



Summary of the Risk Assessment and Risk Management Plan for Licence Application DIR-213

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application for the intentional release of a genetically modified organism (GMO) into the environment. A Risk Assessment and Risk Management Plan (RARMP) for this application has been prepared by the Regulator in accordance with the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation, and finalised following consultation with a wide range of expert, agencies and authorities, and the public. The RARMP concluded that the proposed trial poses negligible risks to human health and safety and the environment and that any risks posed by the dealings can be managed by imposing conditions on the release.

The applicant, Novotech (Australia) Pty Ltd (Novotech), proposes to conduct a clinical trial to evaluate the safety and efficacy of a genetically modified (GM) human adenovirus for the treatment of Australian patients with metastatic melanoma.

The proposed GM adenovirus treatment has been designed to preferentially replicate in and kill cancer cells. The GM adenovirus would be manufactured overseas and imported into Australia. It would be administered by intra-tumoral injection in up to 30 patients with metastatic melanoma at clinical facilities 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, Novotech 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. Novotech would also require approval from the Department of Agriculture, Fisheries and Forestry (DAFF) for import of the GMO into Australia.

The application

Project Title	Clinical trial of a genetically modified human adenovirus for treatment of melanoma
Parent organism	Human adenovirus (HAdV-C6)
Genetic modifications	<p>Modified human adenovirus:</p> <ul style="list-style-type: none">• Replacement of HAdV-C6 hexon hypervariable region (HVR) with HVR from HAdV-C57 (facilitates initial immune evasion)• Deletion within E1A protein (promotes viral replication in tumour cells and facilitates cellular antiviral responses)• Partial deletion of E3 gene replaced with human CD40L (enhances immune activation in target cells)

Principal purpose	The trial is a Phase 1 study designed to evaluate the safety, tolerability and dose escalation study of genetically modified Adze 1.C, for the treatment of Australian patients with melanoma.
Previous clinical trials	None, this is a first in human clinical trial
Limits and controls	
Duration	3 years
Trial size	Up to 30 participants in Australia
Locations	This clinical trial will be conducted within Australia at clinical trial sites and hospitals. The specific clinical trial sites are yet to be identified.
Controls	<p>The GMO will be administered to trial participants within a suitable medical facility;</p> <p>Staff handling the GMO will be trained and wear personal protective equipment;</p> <p>Waste that may contain the GMO will be disposed of via the clinical waste stream;</p> <p>Persons dealing with the GMO must be informed of the risks associated with the GMO, particularly persons who are immunosuppressed or pregnant;</p> <p>The GMO will be transported and stored according to the Regulator's <i>Transport, Storage and Disposal Guidelines</i> appropriate for PC2 organisms</p>

Risk assessment

The risk assessment process considers how the genetic modification 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, taking into account information in the application (including proposed controls), relevant previous approvals and current scientific/technical knowledge. Both the short- and long-term risks are considered.

Credible pathways to potential harm that were considered include the potential exposure of people or animals to the GMO, the potential for the GMO to recombine with other similar viruses and the potential effects of a release of the GMO into the environment.

The risk assessment concludes that the trial poses negligible risks to human health and safety and to the environment. No specific risk treatment measures are required to manage these negligible risks. Important factors in reaching the conclusions of the risk assessment included that the GMO preferentially replicates in cancer cells, and unintended exposure to the GMO would be minimised by the proposed limits and controls outlined in the risk management plan.

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.

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a clinical trial, the licence includes limits on the number of trial participants, locations are limited to hospitals and clinical trial sites, limits on the 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.