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 171

Licence holder: Clinical Network Services (CNS) Pty Ltd

Clinical trial of genetically modified Influenza vaccine (H3N2 M2SR)

Issued: 10 June 2020

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 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, 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.

Dealings permitted by this licence may also be subject to the operation of State legislation.

Further information on licence DIR 171

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

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.

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

'**GM**' means genetically modified.

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

'**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.

'**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 hospitalization 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 Clinical Network Services (CNS) Pty Ltd.

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 conditions 20 and 21.

Description of GMOs covered

6. The GMO covered by this licence is GM influenza virus, 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 GMOs;

b) conduct experiments with the GMOs involving;

i) administer the GMOs to trial participants intranasally;

ii) collect Samples from trial participants; and

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

c) transport the GMOs;

d) dispose of the GMOs;

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 GMOs 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 authorisation for notifiable low risk dealings (NLRD) or GMO 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.

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 1 Limits and control measures

Limits on clinical trials conducted under this licence

18. A maximum of 240 trial participants may be inoculated with the GMOs under the licence.

19. Trial participants inoculated with the GMOs must be healthy children.

20. Inoculation of trial participants must only occur outside of the Australian peak influenza season. The Australian peak influenza season is from 1 May until 31 October every year.

21. Inoculation of trial participants must be completed by 30 April 2023.

22. Administration of the GMOs to trial participants must be conducted within a Clinical trial site.

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

Control measures

General conduct of clinical trials

24. 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 GMOs, 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.

25. The licence holder must ensure that procedures are in place to account for the contents of all vials containing the GMO that are imported into Australia under this licence. The imported GMO vials must be accounted for from import to use or destruction, and records must be made available to the Regulator on request.

Work practices at Clinical trial sites

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

(a) persons administering the GMO must wear personal protective equipment including gloves and gown;

(b) all work surfaces 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;

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

(d) following administration, the trial participant must remain within the Clinical trial site for a minimum of 30 minutes and until the GMO has stopped seeping from the trial participant's nostrils;

(e) tissues or other absorbent material used to wipe or blow the nose immediately following administration of the GMO at the Clinical trial site must be disposed of, in accordance with condition 29.

Transport, storage and disposal of the GMOs

27. The licence holder must ensure that transport of the GMOs is only for the purposes of, or in the course of, another dealing permitted by this licence, for supply in accordance with condition 8 or to enable export.

28. The licence holder must ensure that all GMOs, including material or waste reasonably expected to contain the GMOs, 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;

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

29. All transport, storage and disposal, other than by External service providers, of the GMO or any waste that has been in contact with the GMO, must follow the Requirements for PC2 GMOs in the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* in force at the time, with the following modifications:

(a) where these guidelines require access to the GMO to be restricted (see items 1.1.1.5 and 2.1.15 of the Guidelines v1.1), access must be restricted to persons for whom condition 13 has been met;

(b) for the purposes of item 3.1.4 of the Guidelines v1.1, decontamination and disposal of the GMO must be undertaken by persons for whom condition 13 has been met;

(c) the spill management requirements (items 1.1.1.3 and 2.1.6 of the Guidelines v1.1), do not apply and are replaced with the following sub-condition:

i) in the event of a spill of GMO, the Contingency Plan required under condition 33 must be implemented; and

(d) a consolidated record of all GMO being stored under this condition is maintained and made available to the Regulator upon request.

Note: All stored GMO remains the responsibility of the licence holder.

Transport, storage and disposal of the GMOs by External service providers

30. The licence holder must ensure that GMO, or material or waste that has been in contact with the GMO, transported by External service providers is conducted in accordance with one of the following sub-conditions:

(a) for transport in the course of import, or to enable export, between the Australian border and the Australian premises, the GMO may be packaged and transported according to IATA shipping classification UN 3373, and labelled to indicate (at a minimum) that it contains GMOs; or

(b) for transport entirely within Australia, the GMO may be contained within a sealed, unbreakable primary container, with the outer packaging labelled to indicate, at a minimum:

i) that it contains GMOs;

ii) the contact details of the licence holder;

iii) instructions to notify the licence holder in case of loss or spill of the GMOs and/or of exposure of a person to the GMOs; and

iv) where transport is for the purposes of disposal, that the GMOs must be destroyed by autoclaving or high-temperature incineration.

31. The licence holder must ensure that GMOs and any waste generated during administration of the GMOs to be stored by External service providers is:

(a) at least double contained, with a sealed, unbreakable primary container;

(b) labelled as per condition 30 (a) or (b);

(c) access restricted to authorised persons (i.e. the GMO and associated waste is within a locked unit or an area which has restricted access; and

(d) labelled with instructions to notify the licence holder in case of loss or spill of the GMO; and instructions on how to clean up a spill, as per the Contingency Plan required under condition 33.

Note 1: All stored GMO remains the responsibility of the licence holder.

Note 2: Section 64 of the Act provides that it is a condition of the licence that if a person is authorised by a licence to deal with GMOs and a particular condition of the 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. This appears at condition 17 of this licence.

32. The licence holder must ensure that External service providers are made aware that GMOs may be present in Samples; and any waste generated as part of collection and analysis of these Samples.

Note: This could be achieved by providing general information to the External service provider and does not mandate labelling of individual Samples.

Contingency plans

33. 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 *influenza virus*.

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

34. 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 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 to prevent the spread or persistence of the GMO.

35. 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 36(d).

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

36. 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
(a) 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
(b) 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.

Notice	Content of notice	Timeframe
	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.
(c) 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).
(d) Contingency Plan(s)	Contingency Plan(s), required under condition 33, including the details specified in condition 34.	
(e) Training records	Copies of the signed and dated statements referred to in condition 13.	Within the timeframe stipulated by the Regulator.
(f) 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 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 36(f), that:* • *the licence holder will be taken to have become aware of additional information of a kind mentioned in condition 36(f) 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 36(f), 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.*	Without delay after becoming aware of any new information. *Note: An example of notification without delay 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.*

Notice	Content of notice	Timeframe
	Note 3: Additional information includes any changes at a Clinical trial site, which might increase the likelihood of dispersal of the GMOs.	
(g) Further details regarding additional information	Any further details requested by the Regulator in relation to information provided under condition *36(f)*.	Within the timeframe stipulated by the Regulator
(h) 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.
(i) 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.
(j) 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.

37. 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
(a) Compliance Management Plan	A written Compliance Management Plan must be submitted for each Clinical trial site, detailing to the satisfaction of the Regulator: iv. the name, address and description of the Clinical trial site, including any associated pharmacies/storage areas/analytical facilities v. the key persons responsible for the management of the trial at the site; vi. that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial; vii. 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 *36 (h), (i) and (j)*; viii. 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; ix. the person(s) or class of persons administering the GMO; x. where, within the site, the GMO is expected to be administered; xi. expected date of first administration; xii. transport and disposal procedures for the GMO and waste containing the GMO for the site; and	At least 14 days before first administration of the GMO at that particular Clinical trial site

Notice	Content of notice	Timeframe
	xiii. how compliance with condition 24 will be achieved in relation to analysis of participant Samples 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.*	
(b) Notification of final inoculation	Provide notification to 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 at that particular Clinical trial site

ATTACHMENT A

DIR No: 171

Full Title: Clinical trial of genetically modified Influenza vaccine (H3N2 M2SR)

Organisation Details

Postal address: Clinical Network Services (CNS) Pty Ltd
Level 2
381 MacArthur Avenue
HAMILTON QLD 4072

Phone No: (07) 3719 6000

IBC Details

IBC Name: Clinical Network Services Institutional Biosafety Committee

GMO Description

GMOs covered by this licence:

Influenza A virus genetically modified by introduction or deletion of only the genes or genetic elements listed below.

Parent Organisms:

Common Name: Influenza virus

Scientific Name: Human *Influenza A virus* (derived from A/Puerto Rico/8/34 (PR8) strain)

Modified traits:

Categories: Vaccine – altered antigen expression
Vaccine – pathogenicity attenuation, replication incompetent

Description: The GMO is a live Influenza vaccine derived from the A/Puerto Rico/8/34 (PR8) strain, modified to elicit an immune response to the targeted flu strain A/Singapore/INFIMH-16-0019/2016. In addition, the GMO has been modified to be replication incompetent. Modified genes are listed in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Identity	• Haemagglutinin (HA) genome segment • Neuraminidase (NA) genome segment • Matrix 2 (M2) gene
Modifications	• Replacement of the HA and NA genome segments from the PR8 strain with the corresponding segments from A/Singapore/INFIMH-16-0019/2016 • Modification of the M2 gene of PR8 through insertion of two stop codons into the transmembrane protein domain of the M2 ORF and deletion of 51 nucleotides in the transmembrane protein domain, downstream of the two inserted stop codons
Function	• Haemagglutinin (HA) – antigen expression • Neuraminidase (NA) – antigen expression • Matrix 2 (M2) – replication incompetence

Purpose of the dealings with the GMOs:

To conduct clinical trials assessing the safety, tolerability and efficacy of a genetically modified Influenza vaccine in healthy children.