Australian Government
Department of Health and Aged Care
Office of the Gene Technology Regulator

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Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR 192

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a genetically modified organism (GMO). It qualifies as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Medpace Australia Pty Ltd (Medpace) proposes to conduct a clinical trial to evaluate the safety and efficacy of a genetically modified (GM) chimeric Orthopoxvirus (CF33-hNIS), alone or in combination with an existing cancer therapy (Pembrolizumab), for the treatment of Australian patients with metastatic or advanced solid cancerous tumours.

The GMO was modified from the oncolytic virus CF33, a chimeric Orthopoxvirus (OPXV) strain which has been shown to target cancer cells. The genetic modifications lead to higher levels of viral replication in cancer cells compared to normal cells. Additionally, the genetic modifications facilitate the visualisation of the GMO after administration to patients by medical imaging.

The GMO would be manufactured overseas and imported into Australia. It would be administered by intratumoural injection or by intravenous infusion in up to 18 Australian patients at clinical trial sites and hospitals in Australia.

Clinical trials in Australia are conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Therefore, in addition to approval by the Regulator, Medpace would also require authorisation from TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* and with the *Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Medpace would also require approval from the Department of Agriculture, Fisheries and Forestry for import of the GMO.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed clinical trial poses negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed clinical trial. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether to issue a licence.

The application

Project Title	Clinical trial of a genetically modified (GM) chimeric Orthopoxvirus (CF33-hNIS) as a cancer treatment [1]
Parent organism	Chimeric Orthopoxvirus (CF33)
Genetic modifications	• Deletion of *J2R* gene (viral thymidine kinase) – leading to preferential viral multiplication in cancer cells. • Insertion of the human sodium-iodide symporter (hNIS) gene – to facilitate the visualisation of the virus by medical imaging.
Principal purpose	The proposed trial is a Phase 1 study designed to evaluate the safety and efficacy of a GM chimeric Orthopoxvirus, (known as CF33-hNIS; VAXinia; HOV2), alone and in combination with an existing cancer therapy (Pembrolizumab), for the treatment of Australian patients with metastatic or advanced solid cancerous tumours.
Previous clinical trials	The proposed study is the first clinical trial to be conducted with CF33-hNIS (the GMO).
Proposed limits and controls	
Proposed duration	5 years
Proposed release size	Up to 18 participants would be enrolled in the trial in Australia
Proposed locations	This clinical trial would be conducted within clinical trial sites and hospitals in Australia. The number of sites and specific locations are yet to be determined.
Proposed controls	• The GMO would be administered to trial participants within a suitable medical facility. • Staff preparing and administering the GMO would use personal protective equipment. • Import, transport and storage of the GMO would be carried out according to the OGTR *Guidelines for the* T*ransport, Storage and Disposal of* GMOs. • Waste that may contain the GMO would be disposed of as infectious material (e.g. via the clinical waste stream).

Risk assessment

The risk assessment concludes that risks to the health and safety of people or the environment from the proposed clinical trial are negligible. No specific risk treatment measures are required to manage these negligible risks.

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

[1] The title of the project as supplied by the applicant is "A Phase I, Dose Escalation Safety and Tolerability Study of VAXINIA (CF33-hNIS), Administered Intratumorally or Intravenously as a Monotherapy or in Combination with Pembrolizumab in Adult Patients with Metastatic or Advanced Solid Tumors".

Credible pathways to potential harm that were considered include the; potential exposure of people and animals to the GMO; and the potential for the GMO to transfer or acquire genetic material from other viruses. The potential for the GMO to be released into the environment and its effects were also considered.

Important factors in reaching the conclusions of the risk assessment included that the GMO is designed to preferentially replicate in cancer cells, and unintended exposure to the GMOs would be minimised by the limits and controls.

As risks to the health and safety of people, or the environment, from the proposed trial of the GMO treatment have been assessed as negligible, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management

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. Draft licence conditions are detailed in Chapter 4 of the RARMP.

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a clinical trial, the draft licence includes limits on the number of trial participants, types of facilities used and duration of the trial, as well as a range of controls to minimise the potential for the GMO to spread in the environment. In addition, there are several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements which include an obligation to report any unintended effects.