



Summary of the Risk Assessment and Risk Management Plan for Licence Application No. DIR 217

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for import, transport, storage, and disposal of a non-replicating adenoviral vector-based therapeutic product, nadofaragene firadenovec, as part of its commercial supply in Australia as a treatment for high-grade Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC).

Before nadofaragene firadenovec can be used, Ferring Pharmaceuticals Pty Ltd must also obtain regulatory approval from the Therapeutic Goods Administration (TGA). If registered as a human therapeutic, the TGA may impose conditions relating to the use and labelling of the GM therapeutic. As nadofaragene firadenovec is manufactured overseas, a permit from the Department of Agriculture, Fisheries and Forestry will be required for its import into Australia.

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 experts, agencies and authorities, and the public. The RARMP concluded that the proposed commercial supply of the GM therapeutic poses negligible risks to human health and safety and the environment, and no specific risk treatment measures are required. However, general licence conditions have been imposed to ensure that there is ongoing oversight of the release.

The application

Application number	DIR 217
Applicant	Ferring Pharmaceuticals Pty Ltd
Project Title	Commercial supply of nadofaragene firadenovec for bladder cancer treatment ¹
Parent organism	Human adenovirus C serotype 5 (HAd5)
Modified trait	Replication incompetent HAd5 expressing a human interferon alfa-2b (<i>hIFN-α2b</i>) gene
Genetic modification	- deletion of gene sequences² to improve safety - insertion of the <i>hIFN-α2b</i> gene to produce the protein with anticancer activities
Proposed locations	Australia-wide
Principal purpose	Commercial supply of the GM therapeutic

¹ The original title supplied by the applicant is: *Gene therapy for bladder cancer*.

² Confidential Commercial Information: Some details about the deleted gene sequences have been declared as Confidential Commercial Information under section 185 of the Act.

<i>Previous approvals</i>	The GM therapeutic has not previously been approved in Australia. Internationally, the GM therapeutic has been approved by the Food and Drug Administration (FDA) in the USA.
<i>Proposed period of release</i>	Ongoing from issue of licence

Risk assessment

The risk assessment process considers how the genetic modification and proposed activities conducted with the GM therapeutic in the context of import, transport, storage, and disposal 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, relevant previous approvals, current scientific knowledge and advice received from a wide range of experts, agencies and authorities consulted on the preparation of the RARMP. Both the short and long term risks were considered.

Credible pathways to potential harm that were considered include the potential for accidental exposure of people to the GMO during transport and storage, preparation and administration of the GMO, and during disposal of the GMO and any associated waste; the potential for the GMO to recombine with other similar viruses; the potential for the GMO to integrate into the host genome and the potential for the GMO to be released into the environment and its effects were also considered.

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

The principal reasons for the conclusion of negligible risks associated with the import, transport, storage and disposal of the GMO are:

- the GMO is replication incompetent and susceptible to clearance by the host immune system and, in comparison to wildtype (WT) adenovirus, is unlikely to infect humans and cause disease
- the dose received through accidental exposure would be smaller than that administered to patients
- import, transport, storage, and disposal will follow well established procedures.

Risk management

Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan evaluates and treats identified risks and considers general risk management measures. The risk management plan is given effect through licence conditions.

The risk management plan concludes that risks from the proposed dealings can be managed so that people and the environment are protected by imposing general conditions to ensure that there is ongoing oversight of the therapeutic containing the GMO.

As the level of risk was assessed as negligible, specific risk treatment is not required. However, the Regulator has imposed licence conditions regarding post release review (post-market surveillance) to ensure that there is ongoing oversight of the supply of the GM therapeutic and to allow the collection of ongoing information to verify the findings of the RARMP. The licence also contains several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.