



Summary of the Risk Assessment and Risk Management Plan for Licence Application DIR 137

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application. The licence authorises import, transport, storage and disposal of the attenuated genetically modified (GM) influenza vaccines, known as FluMist®, for the purposes of their commercial supply as therapeutic products.

A Risk Assessment and Risk Management Plan (RARMP) for this application was prepared by the Regulator in accordance with requirements of the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation. A wide range of experts, agencies and authorities, and the public were also consulted before the RARMP was finalised. The RARMP concludes that this commercial release poses negligible risks to human health and safety and to the environment, and consequently, no specific risk treatment measures are proposed. However, general licence conditions have been imposed to ensure that there is ongoing oversight of the licence.

Before these GM influenza vaccines can be used as therapeutic agents, AstraZeneca must also obtain regulatory approval from the Therapeutic Goods Administration (TGA). Medicines and other therapeutic goods for sale in Australia are required to be assessed for quality, safety and efficacy under the *Therapeutic Goods Act 1989* and must be included in the Australian Register of Therapeutic Goods (ARTG). The TGA consult the OGTR during the assessment of applications for therapeutic products that are, or contain, genetically modified organism (GMOs). AstraZeneca will also need approval from the Department of Agriculture and Water Resources for import of the GM vaccines.

The application

Application number	DIR 137
Applicant	AstraZeneca Pty Ltd (AstraZeneca)
Project title	Commercial supply of attenuated GM influenza vaccines ¹
Parent organism	Human <i>influenza A virus</i> and <i>influenza B virus</i>
Introduced genes and modified trait	Hemagglutinin and neuraminidase genomic segments from influenza strains recommended by the Australian Influenza Vaccine Council (AIVC) for seasonal influenza vaccines (antigen expression)

¹ The title of the project as supplied by the applicant is 'Quadrivalent live attenuated influenza vaccine (Q/LAIV) to prevent seasonal influenza (FluMist® Quadrivalent) and monovalent pandemic live attenuated influenza vaccine (P/LAIV) suspensions for nasal administration.'

Proposed release date	Ongoing from the date of approval
Proposed locations	Locations throughout Australia where vaccines are normally stored and administered (subject to registration by the Therapeutic Goods Administration)
Proposed activities	Import, transport, storage and disposal of the GM influenza vaccines for the purpose of their commercial supply as therapeutic products (administration is subject Therapeutic Goods Administration approval)

AstraZeneca proposes the commercial supply of attenuated GM influenza vaccine strains for use as vaccines. Two types of influenza (flu) vaccines are proposed. The first is a seasonal flu vaccine which would contain a mixture of four GM vaccine strains to target currently circulating flu viruses. The second is a contingency flu vaccine which would contain a single GM vaccine strain to target a pandemic flu strain, should one arise.

Subject to approval by the Therapeutic Goods Administration (TGA), the GM vaccines would be manufactured overseas and imported into Australia. They would be administered as a nasal spray by qualified healthcare professionals at locations where flu vaccines would generally be dispensed, such as medical practices and pharmacies.

Influenza A and influenza B viruses are highly infectious pathogens which are endemic in Australia. These viruses transmit predominantly through aerosol droplets generated when a carrier coughs or sneezes, and 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 under two weeks but the elderly, young children, pregnant women and the immunocompromised can suffer more severe symptoms.

In infected individuals, the main immune response is induced by two viral surface proteins, hemagglutinin and neuraminidase. The initials of these two proteins are used when naming influenza A virus subtypes (eg H1N1 or H3N2).

The parent organisms of the GM vaccine strains are attenuated influenza A or influenza B strains that are temperature-sensitive, and therefore do not grow well at body temperature. As a result, GM vaccine strains based on these parent organisms are weakened and less virulent than naturally occurring flu strains.

In the proposed GM vaccine strains, the attenuated parental flu strains would be modified by incorporation of antigens from the current circulating flu strains to provide protection against these flu strains. As flu viruses change rapidly, every year the World Health Organisation (WHO) issues advice on the antigen composition of flu vaccines for the coming flu season. The WHO's recommendations are evaluated by the Australian Influenza Vaccine Committee (AIVC) which provides advice to the TGA on the composition of the seasonal flu vaccine to be supplied each year in Australia. Seasonal flu vaccines, including those currently approved for use in Australia, are reformulated every year based on this advice. The application is for GM flu vaccines which are modified with the recommended antigens for each flu season.

These GM vaccines have not previously been released commercially in Australia. However, vaccines based on the attenuated, temperature-sensitive influenza parent

strains are currently approved for use in the United States of America (USA), Canada and the European Union (EU). These GM 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. The authorisations for these vaccines are held by either AstraZeneca or MedImmune, a subsidiary of AstraZeneca.

Risk assessment

The risk assessment concludes that risks to the health and safety of people, or the environment, from the proposed dealings are negligible.

The risk assessment process considers how the genetic modifications and proposed activities conducted with the GM vaccines might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application (including proposed controls), relevant previous approvals and current scientific/technical knowledge. Both the short and long term impact are considered.

To avoid duplication of regulatory oversight, the Regulator does not assess risks to people receiving or administering the GMO as a therapeutic. However, import, transport and disposal are regulated under the *Gene Technology Act 2000* (the Act), and the Regulator has assessed risks posed to people and to the environment associated with these activities.

Credible pathways to potential harm that were considered included whether or not expression of the introduced genes and genetic modifications could alter characteristics that may impact on the disease burden from the GM vaccine strains, or produce unintended changes in viral characteristics. The opportunity for gene transfer to other organisms, and its effects if it were to occur, was also considered.

The principal reasons for the conclusion of negligible risks are that:

- exposure to the proposed GM flu vaccines would be minimised by well-established clinical, import, transport, storage and disposal procedures
- influenza virus survival outside of a host is limited to short periods, and it is susceptible to common chemical decontaminants
- the proposed GM flu vaccine strains would contain a number of naturally occurring mutations that lead to their attenuation, reducing their ability to replicate, persist and be transmitted
- all of the genes and genome segments in the GM flu vaccines would be derived from existing non-GM flu strains
- there would be limited opportunity for the GM vaccine strains and circulating flu strains to reassort, and resulting reassortants would not be expected to be more virulent.

Risk management plan

The risk management plan describes measures to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan is given effect through licence conditions.

As the level of risk is assessed as negligible, specific risk treatment is not required. However, the Regulator has imposed licence conditions under post-release review

(PRR) to ensure that there is ongoing oversight of the release and to allow the collection of information to verify the findings of the RARMP. The licence also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.