



Australian Government

Department of Health

Office of the Gene Technology Regulator

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

Licence No.: DIR 144

Licence holder: Novotech (Australia) Pty Ltd

Title: Clinical trial of live attenuated genetically modified influenza vaccines

Issued: 1 August 2016

Varied: 9 December 2016

Varied: 06 July 2020

Transferred to Novotech (Australia) Pty Ltd: 18 March 2021

Varied: 19 July 2021

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 website or by telephoning the Office on 1800 181 030.

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 activities involving genetically modified organisms (GMOs).

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 GMOs into the Australian environment.

Other agencies that also regulate GMOs or GM products include Food Standards Australia New Zealand, Australian Pesticides and Veterinary Medicines Authority, Therapeutic Goods Administration, National Industrial Chemicals Notification and Assessment Scheme and the Department of Agriculture. 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 listed in **Attachment A** of this licence. Dealings permitted by this licence may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

Section 1 Interpretations and definitions

1. In this licence:
 - a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;
 - b) words importing a gender include any other gender;
 - c) words in the singular include the plural and words in the plural include the singular;
 - d) words importing 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* (Commonwealth) or the corresponding State legislation under which this licence is issued.

'Analytical facility' means a laboratory or premises that performs testing and/or analysis on biological samples (e.g. blood, tissue, cells, proteins, nucleotides) in Australia.

'Annual Report' means a written report provided to the Regulator within 90 days of each anniversary of issue of this licence containing all the information required by this licence to be provided in the Annual Report.

'Destroy', (or **'Destroyed'** or **'Destruction'**) means, as the case requires, killed by one or more of the following methods:

- a) treatment with chemical disinfectant;
- b) autoclaving;
- c) high-temperature incineration; and
- d) any other methods used by Study Sites for disposal of infectious clinical waste.

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

'Excluded Persons' means persons those with a known immune deficiency, including persons with Human Immunodeficiency Virus (HIV);

'GM' means genetically modified.

'GMOs' means the genetically modified organisms the subject of the dealings authorised by this licence.

'ICH-GCP' means the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - *Guidelines for Good Clinical Practice*.

'Material' means non-biological material used in conjunction with the GMO, such as syringes, swabs, vials, gloves or for the clean-up of spills.

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

'Personal Information' means information or an opinion (including information forming part of a database), whether true or not, and whether recorded in a material form or not, about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion.

'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.

'Study Site' means a medical facility in Australia such as a clinical facility or hospital that is approved in writing by the Regulator for the purposes of conducting this clinical trial.

'TGA GCP Guidelines' means the TGA *Note for Guidance on Good Clinical Practice* designated CPMP/ICH/135/95.

Section 2 General conditions

3. This licence does not authorise dealings with GMOs that are otherwise prohibited as a result of the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.
4. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension.
5. The holder of this licence ('the licence holder') is Novotech (Australia) Pty Ltd.
6. The persons covered by this licence are 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 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 only dealings authorised by this licence are to:
 - a) import the GMO;
 - b) conduct the following experiments with the GMO:
 - i. administration of the GMO to trial participants by nasal administration, intramuscular injection or subcutaneous injection;
 - ii. collection of samples that may reasonably be expected to contain the GMO from trial participants; and
 - iii. *in vitro* analysis of the samples mentioned in (b)(ii).
 - c) transport the GMO;
 - d) dispose of the GMO;

and possession, storage, supply and use of the GMO in the course of any of these dealings.

General conditions on the Licence Holder

9. The licence holder must immediately notify the Regulator in writing if any of the details of the contact person for the licence change.

Note: please address correspondence to ogtr.applications@health.gov.au.

Prior to issuing a licence, the Regulator considers suitability of the applicant to hold a licence. The following conditions address ongoing suitability of the licence holder.

10. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.
11. The licence holder must:
 - a) inform the Regulator immediately in writing, of:
 - i. any relevant conviction of the licence holder occurring after the commencement of this licence; and
 - 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; and

- iii. any event or circumstances occurring after the commencement of this licence that would affect the capacity of the holder of this licence to meet the conditions in it; and
- b) provide any information related to the licence holder's ongoing suitability to hold a licence, if requested, within the stipulated timeframe.

The following conditions seek to ensure that persons conducting the dealings are aware of the licence conditions and appropriate processes are in place to inform people of their obligations.

12. Before commencing the clinical trial with the GMO at each Study Site or Analytical facility, the licence holder must provide the Regulator with:

- a) the names of all organisations and persons (other than trial participants), or functions or positions of persons, who will be covered by the licence at that Study Site or Analytical facility, with a description of their responsibilities; and

Note: Examples of functions or positions are 'Principal Investigator', 'Clinical research assistant' etc.

- b) details of how the persons covered by the licence will be informed of licence conditions;

Note: this may include training, labelling, contractual agreements with other organisations such as contract research organisations, clinical waste treatment providers and courier companies, etc.

- c) details of how the licence holder will ensure compliance with licence conditions at the Study Site or Analytical facility over the period that dealings are being conducted at the Study Site or Analytical facility.

Note: this may include a description of any contracts, agreements, or other enforceable arrangements.

13. Any changes to the information required under Condition 12 must be communicated in writing to the Regulator within 14 days of the changes occurring.

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

- a) the particular condition (including any variations of it);
- b) the cancellation or suspension of the licence;
- c) the surrender of the licence.

Note: No conditions of this licence, including Condition 14, apply to trial participants.

Information required under Condition 14 may be provided to contractors who are engaged solely for the transport and/or disposal of the GMOs through labelling the outermost container of the GMOs.

15. Subject to condition 16, the licence holder must not permit a person covered by this licence to conduct any dealing unless:

- a) the person has been informed of the licence conditions, including any variation of the licence; and
- b) the person has been trained in a manner which enables them to:

- i. safely conduct the dealings in accordance with the conditions of this licence; and
 - ii. meet the work practices and behavioural requirements for conducting the dealings in Study Sites; and
- c) the licence holder has obtained from the person a signed and dated statement that the person:
 - iii. has been informed by the licence holder of the licence conditions including any variation of the licence; and
 - iv. has understood and agreed to be bound by the licence conditions, or its variations; and
 - v. has been trained in accordance with paragraph (b).

16. The licence holder is not required to comply with any part of paragraph (b) or (c) of Condition 15 in relation to the following classes of person:

- a) personnel at Analytical facilities;
- b) contractors transporting the GMOs from the point of import directly to a Study Site, provided the consignment is:
 - i. clearly labelled to indicate (at a minimum) that it contains GMOs and is authorised under the *Gene Technology Act 2000* through licence DIR 144;
 - ii. packaged and transported according to IATA requirements for class UN 3373; and
 - iii. only to be transported within Australia from the point of import directly to a Study Site.
- c) contractors engaged solely for transport and/or disposal of the GMOs within Australia, or for export provided:
 - i. the GMOs are double contained; and
 - ii. the outermost container is labelled to indicate (at a minimum):
 - that it contains GMOs;
 - the contact details for the licence holder; and
 - instructions to notify the licence holder as soon as practicable in case of an unintentional release of the GMOs; and
 - where transport is for the purpose of disposal, that the GMOs must be destroyed by autoclaving, high-temperature incineration, chemical treatment or otherwise destroyed as clinical waste.

17. The licence holder must:

- a) inform the persons covered by this licence that any Personal Information relevant to the administration and/or enforcement of the licence may be released to the Regulator; and
- b) provide the Regulator, if requested, with copies of the signed and dated statements referred to in Condition 15.

Provision of new information to the Regulator

Licence conditions are based on the risk assessment and risk management plan developed in relation to the application using information available at the time of assessment. The following condition requires that any new information that may affect the risk assessment is communicated to the Regulator.

18. The licence holder must inform the Regulator, if the licence holder becomes aware of:
- a) 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
 - 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: The Act requires, for the purposes of the above condition, that:

- a) *the licence holder will be 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 will be 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.*

19. If the licence holder is required to inform the Regulator under Condition 18, the Regulator must be informed as soon as reasonably possible.

General conditions on persons covered by the licence

20. Persons covered by this licence must not deal with the GMO except as expressly permitted by this licence.

21. 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.

Note: The Licence holder must have processes in place to ensure waste contractors are informed of their obligations in relation to Condition 21.

Section 3 Limits and control measures

Note: This licence does not expressly authorise or prohibit any dealings or storage in certified physical containment facilities. Under the Act it is not an offence to deal with a GMO if the dealing is otherwise licenced or if it is an NLRD or an exempt dealing and it complies with all relevant statutory requirements.

Limits on the release

The following licence conditions maintain the risk assessment context within which the application was assessed by imposing limits on where and when experiments with the GMOs may be performed, and on other activities that can be undertaken.

22. The GMOs covered by this licence are CodaVax and FluMist, as described in **Attachment A** of the licence.
23. Details of each Study Site or Analytical facility must be notified to the Regulator at least 7 days before commencement of dealings with the GMOs at that Study Site or Analytical facility.

24. All dealings permitted under this licence must be conducted within Study Sites or Analytical Facilities, except for:

- a) import;
- b) transport;
- c) disposal;

and storage of the GMO in the course of any of these dealings.

25. A maximum of 500 trial participants may be inoculated with the GMOs.

26. Trial participants inoculated with the GMOs must be healthy adults.

Controls on the Release

The following licence conditions manage the identified risks, and maintain the risk assessment context within which the application was assessed.

Conduct of the clinical trial

27. The licence holder must ensure that the trial is conducted according to ICH-GCP and TGA GCP Guidelines and WHO Universal Standard Precautions.

28. The licence holder must ensure that Excluded Persons are excluded from directly handling the GMOs, administering it to patients or caring for trial participants.

29. Procedures must be in place to account for the contents of all vials containing GMOs that are imported into Australia under this licence. The GMOs must be accounted for from import to destruction or export, and records must be made available to the Regulator on request.

30. If any of the events described in Condition 43 occur, the appropriate procedure(s) from the Contingency Plan must be implemented.

Conditions relating to trial participants

31. The licence holder and persons administering the GMO must ensure that exclusion criteria used in selecting trial participants include (but need not be limited to) the following:

- a) persons who are Excluded Persons; and
- b) persons who are unable or unwilling to comply with the requirements listed in Condition 31.

32. The licence holder must ensure that trial participants are educated about the potential for transmission of the GMOs to untreated people and animals and measures to prevent transmission, and obtain trial participants' written agreement that, for 7 days following inoculation with the GMOs, they will:

- a) implement hygiene measures intended to prevent interpersonal transmission of the GMOs, including but not limited to frequent hand washing with soap or hand disinfectant, respiratory hygiene and cough etiquette, and refraining from blood, tissue or organ donation;
- b) not to care for severely immunosuppressed persons who require a protective environment and to avoid contact with such persons;
- c) seal used tissues and other materials used to collect respiratory secretions *or any contaminated bandage* in a primary container (e.g. a sealable plastic bag), place these within a secondary container provided by the Study Site, and store the secondary container such that it is inaccessible to children and animals until it is returned to the Study Site; and

- d) return the secondary container referred to above to the Study Site for disposal as clinical waste.
33. Records of trial participants' agreements as required under Condition 31 must be made available to the Regulator on request.
34. The licence holder must ensure that persons are not enrolled in the trial unless they have indicated that they are not likely to come into contact with Excluded Persons within 7 days of inoculation with the GMOs. This must be documented in writing for each trial participant and records made available to the Regulator on request.
35. The licence holder must ensure trial participants are provided with a supply of primary and secondary containers appropriate for storing and transporting waste back to the Study Site. Secondary containers must be labelled:
- a) to indicate that it contains GMOs;
 - b) to indicate that it must be destroyed by autoclaving, high-temperature incineration, chemical treatment or as clinical waste; and
 - c) with contact details for the Study Site.

Work practices at Study Sites

36. When undertaking a dealing with a GMO at a Study Site, including storage and disposal, persons covered by this licence must employ work practices and behaviours which:
- a) ensure containment of the GMO; and
 - b) do not compromise the health and safety of people; and
 - c) minimise the exposure of persons undertaking the dealings to the GMOs, other than intended exposure of trial participants.
37. For the purposes of Condition 35, the work practices and behaviours must include, but are not limited to, the following:
- a) all inoculations of the GMOs must be administered by suitably qualified and trained medical staff; and
 - b) when dispensing and administering the GMO, clinical trial staff must:
 - i. use a Class II biosafety cabinet to prepare the inoculum;
 - ii. wear personal protective equipment including a laboratory coat or gown, gloves, eye protection and mask;
 - iii. follow institutional procedures for safe handling of sharps.

Patient samples containing the GMO

38. Where a sample taken from a trial participant contains the GMO, or may reasonably be expected to contain the GMO, the sample must be treated as if it were the GMO.

Storage of the GMO

39. Storage of the GMO at Study Sites must be in accordance with Part 2.1 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*, as current at the time of storage.

40. Samples that may reasonably be expected to contain the GMO that are stored in Analytical Facilities must be stored under two levels of containment. The outermost container must be unbreakable and clearly labelled to indicate that it contains or may contain a GMO.

Note: In the case of a small storage unit such as a fridge, freezer or liquid nitrogen container, the secondary container may be the storage unit.

Transport and Disposal of the GMO

41. Transport of the GMO must be in accordance with Part 1.2 of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* in force at the time of transportation, unless:

- a) the transport is by contractors transporting the GMO from the point of import directly to a Study Site, and the transport is in accordance with Condition 16 (b); or
- b) the transport is by contractors for the purpose of disposal and is in accordance with Condition 16 (c);
- c) waste potentially contaminated with the GMO is being returned to the treating Study Site by a trial participant.

42. Decontamination of the GMO or waste containing the GMO must be by autoclaving, high temperature incineration, chemical treatment or other method used by a Study Site for disposal of infectious clinical waste.

43. Unless covered by another authorisation, the GMO and any Material or waste containing the GMO must be destroyed or exported, on or before expiration of the licence.

Note: Condition 28 requires the licence holder to account for all GMOs under this licence from import to destruction or export, and to make records available to the Regulator on request.

Contingency Plans

44. Before any trial participant is inoculated with the GMOs at a Study site, a written Contingency Plan applicable to that Study site must be submitted to the Regulator detailing measures to be taken in the event of:

- a) the unintentional release of the GMO, such as a spill outside of a Study Site;
- b) suspected or confirmed transmission 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 exposure to the GMO, including those known to result from infection with *influenza virus*.

Note: A contingency plan may be applicable to more than one Study site.

Note 2: Serious adverse events linked to exposure to the GMOs must also be reported in the Annual Report to the Regulator.

45. 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; and
- b) if there is a spill of the GMO, such as during import, transport, storage or disposal, 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 appropriate medical treatment to affected persons as necessary;
- 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 prevent the spread or persistence of the GMO.

Section 4 Additional Reporting Requirements

Notice of commencement and completion of the trial

46. The licence holder must notify the Regulator of the following:
- a) the first inoculation of the first trial participant at each Study Site, within 7 days of the event; and
 - b) the final inoculation of the last trial participant at each Study Site, within 30 days of the decision to cease inoculations at the Study Site.

Annual Report

47. The licence holder must provide an Annual Report to the Regulator that includes:
- a) the number of trial participants inoculated with the GMO at each Study Site under this licence in the previous 12 months; and
 - b) details of any Serious adverse events linked to exposure to the GMOs.

Testing methodology

48. The licence holder must provide the Regulator with written methodology to reliably detect both the presence of the GMOs and the genetic modifications in the GMOs authorised by this licence, in a recipient organism. The detection method should be capable of reliably distinguishing between GMOs described in this licence and the parent organisms. A detection method applicable for each GMO must be provided prior to commencing any dealings with that GMO.

DIR No: 144

Full Title: Clinical trial of live attenuated genetically modified influenza vaccines

Organisation Details

Postal address: Novotech (Australia) Pty Ltd
Level 2, 381 MacArthur Ave
Hamilton QLD 4007

Phone No (07) 3137 6200

IBC Details

IBC Name: BioDesk Institutional Biosafety Committee

GMO Description

GMO type 1: *CodaVax and other Synthetic Attenuated Virus Engineering (SAVE) influenza vaccines*

Influenza A and B Virus genetically modified by codon deoptimisation through incorporating a large number of point mutations to the haemagglutinin and neuraminidase genome segments, known as CodaVax or *other Synthetic Attenuated Virus Engineering (SAVE) influenza vaccines*.

Parent Organism:

Common Name: Influenza virus

Scientific Name: Human *influenza A or B virus* (all subtypes and strains)

Modified traits:

Categories: human therapeutic – attenuation

Description: CodaVax or other Synthetic Attenuated Virus Engineering (SAVE) influenza vaccines are live attenuated influenza vaccines derived from influenza A or B virus strains, modified to attenuate the virus while retaining the ability to elicit an immune response. The full complement of influenza virus genome segments, generated by *de novo* DNA synthesis, are transfected into tissue culture cells where they replicate to produce new virions with the desired attenuated genotype.

Nucleic acid responsible for conferring the modified traits:

Source	<ul style="list-style-type: none"> influenza A or B virus strain
Identity	<ul style="list-style-type: none"> Entire haemagglutinin genome segment Entire neuraminidase genome segment
Function	<ul style="list-style-type: none"> Haemagglutinin – receptor binding, fusion of viral and host endosomal membranes; antigenic determinant Neuraminidase – hydrolysis of glycosidic bond between sialic acid and galactose; antigenic determinant
Modification	<ul style="list-style-type: none"> Haemagglutinin and neuraminidase genome segments of the parent virus are modified by incorporating a large number of point mutations which do not alter the encoded protein sequences

GMO type 2:

Attenuated *Influenza A virus* and *influenza B virus* strains, with the following genetic modifications:

- replacement of entire haemagglutinin segment with the equivalent segment from a target strain
- replacement of entire neuraminidase segment with the equivalent segment from a target strain

vaccine preparations of which are known as FluMist®.

Parent Organism

Common Name: Influenza virus

Scientific Name: Human *influenza A virus*, cold-adapted (derived from A/Ann Arbour/6/60)
Human *influenza B virus*, cold-adapted (derived from B/Ann Arbour/1/66)

Modified traits

Category: Altered immune response

Description: The GMOs are live attenuated cold-adapted influenza A and influenza B viruses, modified to elicit an immune response to targeted flu strains. These GMOs are generated using reverse genetics.

Nucleic acid responsible for conferring the modified traits:

Source	<ul style="list-style-type: none">• Contemporary influenza virus strains for targeting with influenza vaccines. These strains would be obtained from the WHO's Global Influenza Surveillance and Response System (GISRS)
Identity	<ul style="list-style-type: none">• Entire haemagglutinin genome segment• Entire neuraminidase genome segment
Function	<ul style="list-style-type: none">• Haemagglutinin – receptor binding, fusion of viral and host endosomal membranes; antigenic determinant• Neuraminidase – hydrolysis of glycosidic bond between sialic acid and galactose; antigenic determinant
Modification	<ul style="list-style-type: none">• These unmodified haemagglutinin and neuraminidase genome segments are substituted for the corresponding segments of the parent cold-adapted strains

Purpose of the dealings with the GMOs:

The purpose of the clinical trials is to assess the safety and tolerability of GM CodaVax or other *Synthetic Attenuated Virus Engineering (SAVE) influenza vaccines* (GMO 1) with the GM FluMist flu vaccines (GMO 2) as a comparator.