Australian Government
Department of Health
Office of the Gene Technology Regulator

Licence for dealings involving a clinical trial of a GMO into the environment

Licence No.: DIR 177

Licence holder: Novotech (Australia) Pty Ltd

Clinical trial of genetically modified human adenovirus for bladder cancer treatment

Issued: 01 February 2021

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 Agriculture, Water and the Environment. 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 177

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.

Section 1 Interpretations and Definitions

1. In this licence:

   (a) unless defined otherwise, words and phrases used have the same meaning as they do in the Act and the Gene Technology Regulations 2001 (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 standard conditions to the extent of any inconsistency.

2. In this licence:

'Act' means the *Gene Technology Act 2000* (Cth) or the corresponding State legislation 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 clinical trial facility or hospital, in Australia, that is notified to the Regulator for the purposes of conducting clinical trials authorised by this licence.

'Contingency Plan' means a written plan detailing measures to be taken if certain events, as specified in Condition 33, occur.

'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.

'Dwell time' means the time elapsed from the instillation of the GMO into the bladder of clinical trial participants, until the drainage of the bladder content one hour later.

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

'**GM**' means genetically modified.

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

'**OGTR**' means the Office of the Gene Technology Regulator.

'**Personal information**' means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

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

(b) whether the information 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 medical environment.

'**Regulator**' means the Gene Technology Regulator.

'**Sample**' means any biological material collected from an inoculated trial participant for analysis as part of the trial, and which may reasonably be expected to contain GMOs.

'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.

'TGA' means Therapeutic Goods Administration.

Section 2 General conditions and obligations

Holder of licence

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

Remaining an accredited organisation

4. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.

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 dealings with the GMOs is restricted in accordance with condition 19.

Description of GMOs covered

6. The GMO covered by this licence is a GM human adenovirus, as described in **Attachment A** of the licence.

Dealings authorised by this licence

7. The dealings authorised by this licence are to:

a) import the GMO;

b) conduct experiments with the GMO:

i) prepare the GMO for administration to trial participants;

ii) administer the GMO to trial participants intravesically;

iii) collect Samples from trial participants, and

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

c) transport the GMO;

d) dispose of the GMO,

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

8. Supply of the GMO for the purposes of dealings by a person or organisation not covered by the 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 licence.

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

Persons covered by the licence

10. The persons covered by this licence are the licence holder and employees, agents or contractors of the licence holder (including External service providers), or the project supervisor(s), 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 this licence.

Obligations of the Licence Holder

11. The licence holder must inform any person covered by this 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 11 does not apply to trial participants.

12. 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 12 may be provided to External service providers who are engaged solely for storage, transport and/or disposal of the GMO and waste containing the GMO through labelling of the outermost container of the GMOs in accordance with Conditions 30 and 31.

13. 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 of the particular licence condition(s) including any variation of them; and

ii) has understood and agreed to be bound by the licence conditions, or 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 safely conduct the dealings in accordance with the conditions of this licence.

14. The licence holder must inform the persons covered by this licence to whom a particular condition applies that any Personal information relevant to the administration and/or enforcement of the licence may be disclosed to the Regulator.

15. The licence holder must ensure that each trial participant is notified that Personal information collected by the licence holder which is relevant to the administration and/or enforcement of the licence may be disclosed to the Regulator.

16. 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

Obligations of persons covered by the licence

17. 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 the 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.

Section 3 Limits and control measures

Limits on clinical trials conducted under this licence

18. A maximum of 60 trial participants may be administered the GMO under the licence.

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

20. Preparation and administration of the GMO to trial participants must be conducted within a Clinical trial site.

21. Administration of the GMO to trial participants must not commence prior to approval by a Human Research Ethics Committee.

Control measures

General conduct of clinical trials

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

(a) maintains containment of the GMOs

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

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

Note: The licence holder may achieve this by only engaging or otherwise authorising persons to conduct dealings who are required to adhere to appropriate standards and guidelines. For example standards developed by the National Pathology Accreditation Advisory Council for pathology practices, the Australian Guidelines for the Prevention and Control of Infection in Healthcare, Guidelines for Good Clinical Practice and the National Safety and Quality Health Service (NSQHS) Standards, or the behavioural requirements for dealings conducted in OGTR certified facilities.

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

Work practices at Clinical trial sites

24. The following work practices and behaviours, where applicable, must be followed during preparation and administration of the GMO:

(a) dealings with the GMO within the Clinical trial site and the Pharmacy must be conducted in such a way as to minimise the likelihood of spills and generation of aerosols and using equipment that is tested and maintained according to the manufacturer's instructions;

(b) all work surfaces used for preparation of the GMO and any equipment potentially contaminated with the GMO must be decontaminated immediately after they have been used for conducting dealings authorised by this licence with a decontaminant that is known to be effective against the GMO. This includes floors in the administration room if required;

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

(d) persons preparing or administering the GMO must wear personal protective equipment including face shield, gloves and gown;

(e) persons preparing or administering the GMO must adhere to procedures for safe handling of sharps in effect at the Clinical trial site;

Note: 'sharps' includes any object (in its intact or broken form) able to pierce human skin.

(f) an absorbent pad must be placed underneath the trial participants and a suitable absorbent material must secure the catheter entry to prevent any leaks. All materials

that have been in contact with the GMO must be disposed of in accordance with condition 29;

(g) during administration of the GMO (including the Dwell time), trial participants must wear a disposable gown and must not leave the trial room, and

(h) following the Dwell time, the content of participants' bladder must be drained via a catheter into a PVC bag, double contained and disposed as clinical waste.

Preventive practices required post-administration

25. Prior to administration of the first dose to each participant, the licence holder must obtain a written agreement from the participant to adhere to condition 25(a) to (j):

(a) for 30 days following each administration of the GMO, trial participants must only urinate in toilets (excluding urinals), and must protect others from exposure to their urine by following instructions imposed by the licence holder;

(b) for the first 5 days following the first administration of the GMO and 24 hours following any subsequent administrations, trial participants must decontaminate their urine and avoid using public toilets, unless absolutely necessary;

(c) for the first 14 days following each administration, trial participants must wash their hands frequently and after every urination using soap and water;

(d) for the first 14 days following each administration, sanitary pads and other sanitary items that have been in direct contact with urine are to be contained in a sealed plastic bag (e.g. zip-lock bag) and disposed with household waste or returned to the Clinical trial site. Toilets must be cleaned as per instructions from licence holder;

(e) for the first 14 days following each administration of the GMO, items that have been in contact with participant's urine (e.g. clothing, sheets, towels) must be laundered according to the instructions provided by the licence holder;

(f) for the first 14 days following each administration, if trial participants have symptoms of respiratory illness, they must wear a mask while in public places and around people, wash their hands frequently using soap and warm water;

(g) for 30 days following each administration, trial participants must avoid physical contact with immunocompromised people, pregnant or nursing women and children under 12 months of age;

(h) for the first 14 days following each administration, trial participants must avoid close-physical contact with other people including any sexual activity;

(i) for the first 14 days following each administration of the GMO, trial participants must not use shared, enclosed bathing and swimming facilities such as, but not limited to bathtubs and swimming pools, and

(j) trial participants must not be pregnant during the duration of the trial.

26. The licence holder must instruct trial participants on decontamination procedures and ensure that trial participants have access to disinfectant that is known to be effective against the GMO (e.g. bleach with a desired concentration of active chlorine).

Transport, storage and disposal of the GMOs

27. 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, for supply in accordance with condition 8, or for export.

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

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

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

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

29. The licence holder must ensure that transport and storage of the GMOs within the Clinical trial site 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 to notify the licence holder in case of loss or spill of the GMOs; and instructions on how to clean up a spill, as per the contingency plan in Condition 33; and

(b) external surfaces of the primary and secondary container 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 12 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, and the GMOs are accompanied by authorised persons for whom Condition 12 has been met, Conditions 29(a)iii), 29(a)iv) and 29(c) do not apply.

30. For the purpose of import or export and transport between the border and the Clinical trial site, the licence holder must ensure the GMO is packaged, labelled, stored and transported in accordance with IATA classification UN 3373 [Category B].

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

Note: In the event of a spill during transport by an External service provider, this licence does not override requirements arising under State or Territory legislation and regulations to manage clinical or biohazardous spills.

Contingency plans

32. At least 14 days prior to first administering the GMO at each Clinical trial site, the licence holder must provide to the Regulator a written Contingency Plan applicable to that Clinical trial site detailing measures to be taken in the event of:

(a) the unintentional release of the GMOs, such as a spill of the GMO;

(b) suspected or confirmed transmission of the GMOs to persons other than trial participants, and

(c) a person exposed to the GMOs (including a trial participant) developing a serious adverse event linked to the GMOs, including those known to result from infection with human adenovirus.

Note: A Contingency Plan may be applicable to more than one Clinical trial site

33. The Contingency Plan must include details of procedures to:

(a) ensure the Regulator is notified as soon as reasonably possible after the licence holder becomes aware of the event;

(b) if there is a spill of the GMO, such as during transport, and storage within a Clinical trial site, implement the following measures:

i) contain the GMOs to prevent further dispersal, and

ii) decontaminate the exposed area with an appropriate chemical disinfectant effective against the GMOs;

(c) if transmission of the GMOs to people other than trial participants is suspected or confirmed, provide medical treatment to affected persons as necessary, and

(d) if a person exposed to the GMO exhibits symptoms of a severe adverse response:

i) provide appropriate medical treatment to the affected person and

ii) implement measures to prevent the spread or persistence of the GMO.

34. If any of the events described in condition 33 occur, the licence holder must ensure that the appropriate procedure(s) from the Contingency Plan are implemented.

Note: The Contingency Plan is to be provided to the Regulator as per condition 33.

Section 4 Reporting and Documentation

The following licence conditions are imposed to demonstrate compliance with other conditions and facilitate monitoring of compliance by staff of the OGTR.

Notifications to the Regulator

35. General notifications must be sent to the Regulator as follows:

Note: Please send all correspondence related to the licence to OGTR.M&C@health.gov.au

Notice	Content of notice	Timeframe
Changes to contact details	Changes to any of the contact details of the contact person(s) for the licence or project supervisor(s) from that notified in the licence application or subsequently.	As soon as practicable.
Ongoing suitability to hold a licence	The licence holder must inform the Regulator of: i. Any relevant conviction of the licence holder; or ii. any revocation or suspension of a licence or permit held by the licence holder under a law of the Australian Government, a State or a foreign country, being a law relating to the health and safety of people or the environment; or iii. any event or circumstances that would affect the capacity of the licence holder to meet the conditions of the licence; and	Immediately after any of these events occur.
	iv. any information related to the licence holder's ongoing suitability to hold a licence, that is requested by the Regulator.	Within the timeframe stipulated by the Regulator.
People covered by the licence	i. Names of all organisations and persons, or functions or positions of the persons, who will be covered by the licence, with a description of their responsibilities; *Note 1: Examples of functions or positions are 'project supervisor', 'pharmacist', 'waste contractor', etc.* ii. details of how the persons covered by the licence will be informed of licence conditions; *Note 2: This may include a description of any contracts, training, labelling, contractual agreements with other organisations or persons* iii. contact details of the project supervisor(s) for the licence.	At least 14 days prior to conducting any dealings with the GMOs (to be updated within 14 days if the notified details change).
Contingency Plan(s)	Contingency Plan(s), required under Condition 32, including the details specified in Condition 33.	
Training records	Copies of the signed and dated statements referred to in Condition 13.	Within the timeframe stipulated by the Regulator.
Additional information required by the Act	The licence holder must inform the Regulator, if the licence holder becomes aware of: i. additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or	Without delay after becoming aware of any new information. *Note: An example of notification without delay*

Notice	Content of notice	Timeframe
	ii. any contraventions of the licence by a person covered by the licence; or iii. any unintended effects of the dealings authorised by the licence. *Note 1: The Act requires, for the purposes of the Condition 35, that:* • *the licence holder will be taken to have become aware of additional information of a kind mentioned in Condition 35 if he or she was reckless as to whether such information existed; and* • *the licence holder will be taken to have become aware of contraventions, or unintended effects, of a kind mentioned in Condition 35, 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.*	*is contact made within a day of the incident via the OGTR free call phone number 1800 181 030, which provides emergency numbers for incidents that occur out of business hours. Notification without delay will allow the OGTR to conduct a risk assessment on the incident and attend the location, if required.*
Further details regarding additional information	Any further details requested by the Regulator in relation to information provided under Condition 35.	Within the timeframe stipulated by the Regulator.
Notification of Serious adverse event	In the event of a trial participant experiencing a Serious adverse event which may potentially be related to the GMO, the licence holder must notify the Regulator	As soon as reasonably possible.
Notification of loss or spill, or exposure of persons	The licence holder must notify the Regulator if they are notified or otherwise become aware of a loss or spill of the GMO, or of the exposure of a person other than a trial participant to the GMO	As soon as reasonably possible.
Signed records or documentation	Upon request from the Regulator, the licence holder must provide any signed records or documents collected under a condition of this licence	Within the timeframe stipulated by the Regulator.

36. Notifications relating to each Clinical trial site must be sent to the Regulator as follows:

Note: please send all correspondence related to the licence to OGTR.M&C@health.gov.au

Notice	Content of notice	Timeframe
Compliance Management Plan	A written Compliance Management Plan must be submitted for each Clinical trial site, detailing to the satisfaction of the Regulator: i. the name, address and description of the Clinical trial site, including any associated pharmacies/storage areas/analytical facilities ii. the key persons responsible for the management of the trial at the site; iii. that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial;	At least 14 days before first administration of the GMO at that particular Clinical trial site.

Notice	Content of notice	Timeframe
	iv. 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 *35*; v. 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; vi. the person(s) or class of persons administering the GMO; vii. where, within the site, the GMO is expected to be administered; viii. expected date of first administration of 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.*	
Notification of final administration	Provide notification to the Regulator, in writing, of the final administration of the GMO to the last trial participant at each Clinical trial site	Within 30 days of the decision to cease administrations at that particular Clinical trial site.

ATTACHMENT A

DIR No: 177

Full Title:	Clinical trial of genetically modified human adenovirus for bladder cancer treatment

Organisation Details

Postal address:	Novotech (Australia) Pty Limited Level 2 381 MacArthur Avenue HAMILTON QLD 4007
Phone No:	0421 515 326

IBC Details

IBC Name:	BioDesk IBC

GMO Description

GMOs covered by this licence:

Human Adenovirus 5 genetically modified by introduction or deletion of only the genes or genetic elements listed below.

Parent Organisms:

Common Name:	Adenovirus
Scientific Name:	Human Adenovirus type 5

Modified traits:

Categories:	human therapeutic - attenuation
Description:	The GMO is a live adenovirus modified to preferentially multiply in and destroy cancer cells. Modified genes are listed in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Identity	• E3-19k gene region • E1a promoter
Modifications	• Replacement of the E3-19k gene region with a human granulocyte macrophage colony-stimulating factor gene (hGM-CSF) • Substitution of the endogenous E1a promoter with a human hE2F-1 promoter
Function	• hGM-CSF stimulates an anti-tumour response • hE2F-1 promoter enables conditional replication RB-pathway defective cancer cells

Purpose of the dealings with the GMOs:

To conduct clinical trials assessing the safety, tolerability and efficacy of the GM treatment in patient that have been unresponsive to other treatments.