Australian Government
Department of Health and Ageing
Office of the Gene Technology Regulator

30 October 2009

APPLICATION FOR LICENCE FOR INTENTIONAL RELEASE OF GMOs INTO THE ENVIRONMENT: Application No. DIR 098

SUMMARY INFORMATION

Project Title:	Commercial release of a genetically modified live viral vaccine to protect against Japanese encephalitis (IMOJEV™[1])
Applicant:	Sanofi Pasteur Pty Ltd
Common name of the parent organism:	Yellow fever vaccine
Scientific name of the parent organism:	*Yellow fever* (YF) 17D vaccine virus
Modified trait:	Altered antigenic profile
Identity of the genes responsible for the modified traits:	• *Japanese encephalitis virus pre-membrane* (*prM*) gene • *Japanese encephalitis virus envelope* (*E*) gene
Proposed Locations:	Medical facilities in Australia
Proposed Release Size:	Commercial
Proposed Release Dates:	Ongoing from date of approval

Introduction

The *Gene Technology Act 2000* (the Act) in conjunction with the *Gene Technology Regulations 2001*, an inter-governmental agreement and corresponding legislation that is being enacted in each State and Territory, comprise Australia's nationally consistent regulatory system for gene technology. Its objective is to protect the health and safety of people, and the environment, by identifying risks posed by or as a result of gene technology, and managing those risks by regulating certain dealings with genetically modified organisms (GMOs).

The Act establishes a statutory officer, the Gene Technology Regulator (the Regulator), to administer the legislation and make decisions under the legislation. The Regulator is supported by the Office of the Gene Technology Regulator (OGTR), an Australian Government regulatory agency located within the Health and Ageing portfolio.

The legislation sets out the requirements for considering applications for licences for dealings with GMOs and the matters that the Regulator must take into account before deciding

[1] The title of the licence application submitted by Sanofi Pasteur Pty Ltd is 'Commercial release – Commercial distribution and prescription of IMOJEV in Australia'.

whether, or not, to issue a licence. The Regulator's *Risk Analysis Framework*[2] outlines the assessment process that will be followed.

The application and the proposed dealings

The Regulator has received an application from Sanofi Pasteur Pty Ltd (Sanofi) for a licence for dealings involving the intentional release of a live genetically modified (GM) viral vaccine as a prescription medicine into the Australian environment.

The GM vaccine is based on a vaccine strain of *Yellow fever virus*, YF 17D, which has been modified to contain genes from *Japanese encephalitis virus* (JEV). Expression of these genes has been shown to elicit a protective immune response in vaccinated people. Sanofi is seeking approval for a commercial release of this vaccine in Australia.

The proposed release would involve the commercial release of GM vaccine known as IMOJEV™. The applicant proposes the commercial release to occur in medical facilities throughout Australia. The vaccine is intended for people travelling to areas where JEV is endemic and, if approved, would be prescribed by registered medical practitioners to persons over 18 years of age.

Parent organism

The parent organism is the highly attenuated vaccine strain YF 17D, a positive sense, single stranded RNA virus from the *Flavivirus* genus. YF 17D has been registered by the Therapeutic Goods Administration (TGA) for use in Australia as a vaccine against yellow fever.

The source of the introduced genes is a highly attenuated vaccine strain of *Japanese encephalitis virus* (JE SA14-14-2). JEV is also a member of the genus *Flavivirus*.
JE SA14-14-2 is not currently registered for use in Australia as a live vaccine. However, it has been registered for use by the TGA as an inactivated vaccine against JEV in Australia.
JE SA14-14-2 has also been registered for use as a live vaccine in China, India, Nepal, South Korea, and Sri Lanka where it has a long history of safe use.

Both virus strains are highly attenuated in humans and have been shown to have a low capacity to replicate in humans or other organisms.

The genetic modifications and their effect

The YF 17D parent virus has been modified to remove the endogenous envelope (E) and pre-membrane (prM) proteins that make up the outer surface of the viral particle and replace them with the equivalent proteins from JE SA14-14-2.

The effect of the genetic modifications is to create a chimeric virus in which the non-structural proteins involved in viral replication are from YF 17D, and the surface glycoproteins that mediate binding to host cells and interactions with the host immune system

[2] More information on the assessment of licence applications is available from the Office of the Gene Technology Regulator (OGTR). Free call 1800 181 030 or at <http://www.ogtr.gov.au>.

are derived from JE SA14-14-2. The vaccine viral particle therefore consists of a YF core surrounded by an envelope comprised of the JEV M and E glycoproteins.

After inoculation with the GM vaccine, the subsequent expression of viral genes in host cells elicits humoral and cell mediated immune responses against the viral membrane and envelope proteins (ie M and E), which provides protective immunity against infection with pathogenic strains of JEV.

Method of genetic modification

The genome of YF 17D was cloned into two DNA plasmids which can be maintained and replicated in transformed bacteria. The YF 17D *prM* and *E* genes were removed and replaced with the JE SA14-14-2 *prM* and *E* genes using standard sub-cloning techniques. The modified virus was recovered by co-transfecting a mammalian cell line with the two linearised plasmids, resulting in homologous recombination and transcription of the RNA genome, translation of the viral proteins and assembly of the GM virus particles.

Previous releases in Australia of the same or similar GMOs

The GM virus proposed for commercial release was approved for clinical trials and experimental research in Australia as contained dealings under licences DNIR 071, DNIR 274, DNIR 319, DNIR 320 and DNIR 366 by the Regulator. The vaccine demonstrated an acceptable safety profile in these clinical trials.

Other regulatory approvals

The applicant has applied to the TGA to have the IMOJEV™ vaccine included on the Australian Register of Therapeutic Goods.

Suitability of Applicant

Section 43(2)(f) of the Act requires the Regulator to be satisfied regarding the suitability of the applicant to hold a licence as a pre-requisite for considering DIR applications. The matters to be considered are outlined in Section 58 of the Act and include relevant convictions, revocation of a licence or permit relating to the health and safety of people, and capacity to meet the conditions of the licence.

The Regulator has determined that Sanofi currently meets the suitability requirements and will verify this continues to be the case prior to making any decision regarding the issuing of a licence.

Consultation process for this DIR application

Since this application is for commercial purposes, it cannot be considered as a limited and controlled release application under section 50A of the Act.

This means that the Regulator is required to seek advice from prescribed experts, agencies and authorities on matters relevant to the Risk Assessment and Risk Management Plan (RARMP) that must be prepared, in accordance with section 51 of the Act. This first round of consultation must include the Gene Technology Technical Advisory Committee, State and Territory Governments, Australian Government agencies, any local council that the Regulator

considers appropriate and the Minister for the Environment, Heritage and the Arts. While the Regulator is not required to seek public comment at this stage, copies of the application are available on request from the OGTR.

In a second round of consultation, the Regulator will then seek comment on the consultation RARMP from the public as well as prescribed experts, agencies and authorities. The RARMP will be finalised, taking into account matters raised in relation to risks to human health and safety and the environment, and form the basis of his decision whether or not to issue a licence.

At this stage, the consultation version of the RARMP is expected to be released for comment in **April 2010.** The public will be invited to provide submissions on the RARMP via advertisements in the media and direct mail to anyone registered on the OGTR mailing list. The RARMP and other related documents will be available on the OGTR website, or in hard copy from the OGTR.

If you have any questions about the application or the assessment process, or wish to register on the mailing list, please contact the OGTR at:

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OGTR Website