April 2016

# Summary of Licence Application DIR-144

**Introduction**

An application has been made under the *Gene Technology Act 2000* (the Act) to conduct a Phase 1 clinical trial using genetically modified organisms (GMOs). This application is classified as a limited and controlled release application as trial participants would be vaccinated with the GMOs in a clinical setting then allowed to leave, with potential for some GMO to be shed into the environment.

**The application**

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| Application number | DIR-144 |
| Applicant | Clinical Network Services (CNS) Pty Ltd |
| Project title | Clinical trial of live attenuated genetically modified influenza vaccines[[1]](#footnote-1) |
| Parent organisms | Human influenza A virus and influenza B virus |
| Modified genes and resulting modified traits | GMO type 1: Modified haemagglutinin (HA) and neuraminidase (NA) genes, for vaccine attenuationGMO type 2: Substituted HA and NA genome segments, for antigen expression |
| Proposed release date | The clinical trial would commence when all the required approvals have been granted |
| Proposed duration | 5 years |
| Proposed location | One clinical facility in Brisbane, Queensland, and potentially other sites |
| Primary purpose | To assess the safety and tolerability of novel GM influenza (flu) vaccines, with GM FluMist flu vaccines as a comparator |

**The proposed dealings**

Clinical Network Services (CNS) Pty Ltd proposes to conduct a clinical trial with live genetically modified (GM) influenza viruses as influenza (flu) vaccines. The trial would assess the safety and tolerability of a new type of flu vaccine developed using a design strategy referred to as Synthetic Attenuated Virus Engineering (SAVE). The study would compare the GM SAVE flu vaccines to another type of GM flu vaccine, FluMist. FluMist is commercially available in the United States of America (USA), Canada and the European Union (EU). It has also been approved by the Gene Technology Regulator (the Regulator) for commercial supply in Australia, and is awaiting approval from the Therapeutic Goods Administration for use as a human therapeutic.

If the clinical trial is approved, both types of the GM vaccine would be nasally administered to a total of up to 500 healthy adult male volunteers, by qualified health professionals in clinical facilities. One clinical site in Queensland has been confirmed for the clinical trial but other sites may be engaged. Blood and urine samples would be collected from trial participants and either analysed in laboratories within Australia or exported for testing overseas. The GM flu vaccines would both be manufactured in the USA and imported into Australia.

**Proposed limits and controls**

To restrict the spread and persistence of the GMO and its genetic material, the applicant has proposed a number of limits and controls, each of which will be considered during the assessment of this application. They include:

* administration by appropriately trained medical staff in a clinical setting, in accordance ICH-GCP conditions*[[2]](#footnote-2)*
* only administering the GM flu vaccines to a total of up to 500 healthy adult male volunteers, over a period of up to 5 years
* limiting access of the GM flu vaccines to medical staff and the pharmacist at the clinical site
* instructing trial participants on procedures to minimise spread of the GMOs, including disposal of GMO contaminated waste
* disposing used, expired or unused containers of the GM flu vaccines as clinical waste
* disposing any items that may be contaminated with the GMOs at the trial site as clinical waste.

**Other regulatory approvals**

Clinical trials must be conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Before commencing, the trial would require approval from the Human Research Ethics Committee at each site, and CNS has indicated that a Clinical Trial Notification will be submitted to the TGA. Import of the GMO would require a permit from the Department of Agriculture.

**Parent organism**

Human influenza A and influenza B viruses are highly infectious pathogens which transmit predominantly through aerosols and droplets generated when a carrier coughs or sneezes. Flu infections peak during the winter months. Symptoms usually present as a sudden onset of mild respiratory illness. In healthy individuals, infection normally resolves in less than two weeks but the elderly, young children, pregnant women and the immunocompromised can suffer more severe symptoms.

In infected individuals, an immune response is induced by two viral surface proteins, hemagglutinin (HA) and neuraminidase (NA). The initials of these two proteins, plus a number denoting the particular variant of each, are used when naming influenza A virus subtypes (eg H1N1 or H3N2).

**Flu vaccines**

Flu vaccines work by activating an immune response without inducing the full-scale illness. The immune system would attack a flu virus if it recognises the key proteins on the viral surface (HA and NA). A common method of introducing the immune system to these proteins is through vaccination with a flu strain that is weakened and cannot replicate quickly in humans. To be effective, the vaccine strain must carry the same antigens as those in the strain predicted to cause the upcoming seasonal epidemic. Since the flu virus mutates frequently, the vaccine composition changes each year.

**The genetic modifications and their effect**

The parent organisms of both types of GM flu vaccine are influenza A or influenza B viruses. In the GM SAVE vaccines, DNA synthesis will be used to introduce a large number of point mutations into the HA and NA genomic segments. These mutations are ‘silent’, meaning that the HA and NA proteins encoded by the GM SAVE vaccines are identical to those in the unmodified parental flu strain. However, the mutations reduce the rate at which these proteins can be produced during infection. Since HA and NA are vital for viral entry into cells and viral release from cells, the predicted effect of the genetic modification is attenuation of the vaccine strain and reduced flu symptoms in vaccinated trial participants.

The active comparator for the clinical trials is FluMist, a type of GM vaccine which was approved for commercial supply by the Regulator under licence DIR 137. Details of this GM vaccine are available from the [OGTR website](http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/DIR137).

**Previous releases of the same or similar GMOs**

The GM SAVE vaccines have not been previously released in Australia or elsewhere. The GM FluMist vaccines are currently approved for use in the USA, Canada and the EU. FluMist vaccines were first released in the USA during the 2003/2004 flu season (as FluMist) and in the EU during the 2012/2013 flu season (as Fluenz). They are currently authorised in the USA and Canada as FluMist Quadrivalent, and in the EU as Fluenz Tetra. Commercial supply of FluMist inAustralia has been approved by the Regulator but its use as a therapeutic is pending approval by the TGA.

**Confidential Commercial Information**

Some information, including the nucleotide sequence of the modified genomic segments and information relating to the production, manufacturing process, characterisation and testing of the GM SAVE vaccines, are under consideration as Confidential Commercial Information (CCI) under section 185 of the Act. Any confidential information will be made available to prescribed experts and agencies consulted on the Risk Assessment and Risk Management Plan (RARMP) for this application.

**Assessment and consultation process for this DIR application**

The Act and the Gene Technology Regulations 2001 set out the requirements for considering licence applications and matters that the Regulator must consider before deciding whether or not to issue a licence. They include the preparation of a Risk Assessment and Risk Management Plan (RARMP) in accordance with Section 50 of the Act.

The application qualifies as a limited and controlled release as the application’s principal purpose is to conduct experiments, and the applicant has proposed limits on the release duration and size, and controls to restrict the spread and persistence of the GMOs and their genetic material in the environment (Section 50A of the Act).

When a consultation RARMP has been prepared, the Regulator will seek comment from the public as well as a wide range of experts, agencies and authorities including the Gene Technology Technical Advisory Committee, State and Territory Governments, Australian Government agencies and the Minister for the Environment (Section 51 of the Act). After taking into consideration matters raised in relation to risks to human health and safety and to the environment, the RARMP will be finalised. The finalised RARMP will inform the Regulator’s decision whether or not to issue a licence.

**The consultation RARMP is expected to be released for comment in May 2016**.The public will be invited to provide submissions on the RARMP via advertisements in the media and via direct mail for those registered on the OGTR mailing list. The RARMP and other related documents will be available on the [OGTR website](http://www.ogtr.gov.au/), or from the OGTR. In the interim, copies of the application are available from the OGTR on request. Please quote application number DIR‑144.

More information on Australia’s national scheme for regulation of gene technology and the assessment process can be found at the [OGTR website](http://www.ogtr.gov.au/). Should you have any questions on the application or the assessment process, or wish to register on the mailing list, please contact the OGTR at:

**Office of the Gene Technology Regulator, MDP 54, GPO Box 9848, Canberra ACT 2601**

**Telephone: 1800 181 030 Facsimile: 02 6271 4202 e-mail:** **ogtr@health.gov.au**

[**OGTR website**](http://www.ogtr.gov.au/) **­ www.ogtr.gov.au**

1. The title of the licence application as submitted by CNS ‘Limited and controlled released of a live-attenuated seasonal influenza vaccine CodaVax and other influenza vaccines manufactured using the SAVE technology vaccine platform in addition to the quadrivalent live attenuated influenza vaccine (FluMist®)’ [↑](#footnote-ref-1)
2. The international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, guidelines for good clinical practice [↑](#footnote-ref-2)