystem resulting from a reduction in the populations of the target organism(s)	n/a

Part 22: Additional information – GMO(s) for bioremediation

You must only respond to this Part if you are proposing to deal with a **GMO(s) that is (are) to be used for bioremediation.**

Information about the expected interaction between the GMO(s) and the target substrate for bioremediation		**Attachment Number**
22.1	Identification of the target substrate(s) for bioremediation	n/a
22.2	Details of the effect the parent organism(s) has on the target substrate(s)	n/a
22.3	Details of the effect the GMO(s) is expected to have on the target substrate(s)	n/a
22.4	A list of the substrates other than the target substrate(s) that can be metabolised by the GMO(s) and that cannot be metabolised by the parent organism(s)	n/a
Information about the GMO(s) and its impact on the environment		
22.5	Details of whether the GMO(s) will be self-sufficient if added to the contaminated site(s) or whether additional measures may be required (for example, provision of supplementary nutrients and growth factors, or other environmental modifications)	n/a
22.6	Details of effects the GMO(s) might have on water, air or soil quality	n/a
22.7	Details of the effects the GMO(s) might have on organisms that ingest it	n/a
22.8	Details of whether the GMO(s) will be dispersed from the site(s) of application and, if so, the proposed mechanisms involved and the likely consequences	n/a

Part 23: Additional information – GMO(s) used as food for human or vertebrate animal consumption

You must only respond to this Part if you are proposing to deal with a **GMO(s) that is (are) intended to be developed for use as a food for consumption by human or animals.**

Information		**Attachment Number**
23.1	Details of: (i) whether the parent organism(s) and/or the donor organism(s) is of a kind already in use as a food for consumption by human beings or animals, or used in the production of such a food; and (ii) whether any processing is needed, or is commonly applied to the parent or donor organism before consumption, and if processing will be different for the GMO(s)	n/a
23.2	Details of any products of the GMO(s) that are expected to concentrate in the food chain to levels which may become toxic	n/a
23.3	Details of any expected changes to the nutritional quality of such food as a result of the genetic modification(s)	n/a
23.4	Details of whether the GMO(s) is a major component of such food as consumed, or a minor component (for example, yeast cells in beer)	n/a

Note: Food that contains GMO(s) or GM products is also subject to regulation by Food Standards Australia New Zealand prior to human consumption (see assessment requirements under the *Australia New Zealand Food Authority Act 1991*).

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Personal information - Privacy Act, 1988

Institutional Biosafety Subcommittee Chair
[redacted]
Institutional Biosafety Subcommittee Secretary
[redacted]
CR COS PROV DER NIUMBER 000256

Memorandum to: - [redacted] Personal Information - Privacy Act, 1988
[redacted]

From - [redacted] Personal Information - Privacy Act, 1988
[redacted]

Date: **15/12/2020**

Regarding: **Approval of application**

Application Reference: [redacted]
UQ safe ref number: **1046**
Chief Investigator: [redacted] Personal Information - Privacy Act, 1988
Pre>ject Tit le: **Toxicology** testing in rodents of a SARS-CoV-2 adenovirus vector vaccine
Category: NLRD- PC2j
Summary of work:
Tetherex is a US-based biotechnology company that has created a live viral vaccine designed to provide immunity against the SARS-CoV-2 vims responsible for COVID-19. TetraQ win undertake a safety study in rodents to evaluate the potential toxicity of this vaccine prior to human testing by Tetherex . The scope of this NLRD dealing is restricted to ad.rninisu·ation of the :final vacc ine product (GMO) to rodents and handling of these animals and also storage of subsequently collected tissues.

Reviewed by: **Committee and Biosafety**

Approval
This record of assessment notes the abovementioned application has been considered by the UQ IBC subcommittee and determined to meet the requirements as stipulated in the relevant UQ Biosafety Procedure, Regulation and/ or Austral ian standard. pproval is granted following declaration by the project leader/ supervisor that;

- *In addition to work practices specified for certified biological facilities, all personnel involved in this dealing must have the appropriate training and experience in procedures and equipment used. All persons involved in this dealing have completed the mandatory online OHS-Biosafety training (via UQ blackboard). Evidence of this training will be available to the /BC and training will be kept current.*
- *All personnel involved in this dealing have been notified of the risks and the appropriate risk* assessments *that may be associate with NLRD/HRB dealings, and*
- *Documented procedures are in place to decontaminate any spills involving* GMOs *inside or outside the nominated facilities*
- *Aware of the requirements stipulated in holding exempt, HRB, NLRD, DNIR, DIR dealings.*

Date: 15/12/20 Signed: [redacted] Personal Information - Privacy Act, 1988

Personal Infonnation - Privacy Act, 1988

[redacted]
[redacted]
The University of Queensland
Brisbane QLD 4072 Australia
[redacted]

Australian Government
Department of Health
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan (Consultation version) for

DIR 184

Clinical trial of recombinant COVID-19 vaccine

Applicant: Avance Clinical Pty Ltd

21 April 2021

This RARMP is open for consultation until 26 May 2021.

Written comments on the risks to human health and safety and the environment posed by this proposed clinical trial of the GM COVID-19 vaccine are invited. You may make your submission

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

or

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

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

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Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR 184

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a genetically modified (GM) COVID-19 vaccine. It qualifies as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Avance Clinical Pty Ltd (Avance) proposes to conduct a clinical trial to evaluate the safety and tolerability of genetically modified human adenovirus serotype 6 (HAdV-C6) as a GM vaccine to treat COVID-19 in adults. This clinical trial involves the intranasal administration of the GM vaccine, which is different to the intramuscular administration of current COVID-19 vaccines.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus discovered in December 2019 in Wuhan, China and is the cause of the COVID-19 disease. The World Health Organization (WHO) declared the outbreak a pandemic on 11th March 2020 and as of 4th March 2021, there have been over 2.5 million deaths reported worldwide.

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, Avance will require authorisation from TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* and with the *Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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

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

The application

Application number	DIR-184
Applicant	Avance Clinical Pty Ltd
Project title	Clinical trial with a genetically modified human adenovirus as a vaccine for the treatment of COVID-19[1]
Parent organism	Human adenovirus 6 (HAdV-C6)

[1] The title of the licence application submitted by Avance Clinical Pty Ltd is "Clinical development of an Adenovirus Vector SARS-CoV-2 vaccine (SC-Ad6-1-002) given by intranasal administration to prevent COVID-19".

Introduced gene and modified trait	• Deletion of:
	  ○ *IIIa* gene (stops virus multiplying)
	  ○ E3 gene (increases immune response to virus)
	• Insertion of a gene encoding the SARS-CoV-2 spike protein (expresses spike protein)

Principle purpose	The proposed trial is a phase I study designed to evaluate the safety, tolerability, immunogenicity and efficacy of SC-Ad6-1 as a second generation, prophylactic vaccine to prevent COVID-19.
Previous clinical trials	This is a first in human clinical trial
Proposed locations	Clinical trials will be conducted at clinical trial sites, hospitals, General Practioner (GP) surgeries, and other medical facilities suitable for clinical trials and vaccine administration within Australia.
Proposed limits and controls	• Import, transport and storage of the genetically modified organism (GMO) will be carried out according to Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* appropriate for PC1 GMOs • The GMO will be administered to trial participants in a suitable medical facility setting. • Staff handling the GMO will be trained and use personal protective equipment. • Waste that may contain the GMO will be disposed of via the clinical waste stream. • Participants will be held at clinical trial site for at least 4 hours after administration and sent home with detailed instructions post-treatment • The clinical trial would enrol a limited numbers of trial participants (up to 1000 healthy volunteers in Australia at multiple sites).

Risk assessment

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

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

Credible pathways to potential harm that were considered include the; potential exposure of people and animals to the GMO; the potential for the GMO to recombine with other similar viruses or to get genes from those viruses; and the potential for the GMO to integrate into the host genome. The potential for the GMO to be released into the environment and its effects were also considered.

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

- The GMO is unable to form infectious viral particles, which will prevent it from multiplying in other cells and is very unlikely to be shed from the vaccine recipient;
- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccinees) would be minimised due to well-established import, transport, storage and disposal procedures; and

- The likelihood of complementation and recombination of 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 GM vaccine have been assessed as negligible, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management

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

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

Table of contents

Abbreviations

AICIS	Australian Industrial Chemicals Introduction Scheme
AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARTG	Australian Register of Therapeutic Goods
CAR	Coxsackie and adenovirus receptor
CCI	Confidential Commercial Information
COVID-19	Coronavirus infectious disease 2019
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
FSANZ	Food Standards Australia New Zealand
g	gram
GM	Genetically modified
GMO	Genetically modified organism
GP	General practitioners
GTTAC	Gene Technology Technical Advisory Committee
HAdV	Human adenovirus
HGT	Horizontal gene transfer
IATA	International Air Transport Association
IN	Intranasal
kb	Kilobase pair of DNA
LGA	Local government area
Mb	Mega base pairs
min	Minute
ml	Milli litre
NSW	New South Wales
OGTR	Office of the Gene Technology Regulator
Orf	Open reading frame
PCR	Polymerase chain reaction
QLD	Queensland
RARMP	Risk Assessment and Risk Management Plan
RNA	Ribonucleic acid
S	Spike
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
the Act	The *Gene Technology Act 2000*

the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
UK	United Kingdom
USA	United States of America
WA	Western Australia
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.

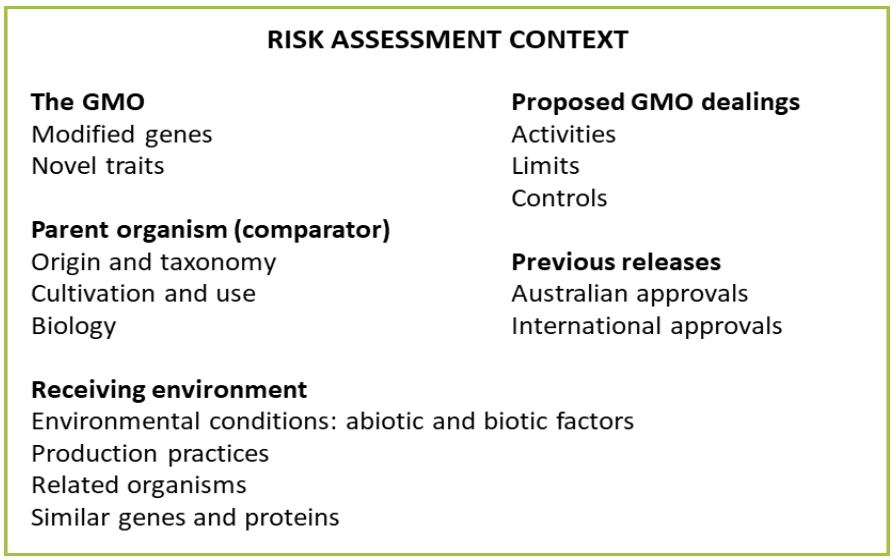

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

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, Water and the Environment (DAWE).

9. Medicines and other therapeutic goods for use in Australia are required to be assessed for quality, safety and efficacy under the *Therapeutic Goods Act 1989* and must be included in the Australian Register of Therapeutic Goods. The TGA is responsible for administering the provisions of this legislation. Clinical trials of therapeutic products that are experimental and under development, prior to a full evaluation and assessment, are also regulated by the TGA through the Clinical Trial Approval (CTA) scheme or the Clinical Trial Notification (CTN) scheme.

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

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

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

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

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

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

Section 2 The proposed dealings

19. SARS-CoV-2 is a novel coronavirus discovered in December 2019 in Wuhan, Hubei province of China and is the cause of the COVID-19 disease. The rapid spread of this virus around the world led the World Health Organization (WHO) to declare the outbreak as a public health emergency of

international concern (PHEIC) on the 30th January 2020 and eventually a pandemic on 11th March 2020 (WHO - Timeline of WHO's response to COVID-19, 2020).

20. The most common symptoms of COVID-19 are fever, tiredness and a dry cough, although some patients develop aches and pains, nasal congestion, runny nose, sore throat or diarrhoea. Symptoms are usually mild with gradual onset and about 80% of infected people recover without specific treatment. However, COVID-19 can cause complications such as severe pneumonia, acute respiratory distress syndrome, and multiple organ failure and in some cases, death. This is especially in older patients and those with pre-existing respiratory or cardiovascular conditions. There is currently two vaccines available for COVID-19 in Australia. As of 2 April 2021, 85 candidate vaccines are in clinical evaluation around the world (WHO -Draft landscape of COVID-19 candidate vaccine, 2021). These vaccines are based on a variety of platforms such as lipid nanoparticle encapsulated mRNA, DNA, adjuvant protein, inactivated virus particles and non-replicating viral vectors.

21. Avance Clinical Pty Ltd (Avance) is seeking authorisation to carry out a clinical trial to assess the safety, tolerability, immunogenicity and efficacy of a genetically modified (GM) vaccine (SC-Ad-1) as a second generation, prophylactic vaccine to prevent COVID-19.

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

(a) importation of the GMO;

(b) conduct the following with the GMO:

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

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

iii. collect samples from trial participants;

iv. analyse samples from trial participants;

(c) transportation of the GMO;

(d) disposal of the GMO;

and the possession (including storage), supply or use of the GMO for the purposes of, or in the course of, any of the above.

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

23. The clinical trial is proposed to take place over a five year period from the date of issue of the licence. Up to 1000 patients in Australia would receive the GMO.

24. The trial would take place at clinical trial sites in Australia listed in Section 2.3.3.

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

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

26. 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:

- ensuring the GM treatment is administered by authorised, appropriately trained medical staff in clinical facilities;
- requiring that clinical trial staff handling and/or administering the GM treatment wear and use personal protective clothing and equipment;

- transport and storage of the GMO and any contaminated waste generated at a clinical trial site must be in accordance with the current version of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs;*
- requiring decontamination of materials and equipment that have been in contact with the GMOs at clinical trial sites using effective disinfectants or disposal using a certified waste contractor in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation;
- providing patients with treatment instructions, and providing instructions to patients about good hand hygiene.

2.3 Details of the proposed dealings

2.3.1 Manufacturing of the GMO

27. The GMO will be manufactured overseas (the United States of America; USA) in accordance with current good manufacturing practice (cGMP). The master cell bank (MCB) will be tested for adventitious agents by sequencing to confirm the absence of the *IIIa* gene. The drug substance and the final GMO product will be tested to confirm identity, quality, purity, potency and safety.

28. The GMO would be supplied in a crimped, stoppered vial as primary containment and will be packaged into a secondary and tertiary shipping carton during transport. Information on the concentration and volumes of vials are indicated in a commercial confidential information (CCI) attachment to the RARMP[2].

2.3.2 Transport, supply and storage of the GMO

29. The GMO would be imported from the USA directly to clinical trial facilities. Biological samples (e.g. blood, urine and mucosal fluid) from trial participants that may contain GMOs would also be collected at various time points in the same clinical trial facilities and be transported to pathology laboratories for analysis.

30. The GMO would be transported into Australia from the USA and within Australia according to the OGTR's *Transport, Storage and Disposal Guidelines* (TSD) for PC1 organisms by commercial courier companies (e.g. World Courier). The details (name, address and contact information) of the consignor and consignee would be present on the outer packaging. The primary packaging (sealed vials) would be contained in an insulated container for validated shipping under frozen conditions (-20°C) in an outer package. The outer package would also be clearly labelled to indicate that it contains a GM COVID-19 vaccine.

31. For transport from the pharmacy to the designated treatment room, the GMO would be contained in primary and secondary containers; recorded to ensure no loss; and staff transporting the GMOs would be trained as in Section 2.3.11. A spill kit would be available at all times in the facilities in case of any spills.

32. Storage of the GMO vaccine would be within the clinical trial sites centres (room temperature, fridge or freezer) with restricted access to prevent access by unauthorised personnel.

2.3.3 Clinical trial sites

33. The clinical trial using the GMO would be carried out in clinical trial sites. One trial site has been identified as Nucleus Network Pty Ltd, in Brisbane. The clinic has an attached PC2 facility (Cert-

[2] Confidential Commercial Information: Some details about the concentration and volume of vials have been declared as Confidential Commercial Information (CCI) under Section 185 of the Act. This information will be made available to the prescribed experts and agencies that will be consulted on this application. CCI is not available to the public.

1916 at QIMR Berghofer Medical Research Institute, QLD). Other proposed clinical trial sites are CMAX (Adelaide, South Australia), Linear (Perth, Western Australia) and Scientia (Sydney, New South Wales). Hospitals, General Practioner (GP) surgeries and other medical facilities suitable for clinical trials and vaccine administration have also been proposed.

34. Cert-1916 is a PC2 Laboratory and does not have any additional conditions or exceptions required to comply with the *Guidelines for Certification of a Physical Containment Level 2 Laboratory*. The applicant has stated that Cert-1916 will only be used for storage. Dealings conducted under DNIR-614 also take place in Cert-1916. DNIR-614 is for 'Manufacture and characterisation of a *P. falciparum* NF54 Inducible Gametocyte Producer (NF54/iGP3) Master Cell Bank for use in Phase I Clinical Trials utilising the Induced Blood Stage Malaria Infection Model'. Genetic recombination between *P. falciparum* and adenovirus are not possible.

2.3.4 Trial design

35. The applicant proposes a phase 1/2 open-label, dose escalation study, which is to be conducted at multiple locations in Australia (as noted in Section 2.3.3). The details of trial design is indicated in a confidential commercial information (CCI) attachment to the RARMP.

2.3.5 Selection of trial participants

36. Relevant inclusion criteria to be used by study site investigators include that:

- participants may be of any gender
- participants must be between 18 and 65 years of age (inclusive) at screening;
- participants be medically healthy without clinically significant abnormalities at the screening visit, at check-in on Day -1 and pre-dose on Day 1, as determined by the Investigator
- male trial participants:
    - if not surgically sterilised and, if engaging in sexual intercourse with a female partner who could become pregnant; must be willing to use a condom in addition to having the female partner use a highly effective contraceptive method from signing the consent form until at least 90 days after the last dose of the GMO;
- female trial participants:
    - must not be breastfeeding; and
    - must agree not to attempt to become pregnant; and
    - of childbearing potential, must have a negative serum pregnancy test at screening and agree to use an acceptable method of highly effective contraception from screening through to at least 90 days after the last dose of study; and
- participants must not donate blood, sperm, ova or organs until 90 days after the last dose of the GMO; and
- participants must be willing to avoid vaccination other than the study agent for 84 days after administration of final dose of the GMO (end of study).

37. Relevant exclusion criteria include:

- history of chronic respiratory disorders including asthma; and

- known previous infection with SARS-CoV-2 or receipt of SARS-CoV-2 (COVID-19) vaccination or presence of antibodies against SARS-CoV-2 or a positive COVID-19 PCR test; and
- vaccination with another agent 30 days prior to registration.

38. 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

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

40. Dilutions of the GMO would be needed, the final volume after dilution of the original vial would be 2 or 4 ml. The preparation of the dose will be performed on an open bench in the pharmacy. This will be carried out aseptically using syringes to transfer solutions between crimped, stoppered vials. Therefore, there would not be open transfer of solutions outside of the syringe or vaccine vial as all solutions would be contained within the sealed primary vial or syringe. The filled capped syringe would be transported to the administration area as described in Section 2.3.2.

2.3.7 Intranasal administration of the GMO

41. The GM vaccine will be administered intranasally (IN) at clinical trial sites. The IN administration will be carried out by study nurse who would be wearing appropriate PPE (face shield/safety glasses, face mask, disposal gown and disposable gloves).

42. Prior to administration, the filled syringe would be capped with an atomiser, which will be used to create an aerosolised mist and deliver a 0.25ml dose into the nasal passage.

43. During administration, clinical trial participants will have their heads tilted back to allow the vaccine to run backwards into the subject's throat and be swallowed. Participants will then be required to stay in the trial site for approximately 4 hours.

44. Any sneezed inoculum or nasal discharge would be caught/collected in tissues, placed in a biohazard bag and disposed as clinical trial waste. Participants would be instructed to disinfect their hands via washing or using an alcohol hand sanitiser.

2.3.8 Decontamination and disposal of the GMO

45. 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 will be also disposed using the same process. Disposal will be carried out by external service providers.

46. Any equipment that is contaminated with the GMO will be cleaned with an appropriate virucidal disinfectant shown to be effective against the GMO.

2.3.9 Sample collection and analysis

47. Following administration of the GMO, blood, urine, and mucosal samples will be collected from trial participants at various time points to determine effectiveness of the vaccination and evaluate patient safety.

48. After collection, blood samples will be centrifuged and aliquoted in preparation for analysis. Samples will be packaged as described in Section 2.3.2 for transport to testing laboratories.

2.3.10 Personal protective clothing

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

2.3.11 Training

50. The applicant's IBC declares that the training and experience of individuals involved in these dealings is satisfactory.

51. Staff handling the GMO would be made aware of the licence conditions and any subsequent amendments. This training will be recorded in the site study file.

52. Use of sentinel trial participants is proposed as described in the CCI attachment to the RARMP, which is made available to the prescribed experts and agencies that are consulted on the RARMP. In addition, all trial participants would be monitored against various baselines and for all adverse events related to the GMO.

2.3.12 Accountability and Monitoring

53. Nucleus Network pharmacy and clinical nursing teams would track and account for the GMO vaccine and trial participants as per Good Clinical Practice (GCP). A documented chain of custody would be in place where; the dispensing of vaccine will be recorded by the pharmacist; the administration would be recorded by the study nurse; and disposal of any unused vial containing the GMO would be conducted after an acquittal process as per GCP.

2.3.13 Contingency plans

54. Spill kits will be available at clinical trial sites and spills will be cleaned up immediately using a virucidal disinfectant according to the clinical trial facility's spill procedures. The sponsor and the IBC will then be notified.

Section 3 Parent organism

55. The GM vaccine is derived from human adenovirus serotype 6 (HAdV-C6). HAdV-C6 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 GM vaccine. As such, the relevant biological properties of HAdVs will be discussed here.

56. Human adenoviruses (HAdVs) are categorised into seven species A to G based on their serology, sequence homology, serum neutralisation, hemagglutinin properties and genomic sequence (Ismail et al., 2018; Lange et al., 2019; Bots and Hoeben, 2020). 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).

57. Despite the high prevalence of HAdV-C in the population, HAdV-C5 vectors have been extensively used as vaccine platforms against various diseases such as HIV, malaria, Ebola virus, influenza virus and tuberculosis (Mennechet et al., 2019). HAdV-C2 and C5 vectors have also been frequently used in clinical trials as cancer therapies (Shaw and Suzuki, 2019; Sato-Dahlman et al., 2020). The less prevalent HAdV-C6 has being proposed as a vaccine candidate because it is likely to have similar biological characteristics to other HAdV-Cs such as HAdV-C5 (Crosby and Barry, 2014; Crosby et al., 2015).

3.1 Pathology

58. HAdVs 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).

59. HAdV infections are generally mild and self-limiting, but could be more severe or lethal in immunocompromised individuals (Mennechet et al., 2019). 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).

60. 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.

61. HAdV-C has been mainly associated with acute respiratory tract infections in children and is the most common serotype reported in most populations (Mennechet et al., 2019).

3.2 Structure and genomic organisation

62. AdVs 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 has 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).

63. 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.

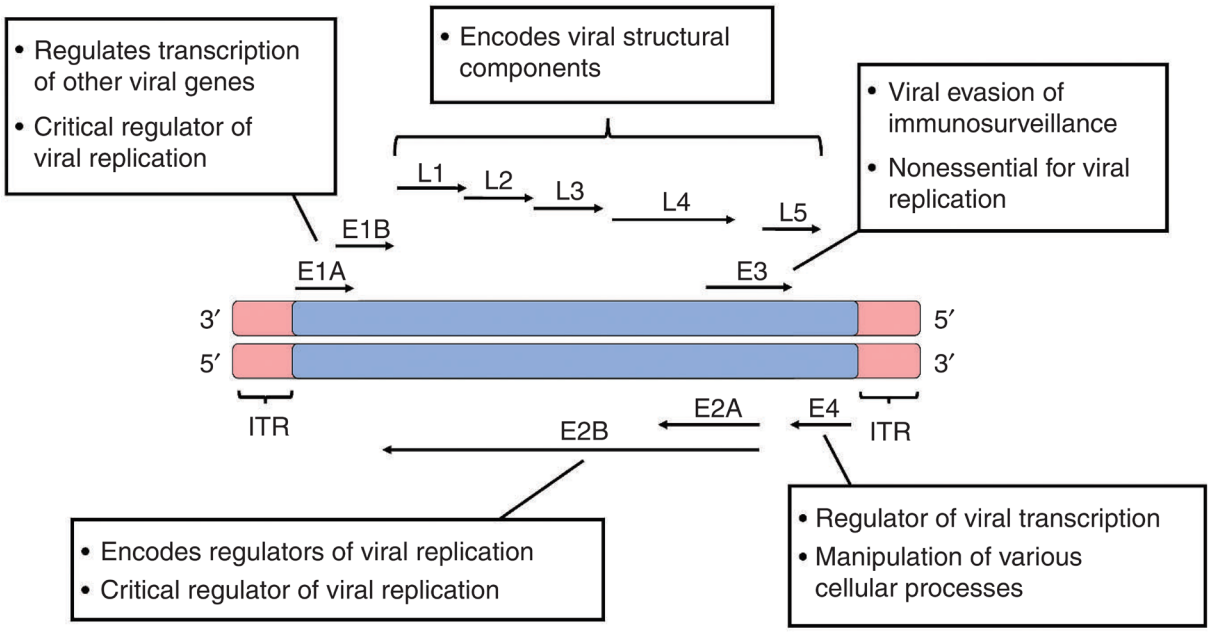

Figure 2: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).

64. 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).

65. The E2 gene is sub-divided into E2A and E2B that encode E2 proteins which 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.

66. Interactions of various proteins encoded by the adenovirus genome are required to form a mature infectious particle. The three major proteins (hexon, penton and fibre) form the external capsid structure and “spikes” of the viral particle. The viral core proteins (V, VII and µ) 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 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 and are 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).

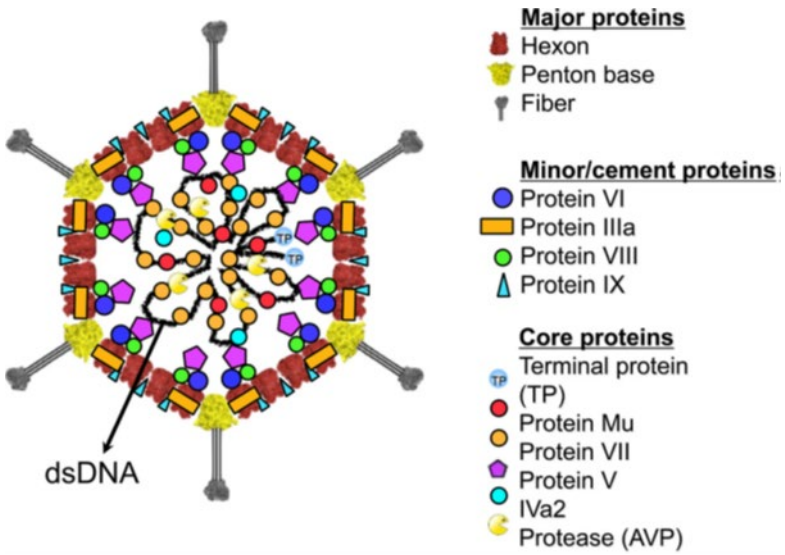

Figure 3: Structural model of human adenovirus (Benevento et al., 2014)

3.3 Viral infection and replication

67. AdVs 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.

68. HAdVs uses the Coxsackie-adenovirus receptor (CAR) transmembrane proteins, CD46, CD80, CD86 and sialic acid to enter the host cells (Zhang and Bergelson, 2005; Lion, 2019). HAdV species C and E use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins as the main receptor to gain entry to a variety of different cell types (Zhang and Bergelson, 2005; Lasaro and Ertl, 2009; Morris et al., 2016; Bots and Hoeben, 2020). *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).

69. The replication of AdVs takes place in the nucleus of the host cell and uses the host cell nuclear machinery to make copies of itself (Figure 3). Briefly, the AdV attaches to the receptors present on the cell membrane leading to internalisation of the virus by endosomal uptake. The virus is then uncoated resulting in the release of viral particles. The viral genome is transported into the nucleus where the transcription occurs (described above in Section 3.2; (Charman et al., 2019). The viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made. The new virus particles are then assembled. Finally, the host cell breaks apart releasing the viruses (Waye and Sing, 2010b). Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes.

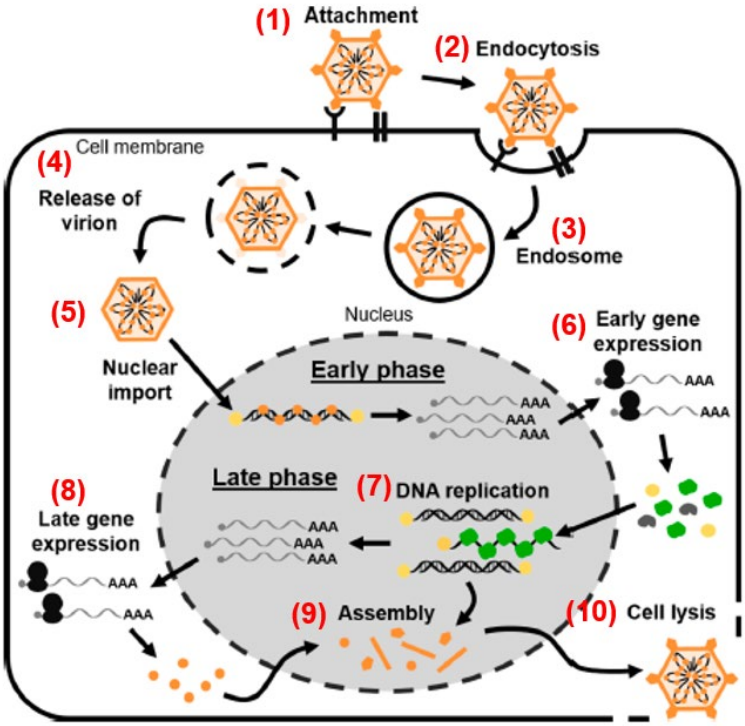

Figure 3: Overview of the adenovirus replication cycle (Charman et al., 2019).

3.4 Mutation and recombination of adenovirus

70. AdV DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999). In addition, AdVs do not have the machinery for efficient integration into the host genome and therefore AdVs exhibit extremely low levels of integration i.e., integration is a rare event (Harui et al., 1999; Desfarges and Ciuffi, 2012; Hoppe et al., 2015; Dehghan et al., 2019). However, random integration of virus DNA into the host genome has been observed in very rare cases (Harui et al., 1999; Stephen et al., 2008).

71. 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 a process called 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). However, bioinformatics analysis suggested that HAdV-E4, a species E adenovirus, was a result of a recombination event between species B and C (Gruber et al., 1993).

72. Bioinformatics 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). This is unlike the largest species HAdV-D, where homologous recombination in these regions were commonly associated with the large diversity of serotypes (Robinson et al., 2011; Robinson et al., 2013; Singh et al., 2013). The hexon protein is a major constituent of the viral capsid and is suggested to be critical for the development of adenovirus vaccines by forming the serum neutralisation epitope; the penton and fibre 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 to alter its cell tropism and alter its ability to evade the immune system.

73. In addition, bioinformatics 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 (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).

3.5 Epidemiology

3.5.1 Host range and transmissibility

74. Humans are the natural host for HAdVs (Custers, 2020). Experimentally, mice, cotton rats and rabbits have been infected with HAdVs to study adenovirus-induced disease (Ismail et al., 2019). Although used in animal models, 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.

75. Transmission of HAdVs from an infected individual is primarily via direct contact with conjunctival secretions, inhalation of aerosols or the faecal-oral route (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Khanal et al., 2018; CDC, 2019b). The virus can also be spread indirectly via contact with infected 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

76. 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 or ocular 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).

77. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing two HAdV serotypes (HAdV-E4 and HAdV-B7). 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

78. 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 4. This data is analysed 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).

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

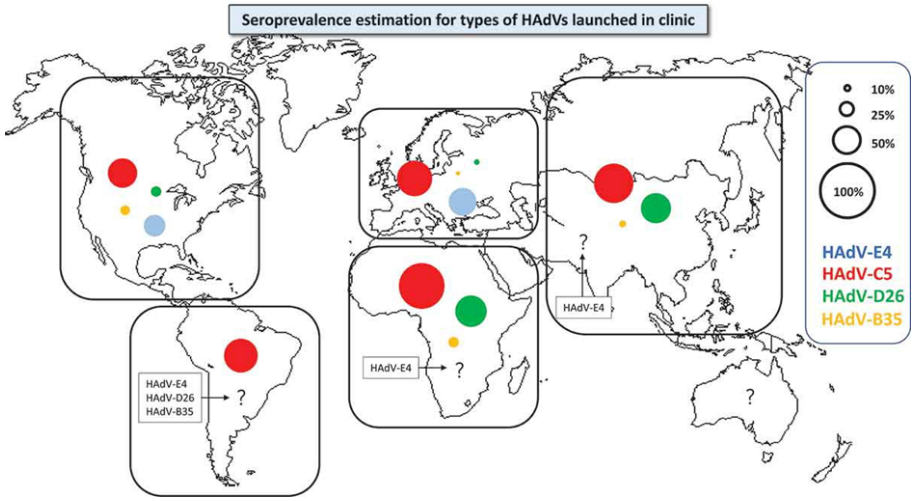

Figure 4: Seroprevalance for adenovirus types used in the clinic (Mennechet et al., 2019)

3.5.4 Control, environmental stability and decontamination methods

80. 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 adenovirus-specific drugs to treat the infection (Waye and Sing, 2010a; CDC, 2019a).

81. AdVs 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). AdVs are also found to be resistant to UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003), thus supporting survival in treated wastewater and sewage, river, ocean and swimming pool water as well as drinking water (Public Health Agency of Canada, 2014).

82. AdVs 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).

83. HAdVs have been detected in various waters worldwide including wastewater, river water, drinking water, ocean and swimming pools (Allard and Vantarakis, 2017). HAdVs are more frequently 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).

84. AdVs are found 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 GM vaccine - nature and effect of the genetic modification

85. The GM vaccine consists of a single-cycle replication HAdV-C6 vector that has been genetically modified to produce a modified SARS-CoV-2 spike glycoprotein (SC-Ad-1). The vector is able to replicate its genome and transgene, but is unable to form a mature infectious particle due to the lack

of the IIIa protein (pIIIa). The GM vaccine is designed to provide protection from infection with SARS-CoV-2 which causes COVID-19 disease.

4.1 The genetic modifications

86. The HAdV-C6 vector has been modified by deletion of two regions; a 1758 base pair (bp) *IIIa* gene deletion; and a 2940 bp deletion of most of E3 region resulting in deletion of immune evasion ORFs 6.7k, 19k, 11.6k, 10.4k, 14.5k, and 14.7k, and the deletion of the E4 UXP ORF. To produce the GM vaccine (SC-Ad6-1), a mammalian expression cassette containing a human cytomegalovirus (CMV) promoter, 3 short hairpin ribonucleic acid (shRNA) target sequence, a Zeocin selectable marker, a simian virus 40 (SV40) polyadenylation signal and a gene encoding a modified full length SARS-CoV-2 spike protein (S protein) (Wuhan isolate; NCBI reference sequence YP_009724390.1) was inserted between the fiber and E4 locus of the HAdV-C6 vector.

Figure 5: Synthetic SC-Ad6-1 expression cassette with the IIIa and E3 genes deleted and the SARS-CoV-2 spike transgenic cassette.

87. During production of the GMO, the missing pIIIa is provided *in trans* in a cell production system. The applicant states that there is no homology between the provided protein and the flanking *IIIa* deletion in the GMO. The cell banks will be tested for replication-competent adenovirus and the final manufactured GMO could be sequenced to confirm the absence of the *IIIa* gene.

88. The S protein is comprised of the receptor binding (S1) and membrane fusion (S2) subunits. The S1 receptor binding domain has been shown to be responsible for host range and tropism (Huang et al., 2016; Li, 2016; Letko et al., 2020; Mousavizadeh and Ghasemi, 2020; Samrat et al., 2020). The S1 subunit facilitates the virus attachment via angiotensin-converting enzyme 2 (ACE2) receptors present on human cells and subsequent fusion of virus and cell membranes, mediating the entry of SARS-CoV-2 into the target host cells. The fusion of the S protein to the host cell membrane is mediated by cleavage of the S protein by host cell proteases, the transmembrane protease/serine subfamily member 2 (TMPRSS2) and furin at specific cleavage sites at the S2' or between the S1 and S2 subunits respectively (Sternberg and Naujokat, 2020). Modifications have been made to the genetic sequence of the S protein in this GMO at specific protease cleavage sites to stabilise the S protein in its pre-fusion state (Bos et al., 2020; Sternberg and Naujokat, 2020).

89. The roles of the SARS-CoV-2 S protein in receptor binding and entry into the host cells make it an attractive vaccine candidate and many developing COVID-19 vaccines have been designed based on it (Bos et al., 2020; Folegatti et al., 2020; Logunov et al., 2020; Sadoff et al., 2020; Samrat et al., 2020; Zhu et al., 2020).

4.2 Effect of the genetic modification

90. The removal of the *IIIa* gene prevents the GMO from forming a mature infectious particle by interfering with the capsid packaging of the virus (Section 3.2). However, because the E1 gene is still intact, the GMO is still able to replicate its genome and transgene. The deletion of the E3 genes reduces the capacity of the GMO to evade the host immune response and the deletion of the E4 UXP ORF is known to cause a mild growth retardation in AdV (Tollefson et al., 2007).

91. The shRNA target sequences are present in the GMO to improve the production yield of the GMO. During the production process, the production of the spike protein by the GMO can be suppressed by shRNA binding to these target sequences when provided in *trans* by helper cells.

However, in this case, the expression of spike protein did not affect the yield of the GMO and hence the helper cells used to produce this GMO were not designed to provide shRNA in *trans*. In addition, the Zeocin selectable marker (which was used for the selection of recombinant bacteria during construction of the GMO) is retained in the GMO to maintain the larger genome size (closer to genome size to WT) to reduce the chance of recombination with a WT AdV.

92. The S protein inserted as a transgene allows the GMO to produce the S protein once it infects human cells. This would then induce an immune response in the host towards the S protein and build an immunity towards SARS-CoV-2.The insertion of the S protein does not interfere with the backbone of the vector or contribute to the generation of replication competent virus. The S protein is also not involved in the formation or the composition of the capsid of the HAdV-D26 vector and therefore is not considered to affect the tropism and host range of the vector.

93. As a result of these genetic modifications, the GMO is able to replicate its genome and transgene in the host cells and would induce an immune response in humans, but would not be able to form mature infectious particles that can further infect cells with the GMO.

4.3 Characterisation of the GMO

94. Data obtained from pre-clinical trials using the proposed GMO and from other pre-clinical trials using the same backbone/platform (SC-Ad6 vector) with different genes for a range of diseases has been used to characterise the GMO.

4.3.1 Genetic stability and molecular characterisation

95. The master cell bank (MCB) for the production of the GM vaccine will be tested for replication-competent adenovirus and the final GM vaccine will also be sequenced to confirm the absence of the *IIIa* gene.

96. AdV 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). In a separate study on immune-deficient mice, intravenous administration of replication incompetent AdV vector showed plausible low integration of the AdV vector into the host genome (Stephen et al., 2010). However, the authors did acknowledge that the most common route of vector delivery for AdV vectors (i.e. IM route of injection) would result in much lower incidence of gene transfer (Stephen et al., 2010). No clinical or human studies have shown integration of AdV vectors into the host genome.

4.3.2 Stability in the environment and decontamination

97. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Other recombinant AdVs (AdV expressing GFP) have been shown to have reduced capacity to survive in fresh surface water, cold water and dark sediments compared to wild-type AdVs (Rigotto et al., 2011; Elmahdy et al., 2018). Since the GMO is unable to replicate, it is likely that it would have similar or reduced survival and persistence in the environment compared to the parent organism and would degrade over time (see Chapter 1, Section 3.5.4).

98. 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).

4.3.3 Pre-clinical studies using SC-Ad6 and other replication deficient adenovirus vectors

99. *In vitro* studies comparing replication competent (RC)-Ad6, replication deficient (RD)-Ad6 and SC-Ad6 were carried out in cell lines from human alveolar basal epithelial (A549), mice liver (Hepa 1-

6), Syrian hamster kidney (HaK), rhesus macaques kidney (FRhK4) and primary human small airway epithelial cells (HSAECs) (Crosby and Barry, 2014; Crosby et al., 2015; Crosby and Barry, 2017). These studies demonstrated that SC-Ad6 vectors were able to replicate their genome and express the reporter protein encoded by the transgene to similar levels as RC-Ad6 vectors; and expression of the reporter protein was higher than that of RD-Ad6 vectors (Crosby and Barry, 2014, 2017). Similar to RC-Ad6 vectors, SC-Ad6 vectors subsequently kill the infected cells. However, they are unable to form infectious viral particles due to the lack of the IIIa protein (Crosby and Barry, 2014).

100. When injected IV into BALB/c mice, all three vectors types were detected in the liver. The RD-Ad6 vector genome and reporter protein levels remained relatively constant compared to the RC-Ad6 and SC-Ad6 vectors, which had higher reporter gene expression levels that peaked at day 2 post IV infection (Crosby and Barry, 2014). Although *in vitro* data between RC-Ad6 and SC-Ad6 vectors demonstrated similar genome replication, *in vivo* data in mice showed that SC-Ad6 replication and expression of the reporter transgene were 3-fold and 7-fold lower than RC-Ad6, respectively (Crosby and Barry, 2014). IM administration of HAdV-6 vectors resulted in reporter transgene expression in the liver in addition to expression at the site of injection (Weaver et al., 2011).

101. Syrian hamsters that had been intranasally (IN) inoculated with all three vector types, showed that the expression of the reporter protein encoded by the transgene to be restricted in the nasal areas, peaking at day 3 and returning to baseline by day 7, with expression from SC-Ad6 and RC-Ad6 being 7 and 12 times higher than RD-Ad6 vector, respectively (Crosby et al., 2015). Mice inoculated with other RD-adenoviral vectors with reporter genes were shown to distribute to the olfactory bulb, epithelial tissues in the lungs; and is not detected in the other tissues such as middle ear, brain, inguinal lymph nodes, ovaries, liver, spleen, kidneys, heart, thyroid gland, thymus, bone marrow, brain or the central nervous system (Lemiale et al., 2003; Damjanovic et al., 2008).

102. Antibodies against the reporter transgene and vectors can be detected at days 3, 6, 12, and at 24 weeks post-immunisation in both the serum and vaginal washes following one IN immunisation (Crosby et al., 2015). In addition, rhesus macaques inoculated orally (sublingual) with RC-Ad6 were able to generate antibodies towards the reporter transgenes.

103. This vector has been used for vaccine candidates for various diseases such as Ebola (Anguiano-Zarate et al., 2018), Influenza A (Crosby et al., 2017), HIV (Matchett et al., 2018; Matchett et al., 2019; Matchett et al., 2020b) and *Clostridium difficile* (Matchett et al., 2020a). These studies have been conducted in various animals including mice, Syrian hamsters, cotton rats and rhesus macaques. Various routes of inoculation (IM, IN and intravaginal) and prime boost methods (same or different route of inoculation) were tested. Overall, these studies demonstrated that the vaccine candidates triggered an immune response towards the peptide expressed by the vector and in some cases were effective in preventing the disease.

4.3.4 Pre-clinical studies using the GMO (SC-Ad6-1)

104. Pre-clinical studies using the GMO have been carried out and are described in the CCI Attachment of the RARMP, which is made available to the prescribed experts and agencies that are consulted on the RARMP.

4.3.5 Clinical trials using SC-Ad6 and other replication deficient adenovirus vectors

105. One clinical trial using the GMO (SC-Ad6-1) via an IM route of administration is currently being assessed by the Regulator and would be carried out prior to the IN route of administration. No clinical studies have been carried out using SC-Ad6-1 in an IN route of administration. Although, there is no available clinical trial data from SC-Ad6 vectors as yet, many RD HAdV vectors have been used as COVID-19 vaccine candidates and showed a good safety profile (Logunov et al., 2020; Sadoff et al., 2020; Zhu et al., 2020; Sadoff et al., 2021).

106. Samples (tonsils, nasal and bronchial brush, bronchoalveolar lavage, blood, stool, urine, saliva) taken from patients on days 1, 3, 7, 14, 21 and 28 post-intranasal inoculation with a RD-AdV vector

expressing cystic fibrosis transmembrane conductance regulator (CFTR) showed no detection of infectious AdV vector (Bellon et al., 1997). However, vector DNA is detected in the nasal and bronchial brush, bronchoalveolar lavage, saliva and tonsils up to 21 days post- infection (Bellon et al., 1997). In a separate study, only one out of twelve patients had a positive culture in the nostrils and rectal samples on day 1 and 2 following inoculation (Knowles et al., 1995).

Section 5 The receiving environment

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

5.1 Site of vaccination

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

109. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and waste disposed of. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance with institutional policies based on Standard Precautions for handling potentially infectious substances and the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

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

5.2 Presence of related viral species in the receiving environment

111. 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.

112. 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 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 animals and humans of all ages 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.

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

114. Adenovirus-based vaccines were previously used for COVID-19. Therefore, similar adenovirus-based vectors (e.g. AstraZeneca and Janssen COVID-19 vaccines) could be present in people or the environment.

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. All of the genes in the GMO would be functionally similar to ones present in the naturally occurring SARS-CoV-2 virus. The genes introduced into the GMO were derived from naturally occurring SARS-CoV-2 virus and so similar genetic material will already be present in the environment.

Section 6 Previous authorisations

117. This GMO has not been previously authorised for commercial supply in any region or country.

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 4). 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.

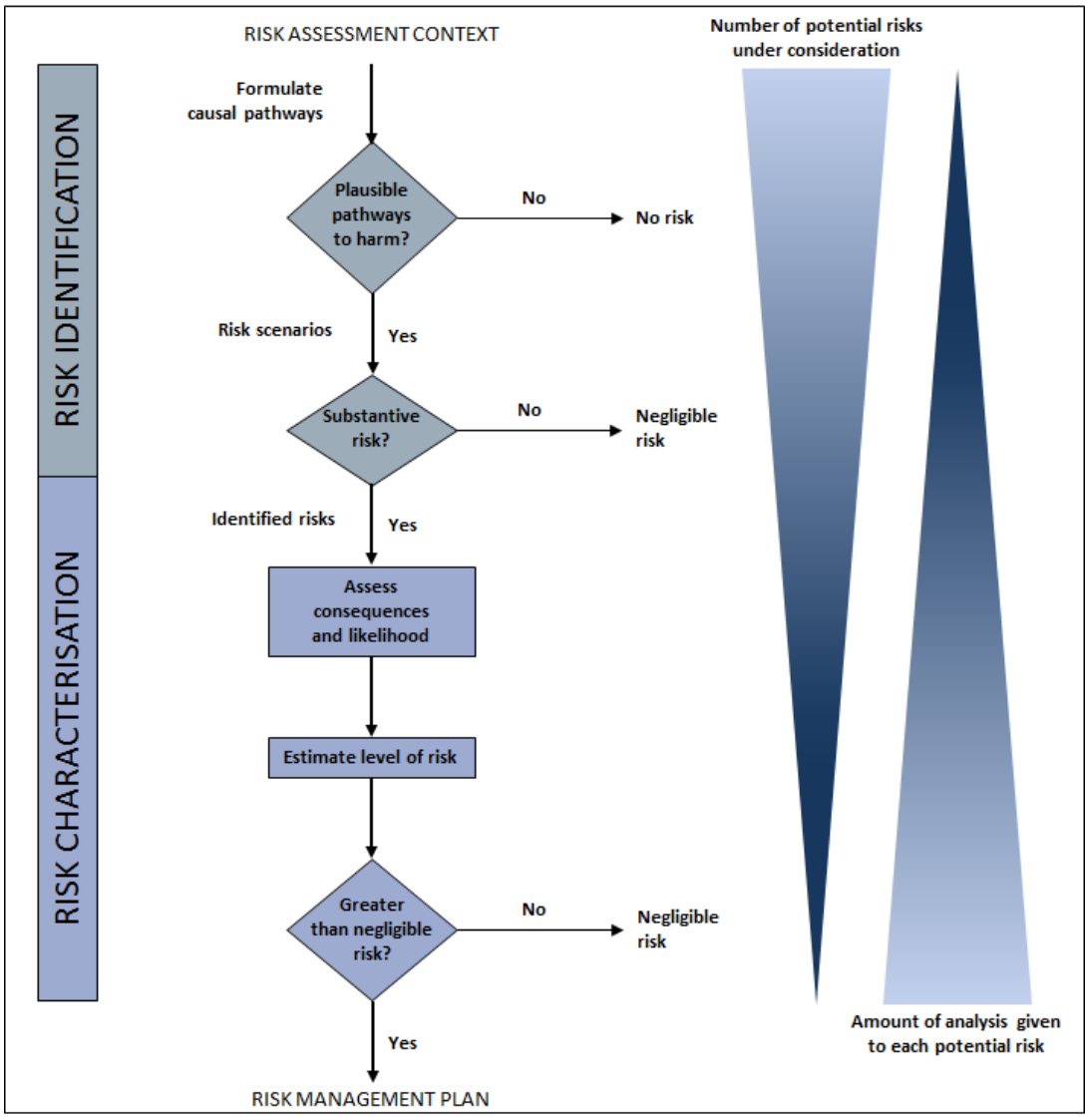

Figure 4: The risk assessment process

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 4), 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 5):

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.

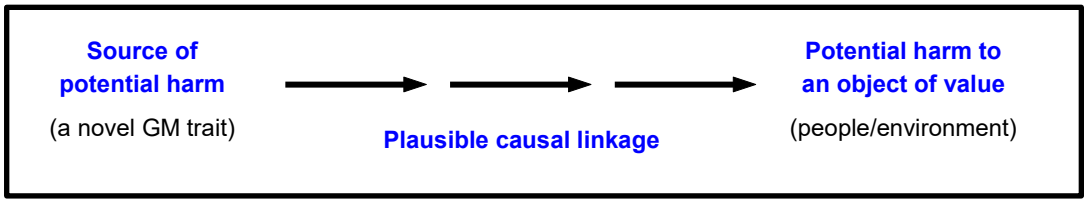

Figure 5: Components of a risk scenario

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. The GMO contains a zeocin antibiotic resistance gene in the transgenic cassette. It is plausible that this resistant gene could be transferred to resident gut bacteria present in the participant or subsequently shed in the environment. However, this gene is of no consequence clinically in animals or humans, since no antibiotics used in animals or humans are inactivated by this gene product. Zeocin is typically used in research for the selection of recombinant bacteria. As discussed in Chapter 1, Section 4.3.5, it is unlikely that any live GMO would be shed into the environment. The ingestion of the GMO in the course of the administration is unlikely to result in the transfer of the resistant gene to resident gut bacteria in the trial participant. HAdV-Cs are sensitive to pH and unlikely to survive the acidic condition of the digestive tract. Therefore, the consequence of the zeocin antibiotic resistance gene being horizontally transferred to compatible bacteria in the trial participant or the environment will not be considered further.

127. 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.

128. 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.

129. As discussed in Chapter 1, Section 4.1, the GMO has been modified by the deletion of the *IIIa* gene; partial deletion of E3 and E4 genes; and by insertion of a gene encoding a modified SARS-CoV-2 spike protein. These introduced genes and their encoded proteins are considered further as a potential source of risk.

2.2 Causal pathway

130. 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.

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

132. 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.

133. 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 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.

134. Recombination between different vaccines using adenovirus platforms is highly unlikely because it is improbable that two or more vaccines are administered at the same time with the same route (IN); the lack of homology between adenoviral vectors further reduces the possibility of recombination; and the viral vectors would most likely be cleared before a second dose is administered. Thus, the potential of recombination between adenoviral vectored vaccines will not be further discussed.

2.3 Potential harms

135. 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

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

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

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

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people 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	Adverse immune reactions (e.g., cytokine storm)	No	• Although the GMO can replicate its genome and transgene, it would not produce further viral particles to sustain an infection. Therefore, the probability of the GMO being shed would be low. • Any reactions to the spike protein would be transient and the GMO would be

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		(b) During import, transport or storage of the GMO (c) Disposal of the GMO (d) Nasal discharge or shedding of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein			rapidly cleared by the immune system. • The dose received through accidental exposure would be far smaller than that administered during vaccination and will not be sufficient to induce an adverse immune response. • Import, transport, storage and disposal will follow well established procedures. • HAdV-C are predominantly respiratory viruses that are sensitive to pH levels in the stomach.
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 as described in Table 2	Adverse immune reactions (e.g., cytokine storm) Disease in people or animals	No	• There would be a low probability of continuous complementation of GMO by AdV because AdV infection is often self-limiting. • Competition with WT AdV for proteins that may complement the GMO. • Low reported HAdV infection rates (including HAdV-C) in Australia. • Recombination among adenoviruses is usually restricted to the same species and are very rare events. • Homologous recombination would be highly unlikely due to the packaging limit of the Sc-Ad-1 vector. • Homologous recombination in regions with high homology, which are 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.

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
					• Multiple recombinations are required to produce a replication competent 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 cannot persist and replicate inside or outside the host, hence GMO is unable to maintain a stable presence in the environment for long periods. • GMO not known to naturally infect non-human hosts and does not infect aquatic species.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through these events: (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO (d) Nasal discharge or shedding of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein
Potential harm	Adverse immune reactions (e.g., cytokine storm)

Risk source

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

Causal Pathway

139. People (person handling the GMO) 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, preparation and intranasal administration of the GMO. It could also be transmitted when contaminated surfaces, such as hands or tissues, make contact with mucous membrane or via needle stick injury. There is also a possibility that the GMO could be shed from the nasal mucus membrane following administration of the GMO. This exposure could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

140. As discussed in Chapter 1, Section 2.1, 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, aerosols formation during administration, preparation and/or due to breakage/spillage of GMO onto surfaces during preparation and administration; or the discharge (e.g. sneezing) of the initial inoculum containing the GMO by the trial participant 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 vaccination services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and the *Australian Immunisation Handbook.*

141. Experiments using radio-labelled albumin as a vaccine surrogate to investigate the absorption of IN delivered vaccines demonstrated that the nasal spray was absorbed with halftimes of clearance ranging from 40-60 minutes, with a mean time of 50 minutes (Bryant et al., 1999). The trial participants are not expected to shed the GMO. However, there is a potential for the trial participants to discharge the initial inoculum containing the GMO following administration. Trial participants would be required to remain at the clinical trial site for 4 hours post-administration. Participants would also be advised to use a tissue to collect any nasal discharge (e.g. sneezing); to appropriately dispose the tissues used at the clinical trial site; and practice good hand hygiene. In addition, trial participants would also be instructed to dispose of any tissues used to wipe nasal secretions into a biohazard bag (provided) for the next 24 hours and return the bag to the clinical trial site at their next visit (Chapter 1, Section 2.1).

142. As part of the IN administration of the GMO, participants could inadvertently ingest some inoculum containing the GMO. Therefore, it is plausible that the GMO could enter the gut and be shed, resulting in the exposure of the GMO to other humans or animals. However, HAdV-Cs are predominantly respiratory viruses compared to HAdV-F, which causes gastrointestinal disease. A study of HAdV-F41 showed that HAdV-F41 is resistant to acid exposure while HAdV-C2 and –C5 demonstrated reduced infectivity after 5 mins of exposure to pH similar to the stomach (Favier et al., 2004). This was attributed to the resistance of the short fiber proteins in HAdV-F to the low pH (pH 2) compared to HAdV-C (Favier et al., 2004). A separate study also demonstrated that HAdV-C5 has a reduced ability to infect differentiated epithelial cells and in rat jejunum compared to HAdV-F41 (Croyle et al., 1998). In addition, as discussed in Chapter 1 , Section 4.3.5, patients administered with a RD-HAdV for gene therapy did not display any shedding from 1 -28 days post IN administration. The GMO is also incapable of forming an infectious viral particle. Therefore, taking into account these factors, the GMO, which belongs to HAdV-C would most likely not persist or be shed through the gastrointestinal tract following IN administration.

143. Caregivers and healthcare personnel who come into close contact with vaccinated people may be inadvertently exposed to the GMO during administration via spillage or accidental aerosol formation from the atomiser. Caregivers and others exposed to the GMO in this way will only be expected to be exposed to low levels of the GMO. Furthermore, formation of replication-competent adenovirus or presence of the vector in healthcare personnel who came into close contact with patients have not been observed in studies using other replication defective adenovirus vectors, which looked into these parameters (Tursz et al., 1996; Schenk-Braat et al., 2007).

144. 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. The GMO is unable to replicate (either inside or outside the host), so viruses in the used vials could not multiply to reach an infective dose. Thus, the dose received through accidental exposure would be far smaller than that administered during vaccination. Therefore, even if an individual or animal is inadvertently exposed to the GMOs, they are unlikely to develop an adverse immune reaction.

145. 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 vaccine; and nasal secretions that may contain the GMO.

146. In addition, the requirements of participants to stay in the clinic for 4 hours post-administration of the GMO, to practice good hand hygiene and sneezing etiquette, would further minimise the potential exposure of other people and animals to the nasal secretions from the participants that may contain the GMO.

Exposure during import, transport and storage of the GMO

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

148. 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 also be handled in the same manner. These practices will lower the likelihood of unintended dispersal of the GMOs.

149. The risk of exposure to the GMO in other people and animals is highly unlikely because the GMO is unable to form infectious viral particles. In addition, no natural HAdV infections of non-human hosts have been described and no replication of HAdVs have been observed in animal models. Further, the presence of animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

150. Antiviral disinfectants would be used as decontamination and disinfection measures after administration of the vaccine or in the case of accidental spills during the supply of the GMO.

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

Exposure during disposal of the GMO

152. 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 GM vaccine are held;
- locations where the GM vaccine is administered.

153. 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 with these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

154. 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

155. 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.

156. The GMO is unable to produce further viral particles which are required to sustain an infection. In addition, any reactions to the spike protein would be transient and the GMO would be rapidly 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.

157. Increased expression of spike protein 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. These proteins are not known to be toxic to humans.

158. As mentioned in Chapter 1, Section 4.1, the SARS-CoV-2 virus enters a host's cells via the ACE2 receptor, which is involved in the renin-angiotensin-aldosterone system. When exposed to the GMO, there is a potential that the spike proteins produced would bind to ACE2, which can prevent the conversion of angiotensin II into angiotensin. This could result in more angiotensin II binding to the ATI1 receptor, which can lead to detrimental effects such as vasoconstriction and enhanced inflammation and/or increased angiotensin II expression in the lungs. However, there has not been any reported cases of such effects. Further, it is very unlikely that the amount of spike protein present in the replicative defective viral vectored vaccine can have a sustained effect on people. To date, vaccines that have used the spike proteins from SARS-CoV-2 have shown a good clinical safety profile (Folegatti et al., 2020; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al.; Zhu et al., 2020).

159. Vaccines against SARS-CoV-2 using the full length spike protein in replicative defective viral vectors including other HAdV based vaccine, have shown the ability to generate neutralising antibodies against SARS-CoV-2 (Folegatti et al., 2020; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al.; Zhu et al., 2020). As mentioned in Chapter 1, Section 4.3.3, pre-clinical studies using this GM vector (SC-Ad6), showed that it was also able to generate an antibody response towards the transgene it carries. Therefore, there is potential for these vaccines to cause antibody-dependant enhancement[3]-mediated viral entry or immunopathology via the generation of sub- or non-neutralising antibodies towards the spike protein (Arvin et al., 2020; Su et al., 2020). However, there has not been any reports of ADE associated with COVID-19 vaccine candidates expressing the spike protein to date. The administration of convalescent plasma from patients who had recovered from SARS-CoV-2 infection into 20,000 patients who had a high risk of severe COVID-19 disease showed low incidence of serious adverse events (Joyner et al., 2020). A recent study using this GM vaccine in hamsters did not show any evidence of ADE (van der Lubbe et al., 2021). Applicant has also provided additional unpublished data, which is in the CCI Attachment to the RARMP and which is made available to the prescribed experts and agencies that are consulted on the RARMP. Further, no ADE was observed with inactivated-whole SARS-CoV-1 (Luo et al., 2018) and DNA vaccine expressing SARS-CoV-2 S protein (Arvin et al., 2020). To date, there is no conclusive evidence demonstrating a risk of ADE in humans in relation to SARS-CoV-2 infection.

[3] Antibody-dependant enhancement (ADE) can occur when pre-existing sub- or non-neutralising antibodies towards a virus can enhance the viral entry into host's cells during secondary viral infections. This antibody-dependant enhancement mediated viral entry has been mostly documented in flaviviruses (e.g. dengue virus) but also observed in various viral infections such as HIV, Ebola and coronaviruses (e.g. MERS and SARS-CoV-1).

Conclusion

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

2.4.2 Risk Scenario 2

<table>
<tr><td>Risk source</td><td>GMO</td></tr>
<tr><td>Causal pathway</td><td>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
↙ ↘
<table><tr><td>Complementation of IIIa, E3 or E4 by AdV
⬇
<u>Production of GMOs:</u>
without immune-evasion properties that is capable of forming mature viral particles (IIIa)
OR
with immune-evasion properties that is unable to form mature viral particles (E3)
OR
with less viral replication capacity (E4)</td><td>Homologous recombination with AdV in spike gene, IIIa, E3, E4 or other regions of high homology
⬇
<u>Formation of:</u>
(i) WT AdV expressing S protein
OR
(ii) WT AdV that is unable to form mature viral particles (IIIa)
AND
GMO that is able to form mature viral particles (IIIa)
OR
(iii) WT AdV expressing E1 or E4 gene from HAdV-C6 (E1 or E4)
AND
GMO with E1 or E4 gene from WT AdV that is unable to form mature viral particles (E1 or E4)
OR
(iv) WT AdV with defective immune evasion properties (E3)
AND
GMO with altered immune evasion properties but still unable to form mature viral particles (E3)
OR
(v) Replication competent AdV or GMO with altered tropism</td></tr></table></td></tr>
<tr><td>Potential harm</td><td>Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals</td></tr>
</table>

Risk source

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

Causal Pathway

162. The transmission of GMO can occur by the pathways mentioned in Risk Scenario 1 which could potentially result in transduction of host cells. If the person or animal exposed to the GMO has an existing infection of AdVs at the same time of exposure 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 an adverse immune reactions and/or disease in people or animals.

Complementation of pIIIa, E3 or E4 by AdV

163. As mentioned in Section 3.5.3, there is a high prevalance 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 *IIIa, E3 or E4* 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 form mature infectious viral particles with immune evasion properties in the host; or a GMO with immune-evasion properties that is unable to form mature viral particles; or a GMO with less viral replication capacity.

164. 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 missing *IIIa*, E3 and E4 genes in the GMO is very low.

165. Multiple copies of protein (IIIa, E3 and E4) would also be required for the formation of an infectious viral particle (Liu et al., 2010; Reddy et al., 2010; Reddy and Nemerow, 2014). As this complementation would usually be provided by WT AdV, there would also be direct competition with WT AdV to form a mature viral particle, which will limit the chances of complementation by these proteins enabling the GMO to form an infectious viral particle.

166. 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

167. 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 also requires the person or animals exposed to the GMO to be infected with a wild-type AdV at the same time. AdV 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 in the nasal passage. Licence conditions will be in place to limit and control the exposure of the GMO to other people or animals via inhalation or contact with mucus tissue via requirements around the wearing of PPE and other transport and disposal procedures.

168. 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). Therefore, 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. These GM recombinants are described in Table 2.

Table 2 Theoretical recombinants of GMO and wild-type Adenoviruses

Recombinant region	Resultant recombinant	Outcome	Likelihood
IIIa between • GMO • WT AdV	• Replication-competent GMO with *IIIa* gene • Attenuated AdV without the *IIIa* gene	• Replication-competent GMO that is still less immune evasive than WT, due to deletion of the E3 region • Attenuated AdV	Unlikely as these regions are not high homology region
E3 between • GMO • WT AdV	• Attenuated GMO with intact E3 region • Replication-competent AdV without the E3 region	• Attenuated GMO with restored immune-evasion properties. However, cannot produce mature viral particles due to deletion of the *IIIa* gene. • Replication-competent AdV without immune evasion properties	Unlikely as these regions are not high homology region
IIIa and E3 between • GMO • WT AdV	• Replication-competent GMO with intact *IIIa* gene and E3 region • Attenuated AdV without the *IIIa* gene and E3 region	• Replication-competent GMO with restored immune evasion properties. • Attenuated AdV without immune evasion properties	Unlikely as these regions are not high homology region
Transgenic cassette between • GMO • WT AdV	• Attenuated GMO without the transgenic cassette • Replication-competent AdV with the transgenic cassette	• Attenuated GMO that is still less immune evasive than WT, due to deletion of the E3 region • Replication-competent AdV expressing the spike protein	Unlikely
Theoretical regions that may recombine (E1 and E4) • GMO • WT AdV	• GMO or WT with different E1 genes • GMO, with E4 *UXP* gene • WT AdV with without *UXP* gene	• No phenotypic changes are expected for GMO and WT • GMO with similar growth rate to WT • Mild retardation in WT AdV growth	Unlikely

169. The transgenic cassette containing the gene encoding the spike protein is inserted between the fiber and E4 flanking region using site specific recombination methods. Therefore the likelihood that recombination between the GMO and WT AdV resulting in WT AdV receiving the spike gene is very unlikely.

170. The GMO could theoretically receive the *IIIa* gene from WT AdV and gain the capacity to form mature viral particles but still lack immune-evasive properties and viral replication capacity due to the absence of E3 and E4 genes respectively. Previous work has shown that other group C adenoviruses (HAdV-5) can regain the deleted gene if the resultant genome does not exceed 105% of the original size. However, adenoviruses that even exceed 100% are less robust and are prone to rearrangement to reduce the genome, indicating that there is a limit to DNA packaging (Bett et al., 1993). Compared to the unmodified HAdV-6, the genome size of the GMO is 101%. Therefore, it is unlikely that the GMO could receive the *IIIa* gene from WT AdV due to the packaging capacity of the GM vector and the low likelihood of recombination events in the *IIIa* region as discussed in Chapter 1, Section 3.4.

171. The GMO could also regain its E3 gene and therefore its immune-evasive properties but remains unable to form mature viral particles from the lack of pIIIa. The resulting GMO would still be cleared by the immune system.

172. 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.

173. Homologous recombination could potentially occur in the E1 and E4 regions. But since the GMO has the E1 and most of the E4 regions intact, it is unlikely to have a major impact on the characteristics of the GMO and WT AdV if any recombination is to occur.

174. Homologous recombination could potentially occur at the hexon, penton and fibre regions of AdV, resulting in the GMO with an altered cell tropism but still remaining unable to form mature viral particles. However, homologous recombination in the hexon, penton and fibre regions is not common in HAdV-C.

Potential harm

175. If complementation were to occur, the GMOs produced in the host cells may be able to form infectious viral particles and possibly increase the persistence of the GMO in the host, resulting in increased expression of spike proteins. Similarly, homologous recombination would increase the expression of the introduced genes i.e., spike proteins. The exposed individuals may generate a stronger antibody response for the spike protein of SARS-CoV-2 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.

176. If homologous recombination were to occur it could result in the formation of replication competent GMO. The person exposed 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

177. The exposure of people to a GMO which has acquired the *IIIa* gene, transferred spike proteins to other AdVs or other recombinant viruses resulting in adverse immune response or disease in people or animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

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

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

Causal Pathway

179. The GMO could be released into the environment through a spill during transport, storage, or disposal or shedding from 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.

180. 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.

181. In the event of a spill without correct decontamination with suitable disinfectants, the GMO could potentially persist/survive 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). Accidental spillage that is not decontaminated could result in the release of the GMO and/or recombinant viruses into the environment. 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.

182. Accidental spill/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. Similar to the parent organism, the GMO could survive in the environment. However, due to its non-replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods and is unlikely to spread. The impact of survival of the GMO in an aquatic environment is likely to be very low as the GMO is replication incompetent and would eventually degrade.

183. 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. Therefore it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source.

184. 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 unable to form mature viral particles, is not known to infect and replicate in animals animal models respectively, the likelihood of infecting other mammals from exposure to the GMO is very low.

185. 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

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

Conclusion

187. 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. Therefore, it does not warrant further assessment.

Section 3 Uncertainty

188. Uncertainty is an intrinsic part of risk analysis[4]. 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.

189. 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.

190. 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.

191. Although the GMO is unlikely to shed based on prior data using similar adenoviral vectors, there is no available clinical bio-distribution and shedding data for this GMO as this is a first in human clinical trial.

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

[4] 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

193. 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.

194. 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.

195. 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.

196. 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.

197. 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, which will prevent it from multiplying in other cells;
- the GMO is unlikely to be shed from the vaccine recipients;
- the likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccines) 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.

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[5]

[5] 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

198. 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.

199. 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.

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

201. 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

202. 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

203. 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

204. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Avance. 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 Avance

205. The proposed clinical trial would involve a maximum of 1000 participants within Australia, and most dealings with the GMOs would take place in medical facilities such as clinical trial units, hospitals, GP surgeries and analytical laboratory facilities. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMOs. The applicant has proposed to complete the study within 5 years of commencement. Conditions maintaining the risk context and proposed limits of the trial such as the maximum number of trial participants and duration of the study and have been included in the draft licence.

206. 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.

207. 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.

208. 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 vaccination with the GMO;
- agree to abstain from donating blood, sperm, ova or organs for 90 days after the last vaccination with the GMO.

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

210. 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 attenuated adenovirus vectors is expected to be minimal and occur for at most a few days. Due to the IN mode of administration and the attenuated nature of the GMO, sexual transmission of the GMO from the trial participants is unlikely. Therefore, use of contraception and a ban on donation of gametes is not required as a licence condition. However, the GMO could be present in small amounts in the blood and has known tropism for the liver. Using the conservative timeframe of 90 days, as proposed by the applicant, abstinence from blood or organ donation would 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 90 days after the last dose of the GMO that they will not donate blood or organs.

211. 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.

212. When the GMO is administered via the IN route, there is a potential for the inoculum to be sneezed out. Given this, draft licence conditions include, requirement of participants to remain on site for at least 4 hours; and instructions provided to participants on proper hand hygiene and

sneezing etiquette. This would include sneezing into tissues and proper disposal of tissues into the provided biohazard bags for 24 hours after IN administration with the GMO.

213. 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.

214. Conditions are included in the draft licence requiring the licence holder to ensure that all GMOs, including material or waste that has been in contact with the GMO, within the clinical trial site, are decontaminated by autoclaving, chemical treatment or by high-temperature incineration. Draft licence conditions require that the licence holder must ensure that the GMO, or material or waste that has been in contact with the GMO, that is to be destroyed by external service providers, is through a clinical waste stream. This is considered satisfactory, provided that the licence holder is only permitted to engage persons who can adhere to appropriate standards to conduct the dealings, as described in Paragraph 215.

215. 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 also 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.

216. 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 written under the condition explains that compliance may be achieved by only engaging persons who are required to adhere to appropriate standards to conduct the dealings.

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

218. 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

219. 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 1000 trial participants, which are to be conducted at clinical trial sites;
- restrict access to the GMO;
- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements;
- ensure appropriate PPE is used;
- restrict personnel permitted to administer the GMO;
- requiring decontamination of the GMO and materials and equipment that have been in contact with the GMO at clinical trial sites using effective disinfectants or disposal using a

certified waste contractor in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation;
- transport and 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

220. 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

221. 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.

222. 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.

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

3.2.2 Contingency plans

224. Should a licence be issued, Avance 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

225. 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, Avance 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

226. 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.

227. 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

228. 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.

229. 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.

230. 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

231. 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 inoculated trial participants at the trial sites.

Section 5 Conclusions of the consultation RARMP

232. 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.

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

Chapter 4 Draft licence conditions

1. In this licence:

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

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

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

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

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

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

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

2. In this licence:

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

'Analytical facility' means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC), and conforming to the AS/NZS 2243.3:2010 Safety in Laboratories: Microbiological Safety and Containment, particularly in relation to the handling of human diagnostic specimens.

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

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

(a) chemical treatment;

(b) autoclaving;

(c) high-temperature incineration; or

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

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

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

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

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

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

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

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

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

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

'Regulator' means the Gene Technology Regulator.

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

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

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

Holder of licence

3. The licence holder is Avance Clinical Pty Ltd.

Remaining an Accredited Organisation

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

Validity of licence

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

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

Persons covered by this licence

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

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

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

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

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

Description of GMOs covered

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

Dealings authorised by this licence

11. The dealings authorised by this licence are to:

(a) import the GMO;

(b) conduct the following experiments with the GMOs:

i) prepare the GMO for administration;

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

iii) collect Samples from trial participants;

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

(c) transport the GMO; and

(d) dispose of the GMOs;

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

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

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

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

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

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

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

(c) the surrender of the licence.

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

Monitoring and audits (section 64)

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

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

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

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

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

Note1: For the purposes of this Condition:

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

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

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

Note 3: Additional information includes any changes at a Clinical trial site, which might increase the likelihood of dispersal of the GMOs.

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

Note: Information required under Condition 18 may be provided to External service providers who are engaged solely for storage and transport of the GMO through labelling of the outermost container of the GMOs in accordance with Condition 34(a).

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

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

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

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

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

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

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

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

Note: The licence may be made available electronically.

Limits on clinical trials conducted under this licence

22. A maximum of 1000 trial participants may be inoculated with the GMO under the licence.

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

Conditions about trial participants

24. 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.

25. The licence holder must ensure that pregnant and breastfeeding women are excluded from being selected as trial participants.

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

(a) practice proper hand hygiene and collect any nasal secretion into tissues for the first 24 hours post- administration; and

(b) dispose of used tissues into biohazard bag provided; and

(c) return the biohazard bags during the follow up visit post-administration; and

(d) not donate blood or organs for 90 days after the last dose of the GMO.

Conditions related to the conduct of the dealings

27. 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.

28. 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 at facilities which adhere to appropriate standards and guidelines, e.g. those developed by the National Pathology Accreditation Advisory Council for pathology practices, or the National Safety and Quality Health Service (NSQHS) Standards.

Preparation and administration of the GMOs and collection of samples

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

30. 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 38(a).

31. For the purposes of Condition 28, the work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

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

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

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

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

(e) following administration of the GMO, the trial participant must remain within the Clinical trial site for a minimum of 4 hours;

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

Transport, storage and disposal of the GMOs

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

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

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

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

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

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

(a) GMOs are 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 on how to clean up a spill, as per the contingency plan in Condition 37; and

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

(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 GMOs can be accounted for and that a loss of GMOs during transport or failure of delivery can be detected; and

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

(g) For the purposes of transport entirely within a building, where the GMOs are accompanied by authorised persons for whom Condition 18 has been met, Conditions 34(a)iii), 34(a)iv) and 34(c) do not apply.

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

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

Contingency plans

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

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

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

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

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

Notification and reporting

*Note: Notices may be by email to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at **Attachment B**.*

38. Prior to first administering the GMO at each Clinical trial site, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

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

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

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

(d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Conditions 40(b) and 40(c);

(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 28 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.

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

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

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

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

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

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

41. 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: 184

Full Title: Clinical trial with a genetically modified human adenovirus as a vaccine for the treatment of COVID-19

Organisation Details

Postal address: Avance Clinical Pty Ltd
Level 1, 2 Ann Nelson Drive
Thebarton,
South Australia, 5031

Phone No: (08) 8159 6388

GMO Description

GMOs covered by this licence:

Human adenovirus C serotype 6 modified by introduction of the spike protein sequence of SARS-CoV-2 (Wuhan isolate) and deletion of the *IIIa* gene and the E3 region

Parent Organisms:

Common Name: *Human adenovirus*

Scientific Name: *Human adenovirus C serotype 6 (HAdV-6 Strain Tonsil 99; American Type Culture Collection (ATCC) (VR-1083)*

Modified traits:

Categories: Vaccine

Description: The GMO, is an attenuated human adenovirus derived from species C serotype 6. It has been modified to express the spike protein sequence of SARS-CoV-2 (Wuhan isolate), which will stimulate the immune response when administered as a vaccine. Attenuation has been achieved by deletion of the *IIIa* gene and the E3 region. 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 codon optimised gene coding for the spike protein of SARS-CoV-2 Wuhan isolate (NCBI reference sequence YP_009724390.1) • 3x short hairpin ribonucleic acid (shRNA) target sequences • LoxP-ZeoR-LoxP (LZL) • SV40 polyadenylation sequence Deletion of: • *IIIa* gene and E3 region
Function	• CMV – Activates transgene expression • SARS-CoV-2 – immunomodulatory - Mammalian-expression of SARS-CoV-2 viral spike protein • shRNA – Targeted during virus manufacture to supress transgene (SARS-CoV-2 viral spike protein) production • LZL – For bacterial selection during GMO development, retained to maintain an increased genome size • SV40 – Termination sequence for protein expression • *IIIa gene* – deletion results in adenovirus attenuation • E3 region – deletion reduces adenovirus immune evasion

Purpose of the dealings with the GMOs:

To conduct clinical trials assessing the safety, tolerability, immunogenicity and efficacy of a genetically modified human adenovirus based vaccine to prevent COVID-19.

Attachment B

Prior to the commencement of the trial	Condition	Timeframe for reporting
A Compliance Management Plan for each trial site, including: • the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; • the key persons responsible for the management of the trial at the site; • the IBC associated with the site (if any) that has been notified of the trial; • the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Condition 40(b), (c); • details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; • the person(s) or class of persons administering the GMO; • where, within the site, the GMO is expected to be administered; • expected date of first administration; and • how compliance with Condition 28 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO	38	Prior to the first administration of the GMO at the Clinical trial site
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	15(a), (c)	As soon as the licence holder becomes aware
Information related to any contravention of the licence by a person covered by the licence	15(b)	As soon as the licence holder becomes aware
Any relevant conviction of the licence holder	16(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	16(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately
Any Serious adverse event which may be related to the GMO	40(a)	As soon as reasonably possible
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	40(b), (c)	As soon as reasonably possible after becoming aware of the event
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	40(d)	As soon as reasonably possible after

Prior to the commencement of the trial	Condition	Timeframe for reporting
		becoming aware of the event
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	41	Within a timeframe stipulated by the Regulator

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Australian Government
Department of Health
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan for

DIR 184

Clinical trial with a genetically modified human adenovirus COVID-19 vaccine

Applicant: Avance Clinical Pty Ltd

June 2021

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Summary of the Risk Assessment and Risk Management Plan

for

Licence Application DIR 184

Decision

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a genetically modified (GM) COVID-19 vaccine. It qualifies as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Avance Clinical Pty Ltd (Avance) proposes to conduct a clinical trial to evaluate the safety and tolerability of genetically modified human adenovirus serotype 6 (HAdV-C6) as a GM vaccine to treat COVID-19 in adults. This clinical trial involves the intranasal administration of the GM vaccine, which is different to the intramuscular (IM) administration of current COVID-19 vaccines.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus discovered in December 2019 in Wuhan, China and is the cause of the COVID-19 disease. The World Health Organization (WHO) declared the outbreak a pandemic on 11th March 2020 and as of 14th June 2021, there have been over 3.8 million deaths reported worldwide.

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, Avance will require authorisation from TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* and with the *Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed supply of the GM vaccine poses negligible risks to human health and safety and the environment, and that any risks posed by the dealings can be managed by imposing conditions on the clinical trial.

The application

Application number	DIR-184
Applicant	Avance Clinical Pty Ltd
Project title	Clinical trial with a genetically modified human adenovirus COVID-19 vaccine[1]
Parent organism	Human adenovirus 6 (HAdV-C6)

Introduced gene and modified trait	• Deletion of:
	  ○ *IIIa* gene (stops virus multiplying)
	  ○ Large portions of E3 gene (increases immune response to virus)
	  ○ E4 UXP ORF (reduce virus growth)
	• Insertion of a gene encoding the SARS-CoV-2 spike protein (expresses spike protein)

Principle purpose	The proposed trial is a phase I study designed to evaluate the safety, tolerability, immunogenicity and efficacy of SC-Ad6-1 as a second generation, prophylactic vaccine to prevent COVID-19.
Previous clinical trials	This is a first in human clinical trial using an intranasal route.
Proposed locations	Clinical trials will be conducted at clinical trial sites and hospitals within Australia.
Proposed limits and controls	• Import, transport and storage of the genetically modified organism (GMO) will be carried out according to Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* appropriate for PC1 GMOs • The GMO will be administered to trial participants in a suitable medical facility setting. • Staff handling the GMO will be trained and use personal protective equipment. • Waste that may contain the GMO will be disposed of via the clinical waste stream. • Participants will be held at clinical trial site for at least 4 hours after administration and sent home with detailed instructions post-treatment. • The clinical trial would enrol a limited numbers of trial participants (up to 1000 healthy volunteers in Australia at multiple sites).

Risk assessment

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

The risk assessment process considers how the genetic modifications and proposed activities conducted with the GMO might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application (including

[1] The title of the licence application submitted by Avance Clinical Pty Ltd is "Clinical development of an Adenovirus Vector SARS-CoV-2 vaccine (SC-Ad6-1-002) given by intranasal administration to prevent COVID-19".

proposed controls), relevant previous approvals and current scientific/technical knowledge. Both the short and long term impact are considered.

Credible pathways to potential harm that were considered include: the potential exposure of people and animals to the GMO; the potential for the GMO to recombine with other similar viruses or to get genes from those viruses; and the potential for the GMO to integrate into the host genome. The potential for the GMO to be released into the environment and its effects were also considered.

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

- The GMO is unable to form infectious viral particles, which will prevent it from multiplying in other cells and is very unlikely to be shed from the vaccine recipient;
- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccinees) would be minimised due to appropriate limits and controls, well-established import, transport, storage and disposal procedures; and
- The likelihood of complementation and recombination of 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 GM vaccine have been assessed as negligible, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management

The risk management plan describes measures to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan is given effect through licence conditions.

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

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Abbreviations

AICIS	Australian Industrial Chemicals Introduction Scheme
AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARTG	Australian Register of Therapeutic Goods
CAR	Coxsackie and adenovirus receptor
CCI	Confidential Commercial Information
COVID-19	Coronavirus infectious disease 2019
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
FSANZ	Food Standards Australia New Zealand
g	gram
GM	Genetically modified
GMO	Genetically modified organism
GP	General practitioners
GTTAC	Gene Technology Technical Advisory Committee
HAdV	Human adenovirus
HGT	Horizontal gene transfer
IATA	International Air Transport Association
IN	Intranasal
kb	Kilobase pair of DNA
LGA	Local government area
Mb	Mega base pairs
min	Minute
ml	Milli litre
NSW	New South Wales
OGTR	Office of the Gene Technology Regulator
Orf	Open reading frame
PCR	Polymerase chain reaction
QLD	Queensland
RARMP	Risk Assessment and Risk Management Plan
RNA	Ribonucleic acid
S	Spike
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
the Act	The *Gene Technology Act 2000*

the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
UK	United Kingdom
USA	United States of America
WA	Western Australia
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.

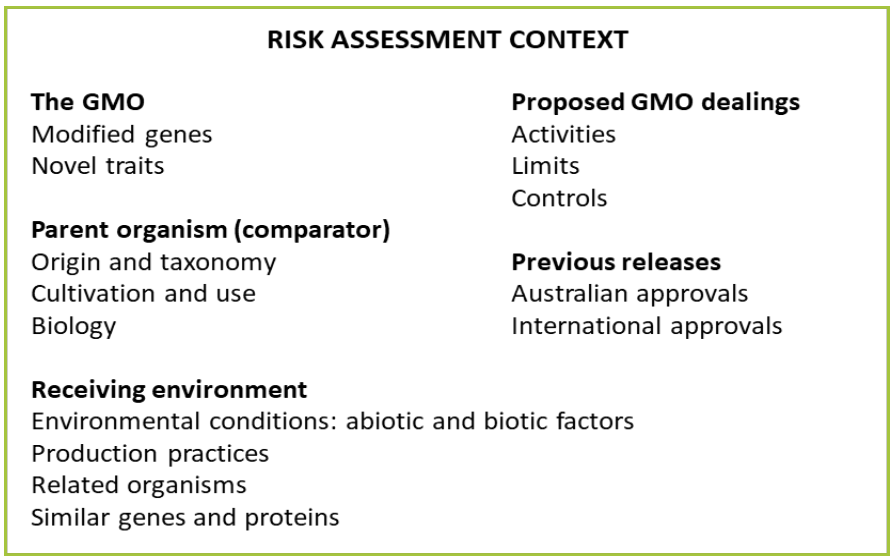

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

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 consultation RARMP from agencies - the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities or agencies prescribed in the Regulations, Australian local councils and the Minister for the Environment and from the public. The advice from the prescribed experts, agencies and authorities, and how it was taken into account, is summarised in Appendix A. Two public submissions were received and their consideration is summarised in Appendix B.

1.1 Interface with other regulatory schemes

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

9. Medicines and other therapeutic goods for use in Australia are required to be assessed for quality, safety and efficacy under the *Therapeutic Goods Act 1989* and must be included in the Australian Register of Therapeutic Goods. The TGA is responsible for administering the provisions of this legislation. Clinical trials of therapeutic products that are experimental and under development, prior to a full evaluation and assessment, are also regulated by the TGA through the Clinical Trial Approval (CTA) scheme or the Clinical Trial Notification (CTN) scheme.

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

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

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

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

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

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

Section 2 The proposed dealings

19. SARS-CoV-2 is a novel coronavirus discovered in December 2019 in Wuhan, Hubei province of China and is the cause of the COVID-19 disease. The rapid spread of this virus around the world led the World Health Organization (WHO) to declare the outbreak as a public health emergency of international concern (PHEIC) on the 30th January 2020 and eventually a pandemic on 11th March 2020 (WHO - Timeline of WHO's response to COVID-19, 2020).

20. The most common symptoms of COVID-19 are fever, tiredness and a dry cough, although some patients develop aches and pains, nasal congestion, runny nose, sore throat or diarrhoea. Symptoms are usually mild with gradual onset and about 80% of infected people recover without specific treatment. However, COVID-19 can cause complications such as severe pneumonia, acute respiratory distress syndrome, and multiple organ failure and in some cases, death. This is especially in older patients and those with pre-existing respiratory or cardiovascular conditions. There are currently two vaccines available for COVID-19 in Australia. As of 28 May 2021, 102 candidate vaccines are in clinical evaluation around the world (WHO -Draft landscape of COVID-19 candidate vaccine, 2021). These vaccines are based on a variety of platforms such as lipid nanoparticle encapsulated mRNA, DNA, adjuvant protein, inactivated virus particles and non-replicating viral vectors.

21. Avance Clinical Pty Ltd (Avance) is seeking authorisation to carry out a clinical trial to assess the safety, tolerability, immunogenicity and efficacy of a genetically modified (GM) vaccine (SC-Ad-1) as a second generation, prophylactic vaccine to prevent COVID-19.

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

(a) importation of the GMO;

(b) conduct the following experiments with the GMO:

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

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

iii. collect samples from trial participants;

iv. analyse samples from trial participants;

(c) transportation of the GMO;

(d) disposal of the GMO;

and the possession (including storage), supply or use of the GMO for the purposes of, or in the course of, any of the above.

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

23. The clinical trial is proposed to take place over a five year period from the date of issue of the licence. Up to 1000 participants in Australia would receive the GMO.

24. The trial would take place at clinical trial sites in Australia listed in Section 2.3.3.

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

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

26. 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:

- ensuring the GM treatment is administered by authorised, appropriately trained medical staff in clinical facilities;
- requiring that clinical trial staff handling and/or administering the GM treatment wear and use personal protective clothing and equipment;
- transport and storage of the GMO and any contaminated waste generated at a clinical trial site must be in accordance with the current version of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs;*
- requiring decontamination of materials and equipment that have been in contact with the GMOs at clinical trial sites using effective disinfectants or disposal using a certified waste contractor in accordance with standard clinical waste disposal practices, as required by relevant Australian and state legislation;
- providing participants with treatment instructions, and providing instructions to patients about good hand hygiene practices.

2.3 Details of the proposed dealings

2.3.1 Manufacturing of the GMO

27. The GMO will be manufactured overseas (the United States of America; USA) in accordance with current good manufacturing practice (cGMP). The master cell bank (MCB) will be tested for adventitious agents by sequencing to confirm the absence of the *IIIa* gene. The drug substance and the final GMO product will be tested to confirm identity, quality, purity, potency and safety.

28. The GMO would be supplied in a crimped, stoppered vial as primary containment and will be packaged into a secondary and tertiary shipping carton during transport. Information on the concentration and volumes of vials are indicated in a commercial confidential information (CCI) attachment to the RARMP[2].

2.3.2 Transport, supply and storage of the GMO

29. The GMO would be imported from the USA directly to clinical trial facilities. Biological samples (e.g. blood, urine and mucosal fluid) from trial participants that may contain GMOs would also be collected at various time points in the same clinical trial facilities and be transported to pathology laboratories for analysis.

30. The GMO would be transported into Australia from the USA and within Australia according to the OGTR's *Transport, Storage and Disposal Guidelines* (TSD) for PC1 organisms by commercial courier companies (e.g. World Courier). The details (name, address and contact information) of the consignor and consignee would be present on the outer packaging. The primary packaging (sealed vials) would be contained in an insulated container for validated shipping under frozen conditions (-20°C) in an outer package. The outer package would also be clearly labelled to indicate that it contains a GM COVID-19 vaccine.

31. For transport from the pharmacy to the designated treatment room, the GMO would be contained in primary and secondary containers; recorded to ensure no loss; and staff transporting the GMOs would be trained as in Section 2.3.11. A spill kit would be available at all times in the facilities in case of any spills.

[2] Confidential Commercial Information: Some details about the concentration and volume of vials have been declared as Confidential Commercial Information (CCI) under Section 185 of the Act. This information has been made available to the prescribed experts and agencies that were consulted on this application. CCI is not available to the public.

32. Storage of the GMO vaccine would be within the clinical trial sites centres (room temperature, fridge or freezer) with restricted access to prevent access by unauthorised personnel.

2.3.3 Clinical trial sites

33. The clinical trial using the GMO would be carried out in clinical trial sites. One trial site has been identified as Nucleus Network Pty Ltd, in Brisbane. The clinic has an attached PC2 facility (Cert-1916 at QIMR Berghofer Medical Research Institute, QLD). Other proposed clinical trial sites are CMAX (Adelaide, South Australia), Linear (Perth, Western Australia) and Scientia (Sydney, New South Wales). Hospitals and other medical facilities suitable for clinical trials and vaccine administration have also been proposed.

34. Cert-1916 is a PC2 Laboratory and does not have any additional conditions or exemptions required to comply with the *Guidelines for Certification of a Physical Containment Level 2 Laboratory*. The applicant has stated that Cert-1916 will only be used for storage. Dealings conducted under DNIR-614 also take place in Cert-1916. DNIR-614 is for 'Manufacture and characterisation of a *P. falciparum* NF54 Inducible Gametocyte Producer (NF54/iGP3) Master Cell Bank for use in Phase I Clinical Trials utilising the Induced Blood Stage Malaria Infection Model'. Genetic recombination between *P. falciparum* and adenovirus is not possible.

2.3.4 Trial design

35. The applicant proposes a phase 1/2 open-label, dose escalation study, which is to be conducted at multiple locations in Australia (as noted in Section 2.3.3). The details of trial design is indicated in a CCI attachment to the RARMP.

2.3.5 Selection of trial participants

36. Relevant inclusion criteria to be used by study site investigators include that:

- participants may be of any gender;
- participants must be between 18 and 65 years of age (inclusive) at screening;
- participants be medically healthy without clinically significant abnormalities at the screening visit, at check-in on Day -1 and pre-dose on Day 1, as determined by the Investigator;
- male trial participants;
    - if not surgically sterilised and, if engaging in sexual intercourse with a female partner who could become pregnant; must be willing to use a condom in addition to having the female partner use a highly effective contraceptive method from signing the consent form until at least 90 days after the last dose of the GMO;
- female trial participants;
    - must not be breastfeeding; and
    - must agree not to attempt to become pregnant; and
    - of childbearing potential, must have a negative serum pregnancy test at screening and agree to use an acceptable method of highly effective contraception from screening through to at least 90 days after the last dose of study; and
- participants must not donate blood, sperm, ova or organs until 90 days after the last dose of the GMO; and

- participants must be willing to avoid vaccination other than the study agent for 84 days after administration of final dose of the GMO (end of study).

37. Relevant exclusion criteria include:

- history of chronic respiratory disorders including asthma, emphysema, interstitial lung disease, pulmonary hypertension, recurrent pneumonia, or recent (≤ 14 days prior to screening) or ongoing respiratory tract infection (Note: If a respiratory disorder is transient, defer immunisation but do not exclude the participant);
- known previous infection with SARS-CoV-2 or receipt of SARS-CoV-2 (COVID-19) vaccination or presence of antibodies against SARS-CoV-2 or a positive COVID-19 PCR test; and
- vaccination with another agent 30 days prior to registration.

38. 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

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

40. Dilutions of the GMO would be needed, the final volume after dilution of the original vial would be 2 or 4 ml. The preparation of the dose will be performed on an open bench in the pharmacy. This will be carried out aseptically using syringes to transfer solutions between crimped, stoppered vials. Therefore, there would not be open transfer of solutions outside of the syringe or vaccine vial as all solutions would be contained within the sealed primary vial or syringe. The filled capped syringe would be transported to the administration area as described in Section 2.3.2.

2.3.7 Intranasal administration of the GMO

41. The GM vaccine will be administered intranasally (IN) at clinical trial sites. The IN administration will be carried out by study nurse who would be wearing appropriate PPE (face shield/safety glasses, N95 or equivalent mask, disposal gown and disposable gloves).

42. Prior to administration, the filled syringe would be capped with an atomiser, which will be used to create an aerosolised mist and deliver a 0.25ml dose directly into the nasal passage.

43. During administration, clinical trial participants will have their heads tilted back to allow the vaccine to run backwards into the subject's throat and be swallowed. Participants will then be required to stay in the trial site for approximately 4 hours.

44. Any sneezed inoculum or nasal discharge would be caught/collected in tissues, placed in a biohazard bag and disposed as clinical trial waste. Participants would be instructed to disinfect their hands via washing or using an alcohol hand sanitiser.

2.3.8 Decontamination and disposal of the GMO

45. Following administration, all residual GMO and associated waste which has come into 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 will be also disposed using the same process. Disposal will be carried out by external service providers.

46. Any equipment that is contaminated with the GMO will be cleaned with an appropriate virucidal disinfectant shown to be effective against the GMO.

2.3.9 Sample collection and analysis

47. Following administration of the GMO, blood, urine, and mucosal samples will be collected from trial participants at various time points to determine effectiveness of the vaccination and evaluate patient safety.

48. After collection, blood samples will be centrifuged and aliquoted in preparation for analysis. Samples will be packaged as described in Section 2.3.2 for transport to testing laboratories.

2.3.10 Personal protective clothing

49. Clinical trial staff involved in the preparation, administration of the GMO to trial participants and in the clean-up of potential spills would be required to wear a disposable gown, gloves, N95 or equivalent mask and eye protection (safety glasses or face-shields).

2.3.11 Training

50. The applicant's IBC declares that the training and experience of individuals involved in these dealings is satisfactory.

51. Staff handling the GMO would be made aware of the licence conditions and any subsequent amendments. This training will be recorded in the site study file.

52. Use of sentinel trial participants is proposed as described in the CCI attachment to the RARMP, which is made available to the prescribed experts and agencies that are consulted on the RARMP. In addition, all trial participants would be monitored against various baselines and for all adverse events related to the GMO.

2.3.12 Accountability and Monitoring

53. Nucleus Network pharmacy and clinical nursing teams would track and account for the GMO vaccine and trial participants as per Good Clinical Practice (GCP). A documented chain of custody would be in place where; the dispensing of vaccine will be recorded by the pharmacist; the administration would be recorded by the study nurse; and disposal of any unused vial containing the GMO would be conducted after an acquittal process as per GCP.

2.3.13 Contingency plans

54. Spill kits will be available at clinical trial sites and spills will be cleaned up immediately using a virucidal disinfectant according to the clinical trial facility's spill procedures. The sponsor and the IBC will then be notified.

Section 3 Parent organism

55. The GM vaccine is derived from human adenovirus serotype 6 (HAdV-C6). HAdV-C6 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 GM vaccine. As such, the relevant biological properties of HAdVs will be discussed here.

56. Human adenoviruses (HAdVs) are categorised into seven species A to G based on their serology, sequence homology, serum neutralisation, hemagglutinin properties and genomic sequence (Ismail et al., 2018; Lange et al., 2019; Bots and Hoeben, 2020). 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).

57. Despite the high prevalence of HAdV-C in the population, HAdV-C5 vectors have been extensively used as vaccine platforms against various diseases such as HIV, malaria, Ebola virus, influenza virus and tuberculosis (Mennechet et al., 2019). HAdV-C2 and C5 vectors have also been frequently used in clinical trials as cancer therapies (Shaw and Suzuki, 2019; Sato-Dahlman et al.,

2020). The less prevalent HAdV-C6 has been proposed as a vaccine candidate because it is likely to have similar biological characteristics to other HAdV-Cs such as HAdV-C5 and the low likelihood of pre-existing immunity towards the vector (Crosby and Barry, 2014; Crosby et al., 2015).

3.1 Pathology

58. HAdVs 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).

59. HAdV infections are generally mild and self-limiting, but could be more severe or lethal in immunocompromised individuals (Mennechet et al., 2019). 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).

60. 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.

61. HAdV-C has been mainly associated with acute respiratory tract infections in children and is the most common serotype reported in most populations (Mennechet et al., 2019).

3.2 Structure and genomic organisation

62. AdVs 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 has 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).

63. 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.

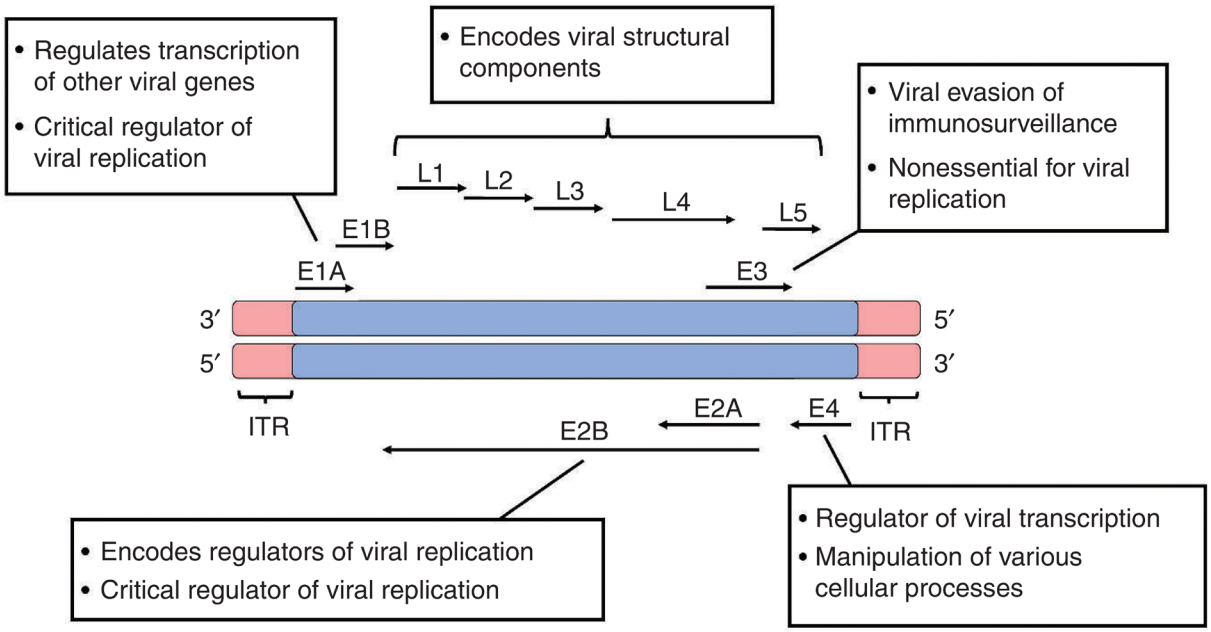

Figure 2: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).

64. 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).

65. The E2 gene is sub-divided into E2A and E2B that encode E2 proteins which 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.

66. Interactions of various proteins encoded by the adenovirus genome are required to form a mature infectious particle. The three major proteins (hexon, penton and fibre) form the external capsid structure and “spikes” of the viral particle. The viral core proteins (V, VII and µ) 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 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 and are 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).

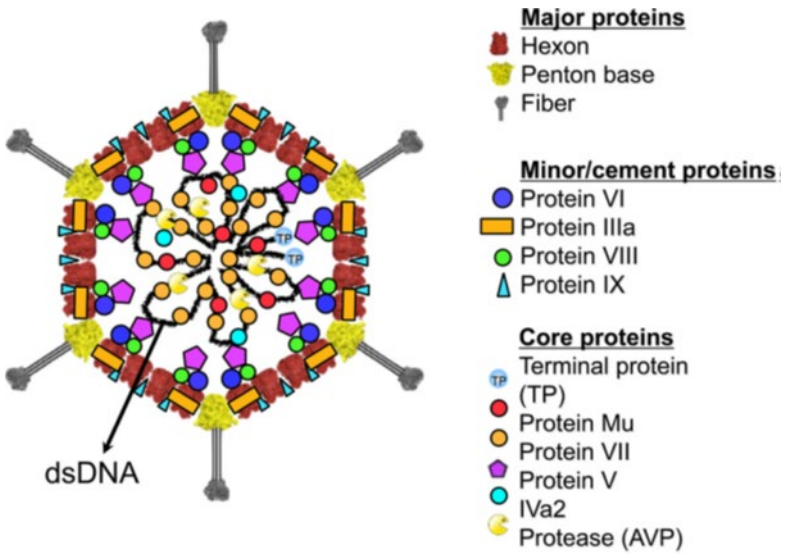

Figure 3: Structural model of human adenovirus (Benevento et al., 2014)

3.3 Viral infection and replication

67. AdVs 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.

68. HAdVs uses the Coxsackie-adenovirus receptor (CAR) transmembrane proteins, CD46, CD80, CD86 and sialic acid to enter the host cells (Zhang and Bergelson, 2005; Lion, 2019). HAdV species C and E use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins as the main receptor to gain entry to a variety of different cell types (Zhang and Bergelson, 2005; Lasaro and Ertl, 2009; Morris et al., 2016; Bots and Hoeben, 2020). *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).

69. The replication of AdVs takes place in the nucleus of the host cell and uses the host cell nuclear machinery to make copies of itself (Figure 4). Briefly, the AdV attaches to the receptors present on the cell membrane leading to internalisation of the virus by endosomal uptake. The virus is then uncoated resulting in the release of viral particles. The viral genome is transported into the nucleus where the transcription occurs (described above in Section 3.2; (Charman et al., 2019)). The viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made. The new virus particles are then assembled. Finally, the host cell breaks apart releasing the viruses (Waye and Sing, 2010b). Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes.

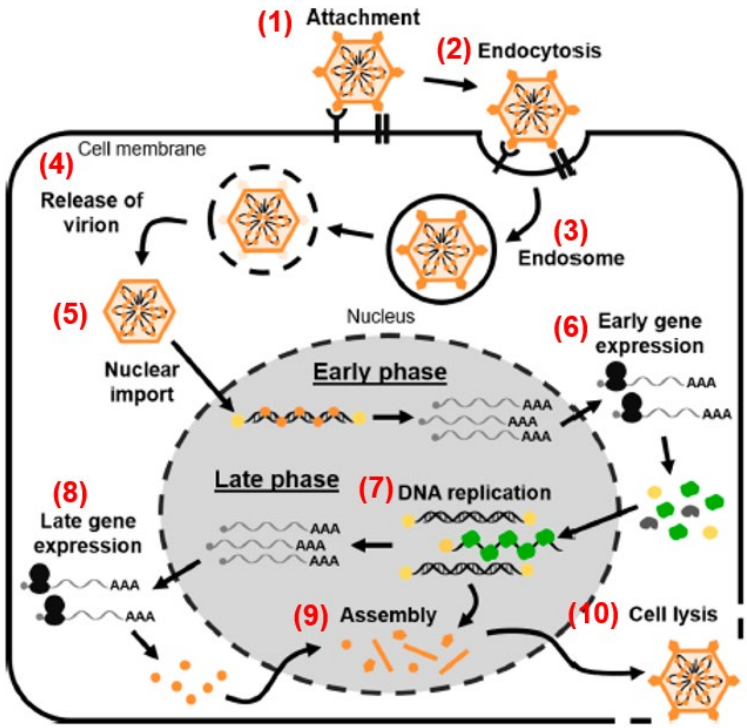

Figure 4: Overview of the adenovirus replication cycle (Charman et al., 2019).

3.4 Mutation and recombination of adenovirus

70. AdV DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999). In addition, AdVs do not have the machinery for efficient integration into the host genome and therefore AdVs exhibit extremely low levels of integration i.e., integration is a rare event (Harui et al., 1999; Desfarges and Ciuffi, 2012; Hoppe et al., 2015; Dehghan et al., 2019). However, random integration of virus DNA into the host genome has been observed in very rare cases (Harui et al., 1999; Stephen et al., 2008).

71. 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 a process called 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). However, bioinformatics analysis suggested that HAdV-E4, a species E adenovirus, was a result of a recombination event between species B and C (Gruber et al., 1993). In addition, more recent genomic sequencing of samples from young children in China suggest novel strains emerging from recombination between HAdV-Cs (Mao et al., 2017; Yu et al., 2020; Ji et al., 2021).

72. Bioinformatics 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). This is unlike the largest species HAdV-D, where homologous recombination in these regions were commonly associated with the large diversity of serotypes (Robinson et al., 2011; Robinson et al., 2013; Singh et al., 2013). The hexon protein is a major constituent of the viral capsid and is suggested to be critical for the development of adenovirus vaccines by forming the serum neutralisation epitope; the penton and fibre 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 to alter its cell tropism and alter its ability to evade the immune system.

73. In addition, bioinformatics 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 (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).

3.5 Epidemiology

3.5.1 Host range and transmissibility

74. Humans are the natural host for HAdVs (Custers, 2020). Experimentally, mice, cotton rats and rabbits have been infected with HAdVs to study adenovirus-induced disease (Ismail et al., 2019). Although used in animal models, 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.

75. Transmission of HAdVs from an infected individual is primarily via direct contact with conjunctival secretions, inhalation of aerosols or the faecal-oral route (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Khanal et al., 2018; CDC, 2019b). The virus can also be spread indirectly via contact with infected 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

76. 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 or ocular 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).

77. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing two HAdV serotypes (HAdV-E4 and HAdV-B7). 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

78. 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. This data is analysed 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).

79. In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health (1991-2000) showed an average of about 1400 reported cases of adenovirus infection per year over 10 years, of whom only about 48 reported cases were identified as HAdV-C6 infection (Spencer, 2002). It is important to note that the data is 21 years old; majority of adenovirus reported infection have not been serotyped; and that testing for adenovirus infections may not be common in Australia. There is no current data on HAdV prevalence in Australia.

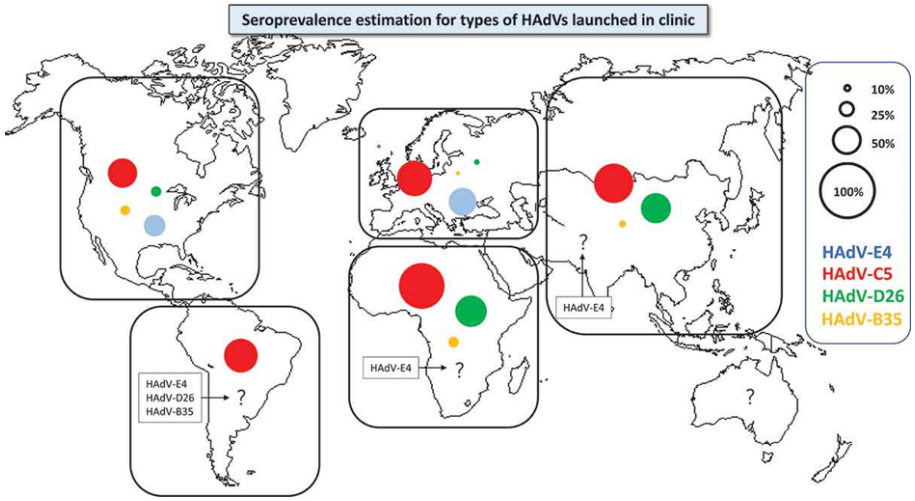

Figure 5: Seroprevalance for adenovirus types used in the clinic (Mennechet et al., 2019)

3.5.4 Control, environmental stability and decontamination methods

80. 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 adenovirus-specific drugs to treat the infection (Waye and Sing, 2010a; CDC, 2019a).

81. AdVs 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). AdVs are also found to be resistant to UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003), thus supporting survival in treated wastewater and sewage, river, ocean and swimming pool water as well as drinking water (Public Health Agency of Canada, 2014).

82. AdVs 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).

83. HAdVs have been detected in various waters worldwide including wastewater, river water, drinking water, ocean and swimming pools (Allard and Vantarakis, 2017). HAdVs are more frequently 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).

84. AdVs are found 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 GM vaccine - nature and effect of the genetic modification

85. The GM vaccine consists of a single-cycle replication HAdV-C6 vector that has been genetically modified to produce a modified SARS-CoV-2 spike glycoprotein (SC-Ad-1). The vector is able to replicate its genome and transgene, but is unable to form a mature infectious particle due to the lack

of the IIIa protein (pIIIa). The GM vaccine is designed to provide protection from infection with SARS-CoV-2 which causes COVID-19 disease.

4.1 The genetic modifications

86. The HAdV-C6 vector has been modified by deletion of two regions; a 1758 base pair (bp) *IIIa* gene deletion; and a 2940 bp deletion of most of E3 region resulting in deletion of immune evasion ORFs 6.7k, 19k, 11.6k, 10.4k, 14.5k, and 14.7k, and the deletion of the E4 UXP ORF. To produce the GM vaccine (SC-Ad6-1), a mammalian expression cassette containing a human cytomegalovirus (CMV) promoter, 3 short hairpin ribonucleic acid (shRNA) target sequence, a Zeocin selectable marker, a simian virus 40 (SV40) polyadenylation signal and a gene encoding a modified full length SARS-CoV-2 spike protein (S protein) (Wuhan isolate; NCBI reference sequence YP_009724390.1) was inserted between the fiber and E4 locus of the HAdV-C6 vector (see Figure 6).

Figure 6: Synthetic SC-Ad6-1 expression cassette with the IIIa and E3 genes deleted and the SARS-CoV-2 spike transgenic cassette.

87. During production of the GMO, the missing pIIIa is provided *in trans* in a cell production system. The applicant states that there is no homology between the provided protein and the flanking *IIIa* deletion in the GMO. The cell banks will be tested for replication-competent adenovirus and the final manufactured GMO could be sequenced to confirm the absence of the *IIIa* gene.

88. The S protein is comprised of the receptor binding (S1) and membrane fusion (S2) subunits. The S1 receptor binding domain has been shown to be responsible for host range and tropism (Huang et al., 2016; Li, 2016; Letko et al., 2020; Mousavizadeh and Ghasemi, 2020; Samrat et al., 2020). The S1 subunit facilitates the virus attachment via angiotensin-converting enzyme 2 (ACE2) receptors present on human cells and subsequent fusion of virus and cell membranes, mediating the entry of SARS-CoV-2 into the target host cells. The fusion of the S protein to the host cell membrane is mediated by cleavage of the S protein by host cell proteases, the transmembrane protease/serine subfamily member 2 (TMPRSS2) and furin at specific cleavage sites at the S2' or between the S1 and S2 subunits respectively (Sternberg and Naujokat, 2020).

89. The roles of the SARS-CoV-2 S protein in receptor binding and entry into the host cells make it an attractive vaccine candidate and many developing COVID-19 vaccines have been designed based on it (Bos et al., 2020; Folegatti et al., 2020; Logunov et al., 2020; Sadoff et al., 2020; Samrat et al., 2020; Zhu et al., 2020).

4.2 Effect of the genetic modification

90. The removal of the *IIIa* gene prevents the GMO from forming a mature infectious particle by interfering with the capsid packaging of the virus (Section 3.2). However, because the E1 gene is still intact, the GMO is still able to replicate its genome and transgene. The deletion of the E3 genes reduces the capacity of the GMO to evade the host immune response and the deletion of the E4 UXP ORF is known to cause a mild growth retardation in AdV (Tollefson et al., 2007).

91. The shRNA target sequences are present in the GMO to improve the production yield of the GMO. During the production process, the production of the spike protein by the GMO can be suppressed by shRNA binding to these target sequences when provided in *trans* by helper cells. However, in this case, the expression of spike protein did not affect the yield of the GMO and hence the helper cells used to produce this GMO were not designed to provide shRNA in *trans*. In addition,

the Zeocin selectable marker (which was used for the selection of recombinant bacteria during construction of the GMO) is retained in the GMO to maintain a larger genome size (closer to genome size to WT) to reduce the chance of recombination with a WT AdV.

92. The S protein inserted as a transgene allows the GMO to produce the S protein once it infects human cells. This would then induce an immune response in the host towards the S protein and build an immunity towards SARS-CoV-2.The insertion of the S protein does not interfere with the backbone of the vector or contribute to the generation of replication competent virus. The S protein is also not involved in the formation or the composition of the capsid of the HAdV-C6 vector and therefore is not considered to affect the tropism and host range of the vector.

93. As a result of these genetic modifications, the GMO is able to replicate its genome and transgene in the host cells and would induce an immune response in humans, but would not be able to form mature infectious particles that can further infect cells with the GMO.

4.3 Characterisation of the GMO

94. Data obtained from pre-clinical trials using the proposed GMO and from other pre-clinical trials using the same backbone/platform (SC-Ad6 vector) with different genes for a range of diseases has been used to characterise the GMO.

4.3.1 Genetic stability and molecular characterisation

95. The master cell bank (MCB) for the production of the GM vaccine will be tested for replication-competent adenovirus and the final GM vaccine will also be sequenced to confirm the absence of the *IIIa* gene.

96. AdV 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). In a separate study on immune-deficient mice, intravenous administration of replication incompetent AdV vector showed plausible low integration of the AdV vector into the host genome (Stephen et al., 2010). However, the authors did suggest that the most common route of vector delivery for AdV vectors (i.e. IM route of injection) would result in much lower incidence of gene transfer (Stephen et al., 2010). No clinical or human studies have shown integration of AdV vectors into the host genome.

4.3.2 Stability in the environment and decontamination

97. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Other recombinant AdVs (AdV expressing GFP) have been shown to have reduced capacity to survive in fresh surface water, cold water and dark sediments compared to wild-type AdVs (Rigotto et al., 2011; Elmahdy et al., 2018). Since the GMO is unable to replicate, it is likely that it would have similar or reduced survival and persistence in the environment compared to the parent organism and would degrade over time (see Chapter 1, Section 3.5.4).

98. 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).

4.3.3 Pre-clinical studies using SC-Ad6 and other replication deficient adenovirus vectors

99. *In vitro* studies comparing replication competent (RC)-Ad6, replication deficient (RD)-Ad6 and SC-Ad6 were carried out in cell lines from human alveolar basal epithelial (A549), mice liver (Hepa 1-6), Syrian hamster kidney (HaK), rhesus macaques kidney (FRhK4) and primary human small airway epithelial cells (HSAECs) (Crosby and Barry, 2014; Crosby et al., 2015; Crosby and Barry, 2017). These studies demonstrated that SC-Ad6 vectors were able to replicate their genome and express the

reporter protein encoded by the transgene to similar levels as RC-Ad6 vectors; and expression of the reporter protein was higher than that of RD-Ad6 vectors (Crosby and Barry, 2014, 2017). Similar to RC-Ad6 vectors, SC-Ad6 vectors subsequently kill the infected cells. However, they are unable to form infectious viral particles due to the lack of the IIIa protein (Crosby and Barry, 2014).

100. When injected intravenously (IV) into BALB/c mice, all three vectors types were detected in the liver. The RD-Ad6 vector genome and reporter protein levels remained relatively constant compared to the RC-Ad6 and SC-Ad6 vectors, which had higher reporter gene expression levels that peaked at day 2 post IV infection (Crosby and Barry, 2014). Although *in vitro* data between RC-Ad6 and SC-Ad6 vectors demonstrated similar genome replication, *in vivo* data in mice showed that SC-Ad6 replication and expression of the reporter transgene were 3-fold and 7-fold lower than RC-Ad6, respectively (Crosby and Barry, 2014). IM administration of HAdV-6 vectors resulted in reporter transgene expression in the liver in addition to expression at the site of injection (Weaver et al., 2011).

101. Syrian hamsters that had been intranasally (IN) inoculated with all three vector types, showed that the expression of the reporter protein encoded by the transgene to be restricted in the nasal areas, peaking at day 3 and returning to baseline by day 7, with expression from SC-Ad6 and RC-Ad6 being 7 and 12 times higher than RD-Ad6 vector, respectively (Crosby et al., 2015). Mice inoculated with other RD-adenoviral vectors with reporter genes were shown to distribute to the olfactory bulb, epithelial tissues in the lungs; and is not detected in the other tissues such as middle ear, brain, inguinal lymph nodes, ovaries, liver, spleen, kidneys, heart, thyroid gland, thymus, bone marrow, brain or the central nervous system (Lemiale et al., 2003; Damjanovic et al., 2008).

102. Antibodies against the reporter transgene and vectors can be detected at days 3, 6, 12, and at 24 weeks post-immunisation in both the serum and vaginal washes following one IN immunisation (Crosby et al., 2015). In addition, rhesus macaques inoculated orally (sublingual) with RC-Ad6 were able to generate antibodies towards the reporter transgenes.

103. This vector has been used for vaccine candidates for various diseases such as Ebola (Anguiano-Zarate et al., 2018), Influenza A (Crosby et al., 2017), HIV (Matchett et al., 2018; Matchett et al., 2019; Matchett et al., 2020b) and *Clostridium difficile* (Matchett et al., 2020a). These studies have been conducted in various animals including mice, Syrian hamsters, cotton rats and rhesus macaques. Various routes of inoculation (IM, IN and intravaginal) and prime boost methods (same or different route of inoculation) were tested. Overall, these studies demonstrated that the vaccine candidates triggered an immune response towards the peptide expressed by the vector and in some cases were effective in preventing the disease.

4.3.4 Pre-clinical studies using the GMO (SC-Ad6-1)

104. Pre-clinical studies using the GMO have been carried out and are described in the CCI Attachment of the RARMP, which is made available to the prescribed experts and agencies that are consulted on the RARMP.

4.3.5 Clinical trials using SC-Ad6 and other replication deficient adenovirus vectors

105. One clinical trial using the GMO (SC-Ad6-1) via an IM route of administration is currently approved by the Regulator. No clinical studies have been carried out using SC-Ad6-1 in an IN route of administration. Although, there is no available clinical trial data from SC-Ad6 vectors as yet, many RD HAdV vectors have been used as COVID-19 vaccine candidates and showed a good safety profile (Logunov et al., 2020; Sadoff et al., 2020; Zhu et al., 2020; Sadoff et al., 2021).

106. Samples (tonsils, nasal and bronchial brush, bronchoalveolar lavage, blood, stool, urine, saliva) taken from patients on days 1, 3, 7, 14, 21 and 28 post-intranasal inoculation with a RD-AdV vector expressing cystic fibrosis transmembrane conductance regulator (CFTR) showed no detection of infectious AdV vector (Bellon et al., 1997). However, vector DNA is detected in the nasal and bronchial brush, bronchoalveolar lavage, saliva and tonsils up to 21 days post- infection (Bellon et al.,

1997). In a separate study, only one out of twelve patients had a positive culture in the nostrils and rectal samples on day 1 and 2 following inoculation (Knowles et al., 1995).

Section 5 The receiving environment

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

5.1 Site of vaccination

108. The intended primary receiving environment will be the nose, nasal turbinates and upper respiratory tract of the clinical trial recipient as the GMO will be delivered directly into the nose using a syringe and an atomiser.

109. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and waste disposed of. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance with institutional policies based on Standard Precautions for handling potentially infectious substances and the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

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

5.2 Presence of related viral species in the receiving environment

111. 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.

112. 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 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 animals and humans of all ages 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.

113. The prevalance of HAdVs in Australia based on previously reported cases and seroprevalance is low as mentioned in Section 3.5.3. However, there remains some uncertainties due to the lack of recent data.

114. Adenovirus-based vaccines were previously used for COVID-19. Therefore, similar adenovirus-based vectors (e.g. AstraZeneca and Janssen COVID-19 vaccines) could be present in people or the environment.

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 gene encoding the spike protein in the GMO would be functionally similar to ones present in the naturally occurring SARS-CoV-2 virus. The genes introduced into the GMO were derived from naturally occurring SARS-CoV-2 virus and so similar genetic material will already be present in the environment.

Section 6 Previous authorisations

117. This GMO has not been previously authorised for commercial supply in any region or country. This GMO was previously authorised for use in a clinical trial via a different mode of administration under licence DNIR-636.

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.

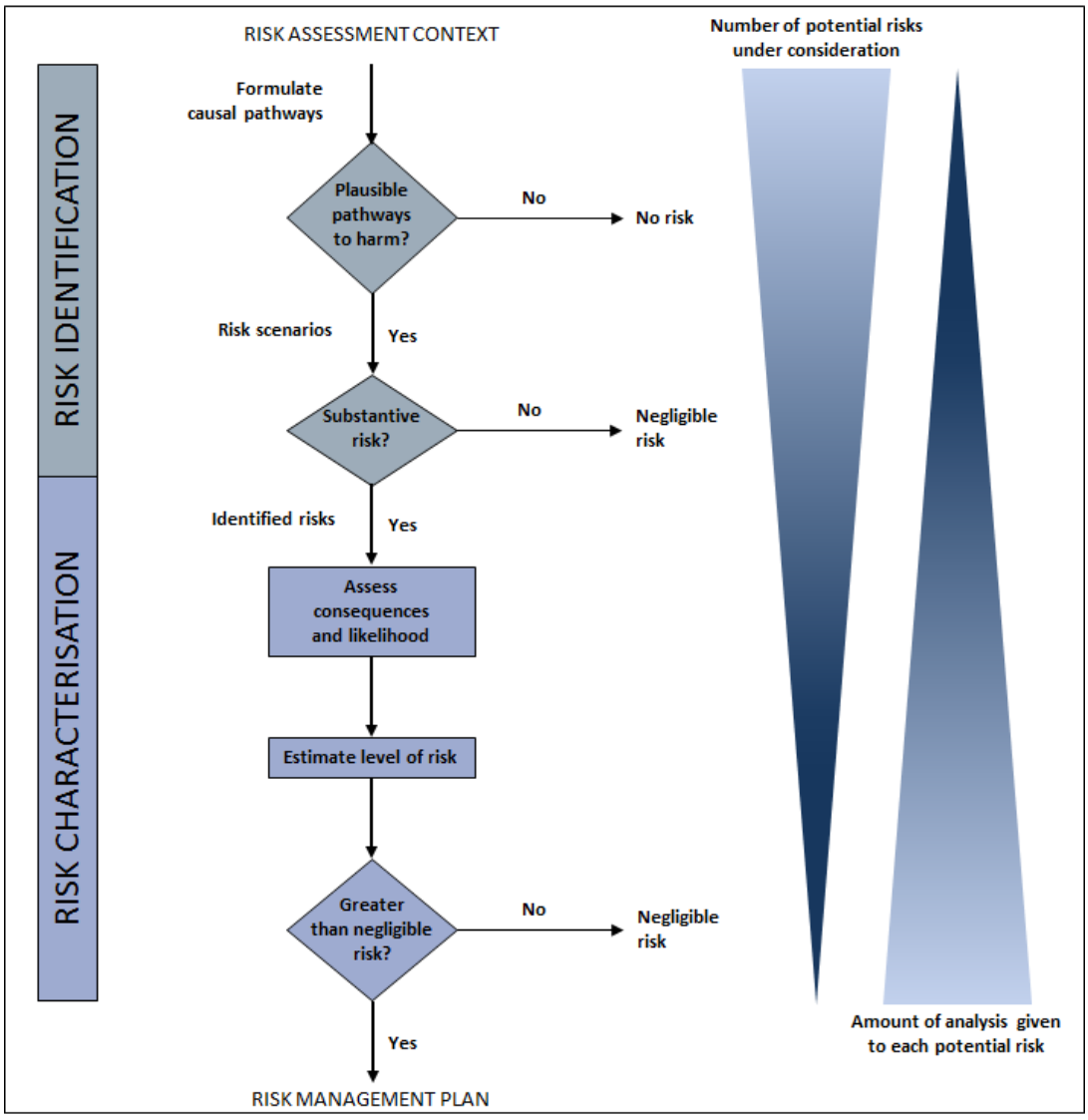

Figure 7: The risk assessment process

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 7), 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.

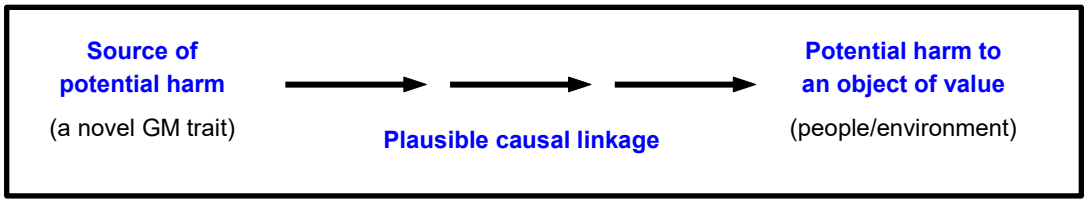

Figure 8: Components of a risk scenario

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. The GMO contains a zeocin antibiotic resistance gene in the transgene cassette. It is plausible that this resistant gene could be transferred to resident gut bacteria present in the participant or subsequently shed in the environment. However, this gene is of no consequence clinically in animals or humans, since no antibiotics used in animals or humans are inactivated by this gene product. Zeocin is typically used in research for the selection of recombinant bacteria. As discussed in Chapter 1, Section 4.3.5, it is unlikely that any live GMO would be shed into the environment. The ingestion of the GMO in the course of the administration is unlikely to result in the transfer of the resistance gene to resident gut bacteria in the trial participant. Although HAdVs are found to be resistant to low and high pH; and stable in the environment at pH 6-8 as discussed in Chapter 1 Section 3.5.4, HAdV-Cs have shown to be sensitive to the pH conditions of the digestive tract . Therefore, the consequence of the zeocin antibiotic resistance gene being horizontally transferred to compatible bacteria in the trial participant or the environment will not be considered further.

127. 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.

128. 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.

129. As discussed in Chapter 1, Section 4.1, the GMO has been modified by the deletion of the *IIIa* gene; partial deletion of E3 and E4 genes; and by insertion of a gene encoding a modified SARS-CoV-2 spike protein. These introduced genes and their encoded proteins are considered further as a potential source of risk.

2.2 Causal pathway

130. 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.

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

132. 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.

133. As mentioned in Chapter 1, Section 3.4, adenoviruses remain episomal throughout the infection and very rarely 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 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.

134. Recombination between different vaccines using adenovirus platforms is highly unlikely because it is improbable that two or more vaccines are administered at the same time with the same route (IN); the lack of homology between adenoviral vectors further reduces the possibility of recombination; and the viral vectors would most likely be cleared before a second dose is administered. Thus, the potential of recombination between adenoviral vectored vaccines will not be further discussed.

2.3 Potential harms

135. 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

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

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

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

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people 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	Adverse immune reactions (e.g., cytokine storm)	No	• Although the GMO can replicate its genome and transgene, it would not produce further viral particles to sustain an infection. Therefore, the probability of the GMO being shed would be low. • Any reactions to the spike protein would be transient and the GMO would be

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		(b) During import, transport or storage of the GMO (c) Disposal of the GMO (d) Nasal discharge or shedding of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein			rapidly cleared by the immune system. • The dose received through accidental exposure would be far smaller than that administered during vaccination and will not be sufficient to induce an adverse immune response. • Import, transport, storage and disposal will follow well established procedures. • HAdV-C are predominantly respiratory viruses that are sensitive to pH levels in the stomach.
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 as described in Table 2	Adverse immune reactions (e.g., cytokine storm) Disease in people or animals	No	• There would be a low probability of continuous complementation of GMO by AdV because AdV infection is often self-limiting. • Competition with WT AdV for proteins that may complement the GMO further limits the likelihood of GMO forming mature virus particles. • Recombination among adenoviruses is usually restricted to the same species. • Homologous recombination would be highly unlikely due to the packaging limit of the Sc-Ad-1 vector. • Homologous recombination in regions with high homology, which are 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.

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
					• Multiple recombinations are required to produce a replication competent 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. • Although the GMO may survive at amounts similar to, or less than WT-AdV, it cannot replicate inside or outside the host. Hence, the GMO would not be able to maintain a continuous presence in the environment compared to a WT virus. • GMO not known to naturally infect non-human hosts and does not infect aquatic species.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through these events: (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO (d) Nasal discharge or shedding of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein
Potential harm	Adverse immune reactions (e.g., cytokine storm)

Risk source

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

Causal Pathway

139. People (person handling the GMO) 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, preparation and intranasal administration of the GMO. It could also be transmitted when contaminated surfaces, such as hands or tissues, make contact with mucous membrane or via needle stick injury. There is also a possibility that the GMO could be shed from the nasal mucus membrane following administration of the GMO. This exposure could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

140. As discussed in Chapter 1, Section 2.1, the 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, aerosols formation during administration, preparation and/or due to breakage/spillage of GMO onto surfaces during preparation and administration; or the discharge (e.g. sneezing) of the initial inoculum containing the GMO by the trial participant 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 vaccination services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and the *Australian Immunisation Handbook.*

141. Experiments using radio-labelled albumin as a vaccine surrogate to investigate the absorption of IN delivered vaccines demonstrated that the nasal spray was absorbed with halftimes of clearance ranging from 40-60 minutes, with a mean time of 50 minutes (Bryant et al., 1999). The trial participants are not expected to shed the GMO. However, there is a potential for the trial participants to discharge the initial inoculum containing the GMO following administration. Trial participants would be required to remain at the clinical trial site for 4 hours post-administration. Participants would also be advised to use a tissue to collect any nasal discharge (e.g. sneezing); to appropriately dispose the tissues used at the clinical trial site; and practice good hand hygiene. In addition, trial participants would also be instructed to dispose of any tissues used to wipe nasal secretions into a biohazard bag (provided) for the next 24 hours and return the bag to the clinical trial site at their next visit (Chapter 1, Section 2.1).

142. As part of the IN administration of the GMO, participants could inadvertently ingest some inoculum containing the GMO. Therefore, it is plausible that the GMO could enter the gut and be shed, resulting in the exposure of the GMO to other humans or animals. However, HAdV-Cs are predominantly respiratory viruses compared to HAdV-F, which causes gastrointestinal disease. A study of HAdV-F41 showed that HAdV-F41 is resistant to acid exposure while HAdV-C2 and –C5 demonstrated reduced infectivity after 5 mins of exposure to pH similar to the stomach (Favier et al., 2004). This was attributed to the resistance of the short fiber proteins in HAdV-F to the low pH (pH 2) compared to HAdV-C (Favier et al., 2004). A separate study also demonstrated that HAdV-C5 has a reduced ability to infect differentiated epithelial cells and in rat jejunum compared to HAdV-F41 (Croyle et al., 1998). The GMO is also incapable of forming an infectious viral particle. Therefore, taking into account these factors, the GMO, which belongs to HAdV-C would most likely not persist or be shed through the gastrointestinal tract following IN administration.

143. Caregivers and healthcare personnel who come into close contact with vaccinated people may be inadvertently exposed to the GMO during administration via spillage or accidental aerosol formation from the atomiser or sneezing post-administration. Caregivers and others exposed to the GMO in this way will only be expected to be exposed to low levels of the GMO. In addition, as discussed in Chapter 1, Section 4.3.5, participants administered with a RD-HAdV for gene therapy did not display any shedding of infectious AdV vector from 1 -28 days post IN administration, however, vector DNA is still detectable up to day 21 post-administration (Bellon et al., 1997). Albeit, a different route of administration (intra-tumoral), the formation of replication-competent adenovirus or presence of the vector in healthcare personnel who came into close contact with patients have not been observed in studies using other replication defective adenovirus vectors, which looked into these parameters (Tursz et al., 1996; Schenk-Braat et al., 2007).

144. 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. The GMO is unable to replicate (either inside or outside the host), so viruses in the used

vials could not multiply to reach an infective dose. Thus, the dose received through accidental exposure would be far smaller than that administered during vaccination. Therefore, even if an individual or animal is inadvertently exposed to the GMOs, they are unlikely to develop an adverse immune reaction.

145. 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 vaccine; and nasal secretions that may contain the GMO.

146. In addition, the requirements of participants to stay in the clinic for 4 hours post-administration of the GMO, to practice good hand hygiene and sneezing etiquette, would further minimise the potential exposure of other people and animals to the nasal secretions from the participants that may contain the GMO.

Exposure during import, transport and storage of the GMO

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

148. 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 also be handled in the same manner. These practices will lower the likelihood of unintended dispersal of the GMOs.

149. The risk of exposure to the GMO in other people and animals is highly unlikely because the GMO is unable to form infectious viral particles. In addition, no natural HAdV infections of non-human hosts have been described and no replication of HAdVs have been observed in animal models. Further, the presence of animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

150. Antiviral disinfectants would be used as decontamination and disinfection measures after administration of the vaccine or in the case of accidental spills during the supply of the GMO.

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

Exposure during disposal of the GMO

152. 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 GM vaccine are held;
- locations where the GM vaccine is administered.

153. 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 with these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

154. 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

155. 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.

156. The GMO is unable to produce further viral particles which are required to sustain an infection. In addition, any reactions to the spike protein would be transient and the GMO would be rapidly 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.

157. Increased expression of spike protein 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. These proteins are not known to be toxic to humans.

158. As mentioned in Chapter 1, Section 4.1, the SARS-CoV-2 virus enters a host's cells via the ACE2 receptor, which is involved in the renin-angiotensin-aldosterone system. When exposed to the GMO, there is a potential that the spike proteins produced would bind to ACE2, which can prevent the conversion of angiotensin II into angiotensin. This could result in more angiotensin II binding to the ATI1 receptor, which can lead to detrimental effects such as vasoconstriction and enhanced inflammation and/or increased angiotensin II expression in the lungs. However, there has not been any reported cases of such effects. Further, it is very unlikely that the amount of spike protein present in the replicative defective viral vectored vaccine can have a sustained effect on people. To date, vaccines that have used the spike proteins from SARS-CoV-2 have shown a good clinical safety profile (Folegatti et al., 2020; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al.; Zhu et al., 2020).

159. Vaccines against SARS-CoV-2 using the full length spike protein in replicative defective viral vectors including other HAdV based vaccine, have shown the ability to generate neutralising antibodies against SARS-CoV-2 (Folegatti et al., 2020; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al.; Zhu et al., 2020). As mentioned in Chapter 1, Section 4.3.3, pre-clinical studies using this GM vector (SC-Ad6), showed that it was also able to generate an antibody response towards the transgene it carries. Therefore, there is potential for these vaccines to cause antibody-dependant enhancement[3]-mediated viral entry or immunopathology via the generation of sub- or non-neutralising antibodies towards the spike protein (Arvin et al., 2020; Su et al., 2020). However, there has not been any reports of ADE associated with COVID-19 vaccine candidates expressing the spike protein to date. The administration of convalescent plasma from patients who had recovered from SARS-CoV-2 infection into 20,000 patients who had a high risk of severe COVID-19 disease showed low incidence of serious adverse events (Joyner et al., 2020). A recent study using

[3] Antibody-dependant enhancement (ADE) can occur when pre-existing sub- or non-neutralising antibodies towards a virus can enhance the viral entry into host's cells during secondary viral infections. This antibody-dependant enhancement mediated viral entry has been mostly documented in flaviviruses (e.g. dengue virus) but also observed in various viral infections such as HIV, Ebola and coronaviruses (e.g. MERS and SARS-CoV-1).

this GM vaccine in hamsters did not show any evidence of ADE (van der Lubbe et al., 2021). Applicant has also provided additional unpublished data, which is in the CCI Attachment to the RARMP and which is made available to the prescribed experts and agencies that are consulted on the RARMP. Further, no ADE was observed with inactivated-whole SARS-CoV-1 (Luo et al., 2018) and DNA vaccine expressing SARS-CoV-2 S protein (Arvin et al., 2020). To date, there is no conclusive evidence demonstrating a risk of ADE in humans in relation to SARS-CoV-2 infection.

Conclusion

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

2.4.2 Risk Scenario 2

<table>
<tr><td>Risk source</td><td>GMO</td></tr>
<tr><td>Causal pathway</td><td>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 of IIIa, E3 or E4 by AdV
⬇
<u>Production of GMOs:</u>
without immune-evasion properties that is capable of forming mature viral particles (IIIa)
OR
with immune-evasion properties that is unable to form mature viral particles (E3)
OR
with less viral replication capacity (E4)

Homologous recombination with AdV in spike gene, IIIa, E3, E4 or other regions of high homology
⬇
<u>Formation of:</u>
(i) WT AdV expressing S protein
OR
(ii) WT AdV that is unable to form mature viral particles (IIIa)
AND
GMO that is able to form mature viral particles (IIIa)
OR
(iii) WT AdV expressing E1 or E4 gene from HAdV-C6 (E1 or E4)
AND
GMO with E1 or E4 gene from WT AdV that is unable to form mature viral particles (E1 or E4)
OR
(iv) WT AdV with defective immune evasion properties (E3)
AND
GMO with altered immune evasion properties but still unable to form mature viral particles (E3)
OR
(v) Replication competent AdV or GMO with altered tropism</td></tr>
<tr><td>Potential harm</td><td>Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals</td></tr>
</table>

Risk source

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

Causal Pathway

162. The transmission of GMO can occur by the pathways mentioned in Risk Scenario 1 which could potentially result in transduction of host cells. If the person or animal exposed to the GMO has an existing infection of AdVs at the same time of exposure 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 an adverse immune reactions and/or disease in people or animals.

Complementation of pIIIa, E3 or E4 by AdV

163. As mentioned in Section 3.5.3, there is a high prevalance 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 *IIIa, E3 or E4* 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 form mature infectious viral particles with immune evasion properties in the host; or a GMO with immune-evasion properties that is unable to form mature viral particles; or a GMO with less viral replication capacity.

164. The last reported prevalence of HAdVs in Australia is very low (Spencer, 2002). Currently, there are uncertainties on the prevalence of HAdVs in Australia. However, 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 missing *IIIa*, E3 and E4 genes in the GMO is very low.

165. Multiple copies of protein (IIIa, E3 and E4) would also be required for the formation of an infectious viral particle (Liu et al., 2010; Reddy et al., 2010; Reddy and Nemerow, 2014). As this complementation would usually be provided by WT AdV, there would also be direct competition with WT AdV to form a mature viral particle, which will limit the chances of complementation by these proteins enabling the GMO to form an infectious viral particle.

166. 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

167. Recombination is common among circulating wild-type adenoviruses in nature. It is seen as a key driver for adenoviral evolution as discussed in Chapter 1, Section 3.4. Similar to complementation, homologous recombination also requires the person or animals exposed to the GMO to be infected with a wild-type AdV at the same time. AdV 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 in the nasal passage. Licence conditions will be in place to limit and control the exposure of the GMO to other people or animals via inhalation or contact with mucus tissue via requirements around the wearing of PPE and other transport and disposal procedures.

168. 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). Therefore, 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. These GM recombinants are described in Table 2.

Table 2 Theoretical recombinants of GMO and wild-type Adenoviruses

Recombinant region	Resultant recombinant	Outcome	Likelihood
IIIa between • GMO • WT AdV	• Replication-competent GMO with *IIIa* gene • Attenuated AdV without the *IIIa* gene	• Replication-competent GMO that is still less immune evasive than WT, due to deletion of the E3 region • Attenuated AdV	Unlikely as these regions are not high homology region
E3 between • GMO • WT AdV	• Attenuated GMO with intact E3 region • Replication-competent AdV without the E3 region	• Attenuated GMO with restored immune-evasion properties. However, cannot produce mature viral particles due to deletion of the *IIIa* gene. • Replication-competent AdV without immune evasion properties	Unlikely as these regions are not high homology region
IIIa and E3 between • GMO • WT AdV	• Replication-competent GMO with intact *IIIa* gene and E3 region • Attenuated AdV without the *IIIa* gene and E3 region	• Replication-competent GMO with restored immune evasion properties. • Attenuated AdV without immune evasion properties	Unlikely as these regions are not high homology region
Transgenic cassette between • GMO • WT AdV	• Attenuated GMO without the transgenic cassette • Replication-competent AdV with the transgenic cassette	• Attenuated GMO that is still less immune evasive than WT, due to deletion of the E3 region • Replication-competent AdV expressing the spike protein	Unlikely
Theoretical regions that may recombine (E1 and E4) • GMO • WT AdV	• GMO or WT with different E1 genes • GMO, with E4 UXP ORF • WT AdV with without UXP ORF	• No phenotypic changes are expected for GMO and WT • GMO with similar growth rate to WT • Mild retardation in WT AdV growth	Unlikely

169. The transgenic cassette containing the gene encoding the spike protein is inserted between the fiber and E4 flanking region using site specific recombination methods. Therefore the likelihood that recombination between the GMO and WT AdV resulting in WT AdV receiving the spike gene is very unlikely.

170. The GMO could theoretically receive the *IIIa* gene from WT AdV and gain the capacity to form mature viral particles but still lack immune-evasive properties and viral replication capacity due to the absence of E3 and E4 genes respectively. Previous work has shown that other group C adenoviruses (HAdV-5) can regain the deleted gene if the resultant genome does not exceed 105% of the original size. However, adenoviruses that even exceed 100% are less robust and are prone to rearrangement to reduce the genome, indicating that there is a limit to DNA packaging (Bett et al., 1993). Compared to the unmodified HAdV-6, the genome size of the GMO is 101%. Therefore, it is unlikely that the GMO could receive the *IIIa* gene from WT AdV due to the packaging capacity of the GM vector and the low likelihood of recombination events in the *IIIa* region as discussed in Chapter 1, Section 3.4.

171. The GMO could also regain its E3 gene and therefore its immune-evasive properties but remains unable to form mature viral particles from the lack of pIIIa. The resulting GMO would still be cleared by the immune system.

172. 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.

173. Homologous recombination could potentially occur in the E1 and E4 regions. But since the GMO has the E1 and most of the E4 regions intact, it is unlikely to have a major impact on the characteristics of the GMO and WT AdV if any recombination is to occur.

174. Homologous recombination could potentially occur at the hexon, penton and fibre regions of AdV, resulting in the GMO with an altered cell tropism but still remaining unable to form mature viral particles. However, homologous recombination in the hexon, penton and fibre regions is not common in HAdV-C.

Potential harm

175. If complementation were to occur, the GMOs produced in the host cells may be able to form infectious viral particles and possibly increase the persistence of the GMO in the host, resulting in increased expression of spike proteins. Similarly, homologous recombination would increase the expression of the introduced genes i.e., spike proteins. The exposed individuals may generate a stronger antibody response for the spike protein of SARS-CoV-2 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.

176. If homologous recombination were to occur it could result in the formation of replication competent GMO. The person exposed 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

177. The exposure of people to a GMO which has acquired the *IIIa* gene, transferred spike proteins to other AdVs or other recombinant viruses resulting in adverse immune response or disease in people or animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

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

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

Causal Pathway

179. The GMO could be released into the environment through a spill during transport, storage, or disposal or shedding from 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.

180. 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.

181. In the event of a spill without correct decontamination with suitable disinfectants, the GMO could potentially persist/survive 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). Accidental spillage that is not decontaminated could result in the release of the GMO and/or recombinant viruses into the environment. 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.

182. Accidental spill/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. Similar to the parent organism, the GMO could survive in the environment. However, due to its non-replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods and is unlikely to spread. The impact of survival of the GMO in an aquatic environment is likely to be very low as the GMO is replication incompetent and would eventually degrade.

183. 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. Therefore it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source.

184. 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 unable to form mature viral particles, is not known to infect and replicate in animals animal models respectively, the likelihood of infecting other mammals from exposure to the GMO is very low.

185. 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

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

Conclusion

187. 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. Therefore, it does not warrant further assessment.

Section 3 Uncertainty

188. Uncertainty is an intrinsic part of risk analysis[4]. 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.

189. 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.

190. 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.

191. Although the GMO is unlikely to shed based on prior data using similar adenoviral vectors, there is no available clinical bio-distribution and shedding data for this GMO as this is a first in human clinical trial using intranasal administration.

192. A rare but serious adverse event (blood clots in large blood vessels accompanied by a low platelet count) has been reported in adult recipients of vaccines using similar adenovirus platforms such as Janssen's COVID-19 vaccine (15 rare events reported out of more than 6.8 million doses administered) (FDA, 2021) and AstraZeneca's COVID-19 vaccine (30 rare events reported out of more than 5 million doses administered in the European Union)(Ostergaard et al., 2021). In Australia, as of 6 May 2021, there have been 11 reported incidences of blood clots linked to the AstraZeneca vaccine

[4] 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.

out of approximately 1.4 million doses administered (TGA, 2021). Although unlikely, there is uncertainty about whether this rare event could occur in a small group of trial participants (up to 1000). In addition, the HREC would be assessing the safety of the vaccine including the formation of blood clots in vaccine recipients as part of their evaluation process for use of this COVID-19 vaccine in Australia. Given that inadvertent exposures are unlikely (as discussed in the above risk scenarios), the occurrence of rare adverse events in those inadvertently exposed to the GMO is considered highly unlikely.

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

Section 4 Risk evaluation

194. 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.

195. 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.

196. 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.

197. 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.

198. 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, which will prevent it from multiplying in other cells;
- the GMO is unlikely to be shed from the vaccine recipients;
- the likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccines) or animals would be minimised due to well-established import, transport, storage and disposal procedures;
- 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 very low.

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[5]

[5] 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

199. 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.

200. 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.

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

202. 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

203. 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

204. 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, 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 licence.

3.1 Limits and controls on the clinical trial

205. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Avance. 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 Avance

206. The proposed clinical trial would involve a maximum of 1000 participants within Australia, and the initial application proposed that most dealings with the GMOs would take place in medical facilities such as clinical trial units, hospitals, GP surgeries and analytical laboratory facilities. However, the applicant has now stated that the trial would only be carried out in dedicated phase I clinical trial sites. One site has been confirmed as Nucleus Network Pty Ltd, Brisbane. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMOs. The applicant has proposed to complete the study within 5 years of commencement. Conditions maintaining the risk context and proposed limits of the trial such as the maximum number of trial participants, duration of the study and the use of clinical trial sites to run the clinical trial have been included in the licence.

207. 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 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.

208. 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.

209. 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 vaccination with the GMO;
- agree to abstain from donating blood, sperm, ova or organs for 90 days after the last vaccination with the GMO.

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

211. 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 attenuated adenovirus vectors is expected to be minimal and occur for at most a few days. Due to the IN mode of administration and the attenuated nature of the GMO, sexual transmission of the GMO from the trial participants is unlikely. Therefore, use of contraception and a ban on donation of gametes is not required as a licence condition. However, the GMO could be present in small amounts in the blood and has known tropism for the liver. Using the conservative timeframe of 90 days, as proposed by the applicant, abstinence from blood or organ donation would minimise the potential for transmission of infectious viral particles. Therefore, the criteria included in the licence are that the licence holder must obtain written agreement from the trial participant that for 90 days after the last dose of the GMO that they will not donate blood or organs.

212. 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.

213. When the GMO is administered via the IN route, there is a potential for the inoculum to be sneezed out. Given this, licence conditions include, requirement of participants to remain on site for at least 4 hours; and instructions provided to participants on proper hand hygiene and sneezing etiquette. This would include sneezing into tissues and proper disposal of tissues into the provided biohazard bags for 24 hours after IN administration with the GMO.

214. The clinical staff handling the GMO would be required to wear PPE including gown, gloves, N95 or equivalent mask and eye protection/face shield. The requirement for the use of N95 or equivalent masks is a conservative approach in order to further minimise exposure of people administering the GM vaccine to potential aerosols generated during administration. These practices would minimise exposure of people handling and administering the GMOs (Risk scenario 1) and have been imposed as licence conditions.

215. Conditions are included in the 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. Licence conditions require that the licence holder must ensure that the GMO, or material or waste that has been in contact with the GMO, that is to be destroyed by external service providers, is through a clinical waste stream. This is considered satisfactory, provided that the licence holder is only permitted to engage persons who can adhere to appropriate standards to conduct the dealings, as described in Paragraph 216.

216. 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 licence also 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.

217. A standard condition is included in the 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 written under the condition explains that compliance may be achieved by only engaging persons who are required to adhere to appropriate standards to conduct the dealings.

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

219. Further conditions imposed in the licence 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

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

- limit the trial to 1000 trial participants, which are to be conducted at clinical trial sites;
- restrict access to the GMO;

- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements;
- ensure appropriate PPE is used;
- restrict personnel permitted to administer the GMO;
- requiring decontamination of the GMO and materials and equipment that have been in contact with the GMO at clinical trial sites using effective disinfectants or disposal using a certified waste contractor in accordance with standard clinical waste disposal practices, as required by the relevant Australian and state legislation;
- transport and 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 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

221. 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

222. 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.

223. The conditions include a requirement for the licence holder to inform the Regulator of any information that would affect their suitability.

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

3.2.2 Contingency plans

225. Avance 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

226. 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, Avance 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

227. The licence requires 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

228. 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

229. 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.

230. 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.

231. 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

232. 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 inoculated trial participants.

Section 5 Conclusions of the RARMP

233. 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.

234. 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.

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Appendix A: Summary of submissions from prescribed experts, agencies and authorities on the consultation RARMP

The Regulator received a number of submissions from prescribed experts, agencies and authorities on the consultation RARMP. All issues raised in submissions that related to risks to the health and safety of people and the environment were considered in the context of the currently available scientific evidence and were used in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence. Advice received is summarised below.

Submission	Summary of issues raised	Comment
1	Council has stated that it, "does not have a specialist scientific expert to make an assessment no comment will be provided".	Submission has been noted.
2	Council has stated that it, "has no official policy on genetically modified products or trials. However, the Council would not support any use of any treatments that has not been proven to be safe and may prove to be harmful to the community. If the treatment is proven to be safe and poses no threat to the greater community then the council would have no objections to its trial use, especially if it is to prove to be an effective Covid-19 Vaccine".	Submission has been noted.
3	Council has stated that it, "has no objection to this proposed clinical trial. Please note Council's Regional Landfill is licenced to receive both Category 1 and Category 2 Regulated Waste however any transport of these waste types may require Waste Tracking and the use of a licenced Transporter which is the responsibility of the producer of such waste".	Submission has been noted.
4	Department has stated, "Overall, Avance Clinical Pty Ltd's application has negligible risks to the health and safety of people and the environment". Specifically, the department is "satisfied that the measures taken to manage the short and long term risks from the proposal are adequate".	Submission has been noted.
5	The Department has suggested including more information on the following factors to support the conclusions of negligible risk in the RARMP: • Persistence, administration route and transmission risk. o *Make clear in RARMP that adenoviruses are persistent and stable in the environment.*	• Amended information on persistence in Table 1 to be consistent with the rest of the RARMP. • The persistence of WT HAdV and the GMO is discussed in Chapter 1, Section 3.5.4 and Section 4.3.2 respectively. • The risks from administration are assessed as negligible due to reasons discussed in Chapter 1, Section 4.3.5. The mode of administration is directly into the

Submission	Summary of issues raised	Comment
	○ *Exposure risk to health care personnel during administration.* ○ *Include information on the shedding profile of adenovirus vectors from a publication by Brandon et al, 2008.* • Consideration should be given to decontamination of all surfaces at the clinical trial site. • Prevalence of wild type HAdV-C in Australia. ○ *Uncertainties in regards to the prevalence of HAdV-C in Australia should be clearly stated as data from Australia is 20 years old.* • Recent evidence of recombination of GMO with wild-type adenovirus. • Consider seroprevalance PCR studies for healthcare workers and vaccines.	nose which has been clarified in Chapter 1, Section 2.3.7. • The RARMP already cited the original publication that was referred to in the review by Brandon *et al*, 2008. • Licence condition 31(b) requires all work surfaces to be decontaminated before and after they have been used for conducting dealings authorised by this licence. • Prevalence of WT HAdV in Australia is clarified in Chapter 1, Section 3.5.3 and in Chapter 2, Section 2.4.2. • Additional information and references pertaining to recombination of HAdVs have been included in Chapter 1, Section 3.4 and Chapter 2, Section 2.4.2. More details of relevant exclusion criteria in Chapter 1 Section 2.3.5 were added to address risk of recombination with wild type adenovirus so those with a current AdV infection are not vaccinated.
6	Department has reviewed the application and has no objections to the licence being issued.	• Submission has been noted.
7	As this GM vaccine is aerosolised and intranasally administered there is a high likelihood of sneezing response in participants which will generate aerosols. Is the administration being undertaken in a room/facility that has negative pressure?	• There is no requirement in the licence for a room with negative pressure to be used. Controls and licence conditions are in place to minimise the aerosol generation and exposure of the GM vaccines to people administering the vaccine (e.g. sneezing into tissues, PPE and trial participants remaining at the clinical trial site) as described in Chapter 2, Section 2.4.1 and the licence.
8	The members noted that, "the information presented in the RARMP concerning the risks associated with the proposed clinical trial with a Genetically Modified Organism (GMO) has detailed sufficiently within the context of its importation, transportation, disposal and storage, including dispensing, and administering	• Submission has been noted.

Submission	Summary of issues raised	Comment
	it to trial participants. They acknowledged that the safety and effectiveness of the GM vaccine in people receiving the vaccine (vaccine recipients) is under the remit of the Therapeutic Goods Administration (TGA)". Overall, the members support the conclusion that the application poses negligible risk of harm to the health and safety of people or the environment.	
9	The Regulator should further consider: • Whether administration should be limited to dedicated clinical facilities. • Controls to restrict potential spread of the GMO immediately after administration, e.g. appropriate personal protective equipment on trial participants. The committees agrees all plausible risk scenarios have been considered and agrees with the overall conclusion of the RARMP.	The applicant initially proposed to include general practice (GP) clinics as a site to conduct this clinical trial. Due to concerns regarding their suitability, the applicant has confirmed that the clinical trial for DIR 184 will only be carried out in dedicated phase I clinical trial sites. No GP clinics will be used in conducting the clinical trial. The risk of exposure to other people have been considered in risk scenarios 1 and 2 of the RARMP. The Regulator has reviewed the administration process, which: • requires the participant to practice proper hand hygiene, collect any nasal secretion (e.g. when sneezing immediately after administration) into tissues and dispose the tissues appropriately; and • appropriate PPE used during the administrative process. The risk of exposure was considered negligible because the limits and controls are considered sufficient to reduce the likelihood of exposure of other people. •

Appendix B: Summary of submissions from the public on the consultation RARMP

The Regulator received 2 submissions from the public on the consultation RARMP. The issue raised in the submission is summarised in the table below. All issues that related to risks to the health and safety of people and the environment were considered in the context of currently available scientific evidence in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence.

Submission	Summary of issues raised	Comment
1	Submitter stated, "Please stop this madness. The world has gone crazy and evil."	Submission has been noted.
2	Submitter is against the clinical trial and has raised concerns about: • deaths from COVID-19 vaccines; and • the purpose of clinical trials when "we already have safe affective cures that have been banned just to push the vaccine agenda. Proven to work and much cheaper and faster."	Submission has been noted. Possible risks for the vaccine recipients will be considered by the TGA. 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, and that any risks posed by the dealings can be managed by imposing conditions on the trial.

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

Licence for dealings involving an intentional release of a GMO into the environment

Licence No.: DIR 184

Licence holder: Avance Clinical Pty Ltd

Clinical trial with a genetically modified human adenovirus COVID-19 vaccine

Issued: 25 June 2021
Varied: 20 January 2023

Gene Technology Regulation in Australia

Australia's gene technology regulatory system operates as part of an integrated legislative framework. The *Gene Technology Act 2000* (Cth) and corresponding state and territory legislation form a substantial part of a nationally consistent regulatory system controlling the development and use of genetically modified organisms.

This licence is issued by the Gene Technology Regulator in accordance with the *Gene Technology Act 2000* and, as applicable, Corresponding State law.

The Gene Technology Regulator is required to consult with, and take into account advice from, a range of key stakeholders, including other regulatory authorities, on risks to human health and safety and to the environment in assessing applications for dealings involving the intentional release of genetically modified organisms into the Australian environment.

Other agencies that also regulate genetically modified organisms or GM products include Food Standards Australia New Zealand, Australian Pesticides and Veterinary Medicines Authority, Therapeutic Goods Administration, Australian Industrial Chemicals Introduction Scheme and the Department of Climate Change, Energy, the Environment and Water. Dealings conducted under any licence issued by the Regulator may also be subject to regulation by one or more of these agencies. It is recommended that the licence holder consult the relevant agency (or agencies) about their regulatory requirements.

The licence authorises the licence holder and persons covered by the licence to conduct specified dealings with the genetically modified organism(s) listed in Attachment A of this licence.

Further information on licence DIR 184

More information about the decision to issue this licence is contained in the Risk Assessment and Risk Management Plan prepared in connection with the assessment of the application for the licence. This document can be obtained from the Office of the Gene Technology Regulator (OGTR) website or by telephoning the Office on 1800 181 030.

CONDITIONS OF THIS LICENCE

1. In this licence:

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

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

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

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

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

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

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

2. In this licence:

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

'Analytical facility' means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC), and conforming to the AS/NZS 2243.3:2010 Safety in Laboratories: Microbiological Safety and Containment, particularly in relation to the handling of human diagnostic specimens.

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

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

(a) chemical treatment;

(b) autoclaving;

(c) high-temperature incineration; or

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

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

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

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

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

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

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

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

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

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

'Regulator' means the Gene Technology Regulator.

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

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

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

Holder of licence

3. The licence holder is Avance Clinical Pty Ltd.

Remaining an Accredited Organisation

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

Validity of licence

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

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

Persons covered by this licence

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

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

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

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

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

Description of GMOs covered

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

Dealings authorised by this licence

11. The dealings authorised by this licence are to:

    (a) import the GMO;

    (b) conduct the following experiments with the GMOs:

        i) prepare the GMO for administration;

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

        iii) collect Samples from trial participants;

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

    (c) transport the GMO; and

    (d) dispose of the GMOs;

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

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

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

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

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

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

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

    (c) the surrender of the licence.

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

Monitoring and audits (section 64)

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

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

15. The licence holder must inform the Regulator, if 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 dispersal of the GMOs.

Informing the Regulator of any material changes of circumstance

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

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

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

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

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

Further conditions with respect to informing persons covered by the licence

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

Note: Information required under Condition 18 may be provided to External service providers who are engaged solely for storage and transport of the GMO through labelling of the outermost container of the GMOs in accordance with Condition 34(a).

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

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

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

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

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

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

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

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

Note: The licence may be made available electronically.

Limits on clinical trials conducted under this licence

22. A maximum of 1000 trial participants may be inoculated with the GMO under the licence.

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

Conditions about trial participants

24. 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.

25. The licence holder must ensure that pregnant and breastfeeding women are excluded from being selected as trial participants.

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

    (a) remain within the Clinical trial site for a minimum of 4 hours; and

    (b) practice proper hand hygiene and collect any nasal secretion into tissues for the first 24 hours post-administration; and

    (c) dispose of used tissues into biohazard bag provided; and

    (d) return the biohazard bags during the follow up visit post-administration; and

    (e) not donate blood or organs for 90 days after the last dose of the GMO.

Conditions related to the conduct of the dealings

27. 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.

28. 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 at facilities which adhere to appropriate standards and guidelines, e.g. those developed by the National Pathology Accreditation Advisory Council for pathology practices, or the National Safety and Quality Health Service (NSQHS) Standards.

Preparation and administration of the GMOs and collection of samples

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

30. 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 38(a).

31. For the purposes of Condition 28, the work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) persons conducting dealings with the GMOs must wear personal protective equipment (PPE), including gowns, gloves and, unless working in a negatively pressured pharmaceutical isolator or a Class II Biological safety cabinet, eye protection and an N95 or equivalent facemask;

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

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

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

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

Transport, storage and disposal of the GMOs

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

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

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

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

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

34. The licence holder must ensure that transport and storage of the GMOs and samples at the Clinical trial site and within the Australian border, and transport for the purpose of import follows these sub-conditions:

(a) GMOs are 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 on how to clean up a spill, as per the contingency plan in Condition 37; and

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

(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 GMOs can be accounted for and that a loss of GMOs during transport or failure of delivery can be detected; and

(d) access to the GMOs is restricted to authorised persons for whom Condition 18 has been met (i.e. the GMOs are within a locked unit or an area which has restricted access). This includes situations where containers are left for collection in a holding area, or left unattended prior to decontamination; 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 GMOs are accompanied by authorised persons for whom Condition 18 has been met, Conditions 34(a)iii), 34(a)iv) and 34(c) do not apply.

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

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

Contingency plans

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

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

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

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

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

Notification and reporting

*Note: Notices may be by email to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at **Attachment B**.*

38. Prior to first administering the GMO at each Clinical trial site, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

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

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

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

(d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Conditions 40(b) and 40(c);

(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 28 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.

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

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

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

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

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

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

41. 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: 184

Full Title: Clinical trial with a genetically modified human adenovirus COVID-19 vaccine

Organisation Details

Postal address: Avance Clinical Pty Ltd
Level 1, 2 Ann Nelson Drive
Thebarton,
South Australia, 5031

Phone No: (08) 8159 6388

GMO Description

GMOs covered by this licence:

Human adenovirus C serotype 6 modified by introduction of the spike protein sequence of SARS-CoV-2 (Wuhan isolate) and deletion of the *IIIa* gene, large portion of the E3 region and E4 UXP ORF. This results in a replication defective vaccine vector that is able to induce an immune response towards the spike protein of SARS-CoV-2.

Parent Organisms:

Common Name: *Human adenovirus*

Scientific Name: *Human adenovirus C serotype 6 (HAdV-6 Strain Tonsil 99; American Type Culture Collection (ATCC) (VR-1083))*

Modified traits:

Categories: Vaccine – altered antigen expression

Vaccine – replication incompetent

Description: The GMO, is an attenuated human adenovirus derived from species C serotype 6. It has been modified to express the spike protein sequence of SARS-CoV-2 (Wuhan isolate), which will stimulate the immune response when administered as a vaccine. Attenuation has been achieved by deletion of the *IIIa* gene, large portion of the E3 region and E4 UXP ORF. Modified genes and regulatory sequences are listed in Table 1 below.

Table 1. Nucleic acid responsible for conferring the modified traits

Identity and modifications	Insert of a transgenic cassette containing: • Cytomegalovirus (CMV) enhancer/promoter • Human codon optimised gene coding for the spike protein of SARS-CoV-2 Wuhan isolate (NCBI reference sequence YP_009724390.1) • 3x short hairpin ribonucleic acid (shRNA) target sequences • LoxP-ZeoR-LoxP (LZL) • SV40 polyadenylation sequence Deletion of: • *IIIa* gene, large portion of E3 region and E4 UXP ORF
Function	• CMV – Activates transgene expression • SARS-CoV-2 – immunomodulatory - Mammalian-expression of SARS-CoV-2 viral spike protein • shRNA – Targeted during virus manufacture to supress transgene (SARS-CoV-2 viral spike protein) production • LZL – For bacterial selection during GMO development, retained to maintain an increased genome size • SV40 – Termination sequence for protein expression • *IIIa gene* – deletion results in adenovirus attenuation • Large portions of the E3 region – deletion reduces adenovirus immune evasion • E4 UXP ORF – deletion results in growth retardation

Purpose of the dealings with the GMOs:

To conduct clinical trials assessing the safety, tolerability, immunogenicity and efficacy of a genetically modified human adenovirus based vaccine to prevent COVID-19.

Attachment B

Prior to the commencement of the trial	Condition	Timeframe for reporting
A Compliance Management Plan for each trial site, including: • the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; • the key persons responsible for the management of the trial at the site; • the IBC associated with the site (if any) that has been notified of the trial; • the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of any self-reported incidents for the purposes of Condition 40(b), (c); • details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; • the person(s) or class of persons administering the GMO; • where, within the site, the GMO is expected to be administered; • expected date of first administration; and • how compliance with Condition 28 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO	38	Prior to the first administration of the GMO at the Clinical trial site
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	15(a), (c)	As soon as the licence holder becomes aware
Information related to any contravention of the licence by a person covered by the licence	15(b)	As soon as the licence holder becomes aware
Any relevant conviction of the licence holder	16(a)	Immediately
Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	16(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately

Prior to the commencement of the trial	Condition	Timeframe for reporting
Any Serious adverse event which may be related to the GMO	40(a)	As soon as reasonably possible
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	40(b), (c)	As soon as reasonably possible after becoming aware of the event
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	40(d)	As soon as reasonably possible after becoming aware of the event
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	41	Within a timeframe stipulated by the Regulator

Australian Government
Department of Health
Office of the Gene Technology Regulator

DIR-184

Clinical trial to determine the safety and efficacy of an adenovirus based COVID-19 vaccine (SC-Ad6-1)

Avance Clinical Pty Ltd

GTTAC Meeting 57
11 May 2021

Consultation process

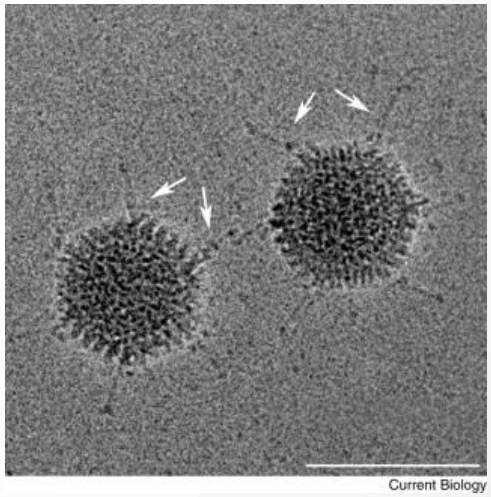
One round of consultation for limited and controlled

- Advice on the consultation Risk Assessment and Risk Management Plan (RARMP)
  - State and Territory governments
  - Prescribed Commonwealth authorities and agencies
  - Local Government Areas
  - Minister for the Environment
  - GTTAC
  - Submissions from the public

Chapter 1 – Risk Assessment Context

Parent organism

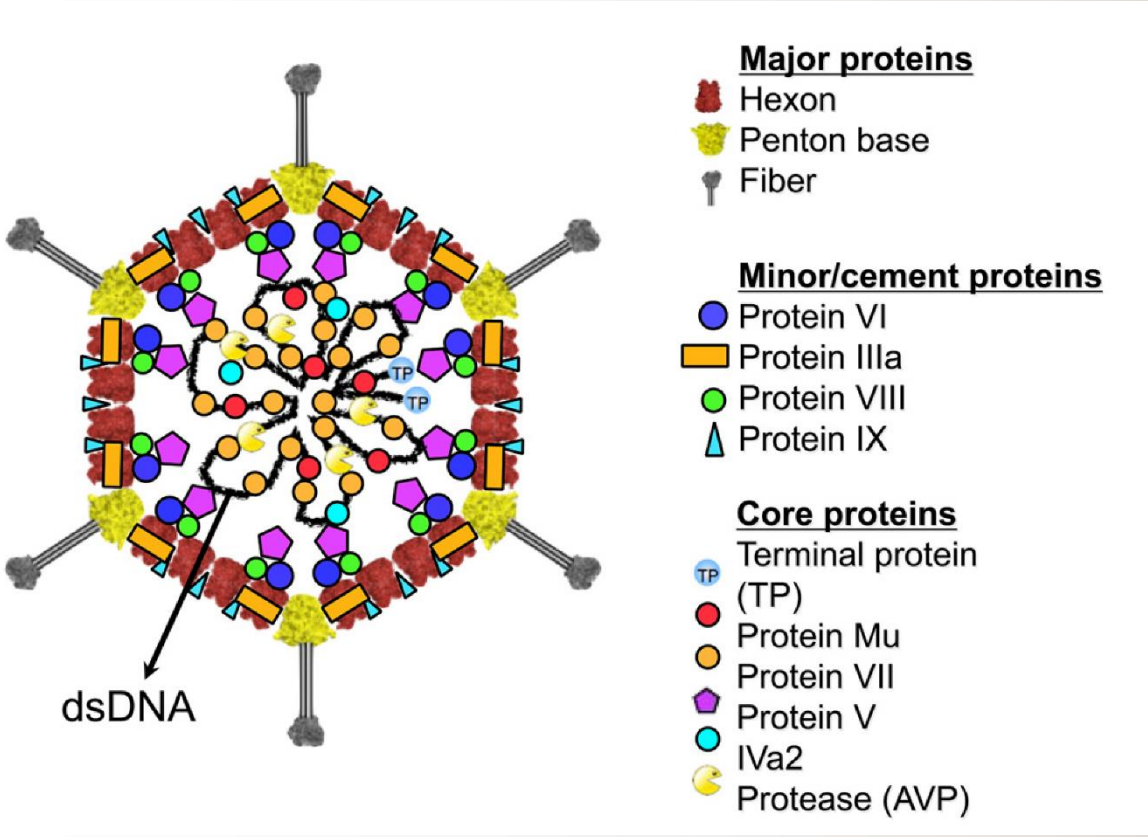
- Human adenovirus 6 (*Adenoviridae; Mastadenovirus)*
- Non-enveloped; icosahedral virus composed of a complex capsid surrounding the linear double-stranded DNA genome and core proteins
- Consists of seven species **(A – G)**
- Humans are natural host: cause mild respiratory tract, gastrointestinal tract and eye infections
- Adenovirus 6 belongs to **species C** – infections usually acquired in early childhood and is associated with respiratory infections.



Cryo-EM structure of human adenovirus 5

(Goosney, D.L. et al, 2017)

Adenovirus structure



Benevento, M., Di Palma, S., Snijder, J., Moyer, C.L., Reddy, V.S., Nemerow, G.R., and Heck, A.J.R. (2014). Adenovirus composition, proteolysis, and disassembly studied by in-depth qualitative and quantitative proteomics. Journal of Biological Chemistry *289*(16), 11421-11430. doi:10.1074/jbc.M113.537498

The GMO – SC-Ad6-1

1. Deletion of:
   - *IIIa* gene – unable to form capsid
   - Large portions of E3 regions – reduce immune evasion
   - E4 (*UXP* gene) – reduced replication

2. Insertion of transgene expression cassette into between Fiber and E4 gene containing:
   - Cytomegalovirus (CMV) promoter; and
   - Codon optimised full-length SARS-CoV-2 spike protein – expression of a stable SARS-CoV-2 spike protein; and
   - 3x shRNA target sites – represses transgene during production; and
   - Zeocin resistant gene – selectable marker; and
   - SV40 termination sequence – terminate protein expression

The GMO – SC-Ad6-1

1. Attenuated adenovirus vectors (e.g. AstraZeneca, Janssen) have the E1 region deleted:
    - Gene involved in viral replication.
    - Can only deliver one transcript of the transgene.

2. The GMO has an intact E1 region, but lack protein IIIa:
    - Can theoretically replicate the transgene 10,000 - 100,000 times in the transduced cell.
    - Unable to form mature infectious virus

3. Modifications potentially require only a single dose to reach similar immunogenicity as current ‘first generation’ COVID-19 vaccines.

Proposal

Purpose: To assess the safety, tolerability, immunogenicity and efficacy of SC-Ad6-1 as a second generation, prophylactic vaccine to prevent COVID-19.

Location: Nucleus network (Brisbane - confirmed), CMAX (Adelaide), Linear (Perth), Scientia (Sydney), hospitals, GP surgeries and other suitable clinical trial sites

Size: Up to 1000 healthy participants.
Phase 1 involves up to 100 participants.

Duration: 5 years

Administration: Intranasal (IN)

Doses <u>Phase I dose escalation:</u>

MAD Nasal™
Teleflex®

- <u>Part A</u>: Single dose at viral particles
- <u>Part B</u>: Two dose as selected from Part A, 21 days apart

Non-clinical data

With same vector

- Used as vaccine candidates for Ebola, Influenza A, HIV and *Clostridium difficile* (mice, Syrian hamsters and rhesus macaques).
- Vaccine candidates were efficacious and in some cases were effective in preventing the disease.

With GMO (SC-Ad6-1)

Other regulatory oversight

Department of Agriculture, Water and Environment (DAWE)

- Regulates importation of vaccine under the *Biosecurity Act 2015.*

TGA

- Assesses the safety, quality and efficacy of the vaccine including patient safety. Clinical trials that are experimental are regulated by the TGA through the Clinical Trial Approval (CTA) or the Clinical Trial Notification (CTN) scheme.

Human Research Ethics Committee (HREC)

- Ethical and scientific assessment of the clinical trial proposal and often considers issues of research governance.

National Safety and Quality Health Service (NSQHS)

- Accreditation of all public and private hospitals and day procedure services

Chapter 2 - Risk Assessment

- Three risk scenarios were postulated for the GMO

Risk Scenario 1

Expression of spike protein

Risk source: GMO

Exposure of other people and animals via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events:

(a) Preparation and administration
(b) During import, transport, storage and disposal
(c) Nasal discharge or shedding

⬇

Transduction of cells by GMO

⬇

Expression of the spike protein

⬇

Adverse immune reaction

Rationale

- GMO cannot form infectious virus particle.
- Smaller dose through accidental exposure.
- Import, transport, storage and disposal will follow well established procedures.

Negligible risk

Risk Scenario 2

Complementation and recombination

Risk source: 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 reaction / disease

Rationale

- Low reported HAdV-C infection rates in Australia.
- Recombination are rare and restricted to the same species.
- Recombination highly unlikely due to the packaging limit of vector.
- Multiple recombinations are required to produce a replication competent HAdV.

Negligible risk

Risk Scenario 3

Spills and sewerage

Risk source: GMO

GMO release into the environment (e.g. sewerage, spills)

⬇

Exposure to people or animals

⬇

As per scenario 1-2

Rationale

- GMO is unable to maintain a stable presence in the environment.
- GMO not known to naturally infect non-human host.
- As discussed in Risk Scenario 1 and 2.

Negligible risk

Conclusions of the Risk Assessment

The proposed clinical trial of the GM COVID-19 vaccine poses negligible risks to the health and safety of people or the environment as a result of gene technology.

Chapter 3 and 4

- As the level of risk is assessed as negligible, specific risk treatment is not required.
- However, general licence conditions are proposed to manage the risk context.
- The risk management plan is detailed in Chapter 3 of the consultation RARMP.
- The draft licence conditions are detailed in Chapter 4.

Key licence conditions

- Exclusion of pregnant and breast feeding women;
- PPE and relevant work practices during the preparation and administration of the GMO;
- Disposal and decontamination of GM waste;
- Requirements for the licence holder to educate trial participants on behaviours post GMO-administration;
- No blood or organ donations for 90 days after last dose;
- Contingency plan

Advice sought

- Does the committee agree that the post-administration procedure described in the consultation RARMP and included as licence condition 26 is sufficient to prevent the spread of the GMO in the environment and limit the exposure of carers and medical staff to the GMO?
- Does the risk assessment identify all plausible risk scenarios by which the proposed dealings could potentially give rise to risks relating to the health and safety of people or the environment?
- Does the committee agree that the limits and controls proposed in the draft licence to prevent the spread of the GMO are appropriate for the clinical trial?
- Is there additional relevant information that should be considered?
- Does the committee agree with the overall conclusion of the RARMP?

Theoretical recombination scenarios

Recombinant region	Resultant recombinant	Outcome	Likelihood
IIIa between • GMO • WT AdV	• Replication-competent GMO with *IIIa* gene • Attenuated AdV without the *IIIa* gene	• Replication-competent GMO that is still less immune evasive than WT, due to deletion of the E3 region • Attenuated AdV	Unlikely as these regions are not high homology region
E3 between • GMO • WT AdV	• Attenuated GMO with intact E3 region • Replication-competent AdV without the E3 region	• Attenuated GMO with restored immune-evasion properties. However, cannot produce mature viral particles due to deletion of the *IIIa* gene. • Replication-competent AdV without immune evasion properties	Unlikely as these regions are not high homology region
IIIa and E3 between • GMO • WT AdV	• Replication-competent GMO with intact *IIIa* gene and E3 region • Attenuated AdV without the *IIIa* gene and E3 region	• Replication-competent GMO with restored immune evasion properties. • Attenuated AdV without immune evasion properties	Unlikely as these regions are not high homology region
Transgenic cassette between • GMO • WT AdV	• Attenuated GMO without the transgenic cassette • Replication-competent AdV with the transgenic cassette	• Attenuated GMO that is still less immune evasive than WT, due to deletion of the E3 region • Replication-competent AdV expressing the spike protein	Unlikely
Theoretical regions that may recombine (E1 and E4) • GMO • WT AdV	• GMO or WT with different E1 genes • GMO, with E4 *UXP* gene • WT AdV with without *UXP* gene	• No phenotypic changes are expected for GMO and WT • GMO with similar growth rate to WT • Mild retardation in WT AdV growth	Unlikely