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