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

January 2026

Risk Assessment and Risk Management Plan (Consultation version) for

DIR-223

Clinical trials of a genetically modified adenovirus for treatment of bladder cancer

Applicant: Ferring Pharmaceuticals Pty Ltd

This RARMP is open for consultation until 6 March 2026.

Written comments on the risks to human health and safety and the environment posed by this proposed clinical trial of the GM human adenovirus treatment are invited. You may make your submission

Via the consultation hub:	https://consultations.health.gov.au (search for DIR 223)
via email to:	ogtr@health.gov.au
or via mail to:	The Office of the Gene Technology Regulator,
	MDP 54 GPO Box 9848, Canberra ACT 2601

Please note that issues regarding patient safety and the quality of the therapeutic **do not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR-223

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 a Dealing involving the Intentional Release (DIR) of GMOs into the Australian environment under the *Gene Technology Act 2000*.

The applicant, Ferring Pharmaceuticals Pty Ltd (Ferring), proposes to conduct a clinical trial to evaluate the safety and efficacy of a genetically modified (GM) human adenovirus, nadofaragene firadenovec, for the treatment of Australian patients with bladder cancer.

Nadofaragene firadenovec was developed for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours. The GM adenovirus would be manufactured overseas and imported into Australia. It would be administered by bladder instillation in up to 13 patients with non-muscle invasive bladder cancer 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, Ferring 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. Ferring would also require approval from the Department of Agriculture, Fisheries and Forestry (DAFF) for import of the GMO into Australia.

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 adenovirus for treatment of bladder cancer[1]
Parent organism	Human adenovirus type 5 (HAd5)

[1] This application was originally submitted in 2 parts. The original titles supplied by the applicant were: "A phase 3, randomised, multi-centre, open-label trial to evaluate the safety and efficacy of intravesical nadofaragene firadenovec alone or in combination with chemotherapy (gemcitabine and docetaxel) or immunotherapy (pembrolizumab) in subjects with high-grade Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC)"; and "A Phase 3b, Randomised, Controlled Trial of Nadofaragene Firadenovec vs. Observation in Subjects with Intermediate Risk (IR) Non-Muscle Invasive Bladder Cancer (NMIBC)".

Genetic modifications	
Introduced genes	Modified human adenovirus: • deletion of gene sequences[2] to improve safety • insertion of the human interferon alpha-2b (*hIFN-α2b*) gene to produce the protein with anticancer activities
Principal purpose	The proposed trials are Phase 3 and 3b studies designed to evaluate the safety and efficacy of a genetically modified (GM) adenovirus for the treatment of Australian patients with bladder cancer
Previous approvals	• Licence DIR 217 was issued on 17 October 2025 for dealings associated with the commercial supply of the GMO in Australia. • Clinical trials (Phases 1-3) were undertaken in the United States (US). • In December 2022, the US Food and Drug Administration approved this GMO for the treatment of high-grade bladder cancers.
Proposed limits and controls	
Locations	Up to 10 clinical trial sites (medical facilities) in New South Wales and Victoria
Trial size	Up to 13 clinical trial participants in Australia across the two phases
Duration	5 years
Controls	• The GMO would be administered to trial participants within clinical trial sites • Staff handling the GMO would be trained and use personal protective equipment • Higher risk staff would be excluded from handling the GMO • The GMO would be transported and stored according to the Regulator's *Transport, Storage and Disposal Guidelines*. • Waste that may contain GMO would be destroyed according to clinical trial site procedures appropriate for PC2 GMOs.

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 and animals to the GMO, the potential for the GMO to recombine with other similar viruses and the potential for the GMO to integrate into the host genome.

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 is replication incompetent, unintended exposure to the GMO would be minimised by the proposed limits and controls

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

outlined in the draft risk management plan and that the likelihood of complementation and recombination of the GMO with other adenoviruses is low.

As risks to the health and safety of people, or the environment, from the proposed trial of the treatment with the GMO 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, locations 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.

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Abbreviations

AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
CDC	Centers for Disease Control and Prevention
DIR	Dealings Involving Intentional Release
DNA	Deoxyribonucleic acid
FSANZ	Food Standards Australia New Zealand
GTTAC	Gene Technology Technical Advisory Committee
GM	Genetically modified
GMO	Genetically modified organism
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
IBC	Institutional Biosafety Committee
ICH-GCP	*Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
mL	Millilitre
min	Minute
NHMRC	National Health and Medical Research Council
NPAAC	National Pathology Accreditation Advisory Council
NSQHS	National Safety and Quality Health Service Standards
OGTR	Office of the Gene Technology Regulator
PPE	Personal Protective Equipment
PCR	Polymerase chain reaction
RAF	Risk Analysis Framework
RARMP	Risk Assessment and Risk Management Plan
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
TGA	Therapeutic Goods Administration
TSDs	The Regulator's *Guidelines for Transport, Storage and Disposal*
USA	United States of America
WHO	World Health Organization

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.

4. The *Risk Analysis Framework* (RAF) (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR website).

5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Risks to the health and safety of people or the environment posed by the proposed supply are assessed within this context. Chapter 1 describes the risk assessment context for this application.

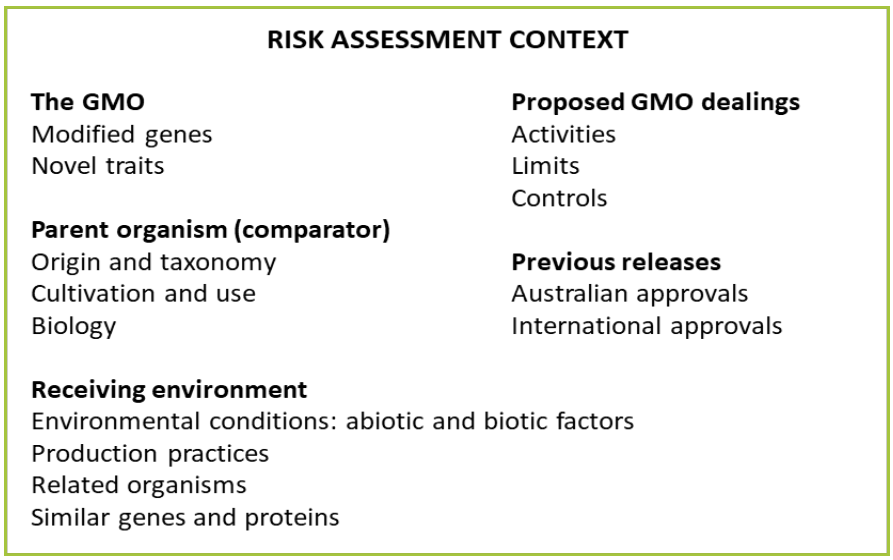

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. In accordance with Section 50A of the Act, this application is considered to be a limited and controlled release application, as the Regulator was satisfied that it meets the criteria prescribed by the Act. Therefore, the Regulator was not required to consult with prescribed experts, agencies and authorities before preparation of the RARMP.

1.1 Interface with other regulatory schemes

7. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. The GMOs and any proposed dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including Food Standards Australia New Zealand (FSANZ), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA), the Australian Industrial Chemicals Introduction Scheme (AICIS) and the Department of Agriculture, Fisheries and Forestry (DAFF).

8. Medicines and other therapeutic goods for use 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. The TGA is responsible for administering the provisions of this legislation. Clinical trials of therapeutic products that are experimental and under development, prior to a full evaluation and assessment, are also regulated by the TGA through the Clinical Trial Approval (CTA) scheme or the Clinical Trial Notification (CTN) scheme.

9. For clinical trials, the TGA has regulatory responsibility for the supply of unapproved therapeutic products. In terms of risk to individuals participating in a clinical trial, the TGA (as the primary regulatory agency), the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles in ensuring participants' safety under the *Therapeutic Goods Act 1989*. However, where the trial involves a GMO, authorisation is also required under gene technology legislation. To avoid duplication of regulatory oversight, and as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment. This includes risks to people preparing and administering the GM virus, and risks associated with import, transport and disposal of the GMO.

10. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guidelines for Good Clinical Practice (ICH-GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH 1996). The guideline was developed with consideration of the current good clinical practices of the European Union (EU), Japan, and the United States of America (USA), as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). The TGA has adopted the ICH-GCP in principle as Note for Guidance on Good Clinical Practice (designated CPMP/ICH/135/95) (Therapeutic Goods Administration 2000), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

11. The National Health and Medical Research Council (NHMRC) has issued the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council et al., 2018). This document sets the Australian standard against which all research involving humans is reviewed. The *Therapeutic Goods Act 1989* requires that the use of a therapeutic good in a clinical trial must be in accordance with the ethical standards set out in this document.

12. Approval by a HREC is also a fundamental requirement of a clinical trial. HRECs conduct both ethical and scientific assessment of the proposal and in addition often consider issues of research governance. Other elements of governance of clinical trials that are considered by HRECs include appropriate informed consent, specific inclusion and exclusion criteria, data monitoring and GMO accounting and reconciliation.

13. DAFF administers Australian biosecurity conditions for the importation of biological products under the *Biosecurity Act 2015*. Biological products include animal or microbial derived products such as foods, therapeutics, laboratory materials and vaccines (including GMO).

14. Analysis of biological samples collected from trial participants administered with the GMO would occur at clinical trial sites, or at pathology laboratories. These facilities are regulated by State and Territory governments and adhere to professional standards for safety, disease control (Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019) and handling of pathology samples (National Pathology Accreditation Advisory Council; NPAAC).

15. NPAAC advises Commonwealth, State and Territory health ministers on matters relating to the accreditation of pathology laboratories. NPAAC plays a key role in ensuring the quality of Australian pathology services and is responsible for the development and maintenance of standards and guidelines for pathology practices. The standards include safety precautions to protect the safety of workers from exposure to infectious microorganisms in pathology laboratories. While compliance with NPAAC standards and guidelines is not mandatory, there is a strong motivation for pathology services to comply, as Medicare benefits are only payable for pathology services if conducted in an appropriate Accredited Pathology Laboratory (APL) category, by an Approved Pathology Practitioner (APP) employed by an Approved Pathology Authority (APA). Accreditation of pathology services is overseen by Services Australia (formerly Department of Human Services), and currently, the only endorsed assessing body for pathology accreditation is the National Association of Testing Authorities (NATA).

16. The state and territory governments regulate hospitals and other medical facilities in Australia. All public and private hospitals and day procedure services need to be accredited to the National Safety and Quality Health Service (NSQHS) Standards developed by the Australian Commission on Safety and Quality in Healthcare (the Commission) and endorsed by the state and territory Health Ministers. The Commission coordinates accreditation processes via the Australian Health Service Safety and Quality Accreditation (AHSSQA) scheme. The NSQHS Standards provide a quality assurance mechanism that tests whether relevant systems are in place to ensure that the minimum standards of safety and quality are met. The safety aspects addressed by the NSQHS Standards include the safe use of sharps, disinfection, sterilisation and appropriate handling of potentially infectious substances. Additionally, the Commission has developed the National Model Clinical Guidance Framework, which is based on, and builds on NSQHS Standards to ensure that clinical governance systems are implemented effectively and to support better care for patients and consumers.

17. Hospitals and pathology laboratories, including their workers, managers and executives, all have a role in making the workplace safe and managing the risks associated with handling potentially infectious substances including the proposed GMO. There are minimum infection prevention practices that apply to all health care in any setting where health care is provided. These prevention practices were initially developed by the Centers for Disease Control and Prevention (CDC) and are known as the standard precautions for working with potentially infectious material. The standard precautions are described in the Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019).

Section 2 The proposed dealings

18. Ferring Pharmaceuticals Pty Ltd (Ferring) is seeking authorisation to carry out Phase 3 and 3b clinical trials to assess the safety and efficacy of a genetically modified (GM) human adenovirus (HAdV) nadofaragene firadenovec (also known as nadofaragene firadenovec-vncg, rAd-IFN/Syn3 and ADSTILADRIN), in Australia. The GM therapeutic is administered by intravesical (bladder) instillation.

19. The dealings involved in the proposed clinical trial are:

(a) import the GMO;

(b) conduct the following experiments with the GMO:

i. prepare the GMO for administration to trial participants;

ii. administer the GMO to clinical trial participants by intravesical (bladder) instillation;

iii. collect samples from trial participants;

iv. analyse the samples;

(c) transport the GMO;

(d) dispose of the GMO;

and the possession (including storage), supply and use of the GMO for the purposes of, or in the course of, any of these dealings.

20. Licence DIR 217 was issued on 17 October 2025 for dealings associated with the commercial supply of the GMO in Australia and covers import, transport, storage and disposal of the GMO. Therefore, to avoid duplication, for this licence only dealings occurring at the clinical trial site or downstream dealings such as transport and disposal of clinical waste containing the GMO will be assessed.

2.1 The proposed limits of the trial (duration, scale, location, people)

21. The clinical trial is proposed to take place over a 5-year period from the date of issue of the licence. Up to 13 participants in Australia (5 for the Phase 3 and 8 for the Phase 3b) would receive multiple doses of the GMO via intravesical instillation.

22. The clinical trial is proposed to take place at up to 10 different clinical trial facilities and hospitals in New South Wales and Victoria.

23. Only trained and authorised staff would conduct dealings with the GMO. Administration of the GMO to trial participants would be conducted by highly trained staff.

2.2 The proposed controls to restrict the spread and persistence of the GMO in the environment

24. The applicant has proposed a number of controls to minimise exposure to the GMO, and to restrict the spread and persistence of the GMO in the environment. These include:

- Only trained personnel would conduct dealings with the GMO. Staff preparing and administering the GMO would be experienced in the use and disposal of sharps.
- Staff considered to be at risk (see Paragraph 42) would be excluded from handling the GMO.
- Staff preparing or administering the GMO would be required to wear appropriate PPE during the procedures.
- Transport to and storage of the GMO at a clinical trial facility where it will be administered will be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs).
- Disinfecting surfaces and equipment that come into contact with the GMO using an effective disinfectant.
- Providing patients with instructions to add equal volume of virucidal agent to the toilet bowl prior to voiding and wait 15 minutes before flushing the toilet.

2.3 Details of the proposed dealings

2.3.1 Manufacturing and import of the GMO

25. Nadofaragene firadenovec is manufactured by FinVector Oy (FinVector) in Finland. Ferring proposes to import the GM therapeutic into Australia from FinVector. The GM therapeutic would be shipped from FinVector in sealed containers with tamper proof seals in appropriate secondary

packaging. Each unit-dose[3] of the ready-to-use pack contains 4 single-dose vials. The unit-dose pack contains absorbent material under the vials.

26. When ordered by a clinic, a unit-dose pack will be distributed directly to medical facilities with a smaller shipper in a bio-hazard bag surrounded by dry ice. The unit-dose pack will not be repackaged but the box will have a serial number for distribution control.

27. The GMO would be imported according to the packaging and labelling requirements of the International Air Transport Association (IATA) code UN 1845 and would be covered under licence DIR 217.

2.3.2 Transport and storage of the GMO

28. Procedures will be in place to ensure that all transported GMOs can be accounted for, and that a loss of GMOs during transport can be detected; and access to the GMO will be restricted to authorised persons conducting dealings under the licence, who have been informed by the licence holder of any licence conditions that apply to them. This includes situations where containers are left for collection in a holding area.

29. The external surface of the primary and secondary container will be decontaminated before and after transport.

30. On receipt at the clinic, the unit-dose will be stored in a secure freezer until it is needed for a patient. Access to the GMO will be restricted to authorised persons conducting dealings under the licence, who have been informed by the licence holder of any licence conditions that apply to them.

31. The proposed method of supply and storage of the GMO, as advised by the applicant, would be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSD).

2.3.3 Clinical trial sites

32. The clinical trial is proposed to take place at up to 9 different clinical trial facilities and hospitals in New South Wales and Victoria, including John Hunter Hospital, Austin Health, Royal Melbourne Hospital, Cancer Care Macarthur, Barwon Health, Blacktown Hospital, Liverpool Hospital, Concord Repatriation General Hospital and Wollongong Private Hospital. The activities that may be undertaken at these sites are storage and preparation of the GMO, administration of the GMO to participants, and collection and analysis of biological samples containing the GMO.

33. The applicant has selected these trial sites based on their patient populations, having suitably trained staff to conduct a clinical trial with a GMO, having procedures in place to prevent unauthorised access to the site, and having procedures in place to appropriately track, handle and dispose of the GMO.

2.3.4 The clinical trial

34. The applicant proposes to conduct Phase 3 and 3b trials with the GMO at multiple locations in Australia (as noted in Section 2.3.3).

Phase 3 trial

35. The Phase 3 trial is a randomised, multi-centre, open label trial to evaluate the safety and efficacy of intravesical GMO given alone or in combination with chemotherapy (intravesical gemcitabine and docetaxel) or immunotherapy (IV pembrolizumab) in subjects with high-grade BCG-

[3] A unit-dose refers to the amount of drug in a single dose that is to be administered to a patient.

unresponsive NMIBC. Prior to screening, eligible subjects will have gone through a transurethral resection of the bladder tumour.

36. Participants will receive doses of the GMO every 3 months, then treatment is optional from 12 to 24 months. There are 3 treatment arms: intravesical GMO only, intravesical GMO + intravesical chemotherapy of gemcitabine and docetaxel weekly for 6 weeks then monthly, and intravesical GMO + intravenous (IV) immunotherapy with pembrolizumab every 6 weeks. Participants will be monitored for up to 36 months.

Phase 3b trial

37. The Phase 3b trial is a randomised, multi-centre, open-label trial to evaluate the safety and efficacy of the GMO given every 3 months versus observation in subjects with intermediate risk (IR) NMIBC. Prior to screening, eligible subjects will have gone through a transurethral resection of the bladder tumour.

38. Participants will be randomised into one of 2 treatment arms. Arm 1 is the GMO administered into the bladder every 3 months for up to 24 months (maximum of 8 doses). Arm 2 is an observation arm with scheduled surveillance. GMO treatment will be offered to participants in Arm 2 if there is recurrence of their IR NMIBC within the 24 months. Participants will be monitored up to 60 months.

2.3.5 Selection of trial participants

39. Inclusion criteria proposed by the applicant relevant to this assessment include that trial participants must:

- be 18 years of age or older at screening
- Phase 3 trial only: have high-grade NMIBC that was unresponsive to ≥2 courses of Bacillus Calmette-Guerin (BCG) therapy within the last 12 months
- Phase 3b trial only: have newly diagnosed or recurrent intermediate risk (IR) non-muscle invasive bladder cancer
- female participants of childbearing potential must have a negative highly sensitive urine or serum pregnancy test prior to study entry and be willing to use effective forms of contraception during treatment and for 6 months after the last dose
- Phase 3 trial only: non-sterile male participants with female partners of reproductive potential must be willing to use effective forms of contraception during treatment and for 3 months after the last dose
- Phase 3b trial only: male participants must be willing to use a male condom and effective contraception during treatment and for 3 months after the last dose.

40. Relevant exclusion criteria apply to people who:

- are pregnant or lactating
- refuse contraception requirements during and after treatment
- have current or prior autoimmune disease
- are immunocompromised, or immunodeficient, or undergoing any form of treatment known to cause immunosuppression
- have received previous treatment with the GMO

- have used other adenovirus-vector based therapies with 14 days before or after instillation of the GMO
- Phase 3 trial only: cannot hold instillation for 1 hour
- Phase 3b trial only: have significant urinary incontinence or known bladder instability
- Phase 3b trial only: have known active hepatitis B or C.

41. In addition, participants may be excluded for any reason that, in the opinion of the investigator, makes the participant unsuitable for the study.

2.3.6 Preparation of the GMO for administration

42. Qualified personnel at the trial site (e.g. pharmacists) will prepare the GMO for administration. The applicant proposes that individuals who are immunosuppressed, immune-deficient, or pregnant should not prepare, administer, or come into contact with the GMO.

43. Preparation steps will be conducted using aseptic techniques in a Class 2 biological safety cabinet (BSC-2) or equivalent to ensure sterility of the product and personnel protection. After thawing, the contents of each of the 4 vials is drawn into syringes and diluted to a final instillation volume of 75 mL (3×10^{11} viral particles (vp)/mL). To prevent needle stick injuries, vented vial adapters are used to transfer the GMO from the vial to the syringe.

2.3.7 Intravesical administration of the GMO

44. The GMO would be administered via intravesical administration at clinical trial sites. The intravesical administration would be carried out by appropriately trained clinical trial personnel (e.g. clinicians or nurses) who would be wearing appropriate PPE including gloves, eye wear (safety glasses, goggles or face shields) and lab scrubs/gowns.

45. The GMO solution (75 mL) will be instilled into the bladder via a urinary catheter followed by 1 hour dwell time during which the participant will be repositioned every 15 minutes from left to right, back and abdomen to maximise bladder surface exposure. The entire process is managed in an outpatient setting, amounting to roughly 2 to 2.5 hours in total per visit for trial participants.

2.3.8 Decontamination and disposal of the GMO

46. Following administration, all residual GMO and associated waste which has come into contact with the GMO would be disposed of in accordance with the relevant State and Territory legislated procedures for clinical/medical waste disposal, which can include high temperature incineration. Any unused vials of the GMO would be also disposed of using the same process. Disposal would be carried out by external service providers via the clinical waste stream.

47. Any surfaces or equipment that come into contact with the GMO will be decontaminated using an effective disinfectant, including 0.25% peracetic acid, iodine, 10% bleach or 0.5 % sodium hypochlorite.

48. As there may be transient, low-level shedding of the GMO in urine for several days after administration, for 2 days after instillation the participants will be instructed to add an equal volume of virucidal agent to the toilet bowl prior to voiding and wait 15 minutes before flushing the toilet.

2.3.9 Sample collection and analysis

49. Biological samples such as blood, urine, and tissue biopsies (bladder and/or prostatic urethra) for disease evaluation and pregnancy testing (if clinically indicated) will be collected prior to each dose of the GMO.

50. The samples will be collected by clinicians or nurses at participating sites as per the site's standard operating procedures, including while wearing PPE such as gloves, mask and eye wear

(safety glasses, googles or face shields). In addition, a trial-specific laboratory manual will be provided to the participating sites describing in detail how to handle, store and transport the biological samples.

51. After collection, clinical site staff may need to process the samples according to the study protocol. All sample processing steps would be performed following appropriate safety precautions and in compliance with standard clinical pathology procedures or other relevant guidelines.

52. Samples may be analysed at the clinical trial sites, transported to a central laboratory in Australia or exported for analysis.

2.3.10 Personal protective clothing

53. Clinical trial staff involved in the preparation and administration of the GMO to trial participants and in the clean-up of spills would wear PPE, for example gloves, gown, plastic apron, surgical mask, and eye wear (safety glasses, goggles or face shield).

2.3.11 Training

54. If the licence is issued, Ferring would have responsibility for ensuring training of personnel and compliance with licence conditions.

55. The applicant has indicated that appropriate training (e.g. training in all procedures specific to the GMO including preparation, handling, administration, spill procedures, containment and disposal etc.) materials would be provided to all personnel involved in the trial.

56. The doses of GMO would be prepared by trained pharmacists or pharmacy technicians in a BSC-2. Those staff would be trained on the preparation of the GMO and handling of sharps to minimise the likelihood of exposure.

2.3.12 Accountability and Monitoring

57. The applicant has proposed that trial participants would be instructed to monitor themselves for signs of infection or adverse reactions such as fever, flu-like symptoms or injection site reactions.

58. Any unintended exposure to the GMO through injury or direct contact would be reported to the Regulator.

2.3.13 Contingency plans

59. In the event of exposure of people to the GMO via sharps injury or contact with broken skin, the applicant proposes such persons would be instructed to implement institutional needlestick or exposure guidelines, which may include the following:

(a) encourage bleeding at the site;

(b) wash the area thoroughly with soap and water;

(c) seek appropriate medical attention; and

(d) report the incident to the principal investigator, who will inform the licence holder, who will notify the Regulator.

60. In the event of unintentional release of the GMO due to spills, personnel would be instructed to follow spill management procedures, including that;

(a) the GMO will be contained to prevent further dispersal;

(b) persons cleaning up the GMO will wear PPE including gloves, gown, plastic apron, surgical mask, and eye shield or goggles;

(c) the exposed area will be decontaminated with an appropriate chemical disinfectant effective against the GMO;

(d) any material used to clean up the spill or PPE worn during the clean-up will be decontaminated;

(e) clinical trial staff will notify the licence holder as soon as reasonably practicable; and

(f) the licence holder will notify the Regulator as soon as reasonably practicable.

Section 3 Parent organism

61. The characteristics of the parent organism provide a baseline for comparing the potential for harm from dealings with the GMO. The GM therapeutic is derived from the human adenovirus species C serotype 5 (HAdV-C5). As such, the relevant biological properties of HAdVs will be discussed here.

62. Adenoviruses (AdVs) are within the genus Mastadenovirus in the Adenoviridae family (Scarsella et al., 2024) and are classified as Risk Group 2 microorganisms (Standards Australia/New Zealand, 2022). HAdVs are common pathogens of humans. They can cause periodic outbreaks of respiratory diseases, problems in ocular, gastrointestinal, and genito-urinary systems. Occasionally, they can lead to metabolic disorders (Ismail et al., 2018a). HAdVs are categorised into 7 species, A to G, based on their serology, sequence homology, serum neutralisation, haemagglutinin properties and genomic sequence (Bots and Hoeben, 2020; Lange et al., 2019; Leikas et al., 2023a). Up to 116 genotypes of HAdV have been assigned (HAdV Working Group website, accessed June 2025). Different HAdV species are associated with different diseases: species C, E and some B species are the most common cause of respiratory diseases; species A, F, G and some D species are responsible for gastrointestinal infections; species D and E can also cause ocular diseases, and some B species can cause urinary tract infections (Ismail et al., 2018a; Leikas et al., 2023a).

63. Human adenovirus-C5 belongs to species C, which comprises 5 serotypes (C1, C2, C5, C6 and C57) that are commonly associated with acute respiratory tract infections in children (Mennechet et al., 2019b; Wurzel et al., 2014). Despite the high prevalence of HAdV-C in the population, HAdV-C5 vectors have been frequently used in clinical trials as cancer therapies (Leikas et al., 2023a; Sato-Dahlman et al., 2020; Shaw and Suzuki, 2019).

3.1 Pathology

64. Human adenoviruses are common human pathogens and cause a wide range of illnesses such as common cold; sore throat; bronchitis; pneumonia; diarrhoea; conjunctivitis; fever; inflammation of the stomach, intestine and bladder; and neurologic disease (conditions that affect the brain and spinal cord) (CDC, 2019a; Leikas et al., 2023a; Public Health Agency of Canada, 2014).

65. Infections with HAdV are generally mild and self-limiting, but could be more severe or lethal in immunocompromised individuals or in the very young (Leikas et al., 2023a; Mennechet et al., 2019a). Overall, HAdV infections are responsible for about 2-5% of all respiratory infections in humans (Allard and Vantarakis, 2017) and are the most common cause of conjunctivitis in the world (Pihos, 2013).

66. Outbreaks of HAdVs-associated respiratory disease are more common in the late winter, spring and early summer, however infections can occur throughout the year. After natural HAdV infection, the incubation period of HAdVs ranges from 2 days to 2 weeks, depending on the viral species and serotype as well as the mechanism of acquisition (Allard and Vantarakis, 2017; Public Health Agency of Canada, 2014). For respiratory infections, the incubation period is generally 4-8 days, whereas it is 3-10 days for intestinal infections (Allard and Vantarakis, 2017). The symptoms of mild infection usually last for a few days to a week but for the severe infections, symptoms may last longer.

67. The parental species, HAdV-C, has been mainly associated with acute respiratory tract infections in children and is the most common serotype reported in most populations, with anti-

HAdV-C5 antibodies detected in almost 85% of the population (Leikas et al., 2023a; Mennechet et al., 2019a).

3.2 Structure and genomic organisation

68. Adenoviruses are non-enveloped, double-stranded DNA viruses with an icosahedral capsid comprising of 3 major (hexon, penton base and fiber) and 4 minor (protein IX, VIII, IIIa and VI) proteins; other proteins (V, VII, μ, Iva2, terminal protein and adenovirus protease); and a core that contains DNA (Robinson et al., 2011; Yu et al., 2017). The genome of AdVs is approximately 30-35 kilobases (kb) which includes 30-40 genes (Charman et al., 2019; Lasaro and Ertl, 2009). The genome is flanked by inverted terminal repeats (ITRs).

69. The HAdV genome consists of early and late genes, which are organised into transcription units (Figure 2). The early genes (E1, E2, E3 and E4) are involved in directly activating transcription of other viral regions, altering the host cellular environment to enhance viral replication, and co-ordination of viral DNA replication (Afkhami et al., 2016; Lasaro and Ertl, 2009; Roy et al., 2004; Saha and Parks, 2017). The late genes (L1 to L5) encode components of the viral shell and other proteins that are involved in assembly of the capsid and are essential for production of new virus particles.

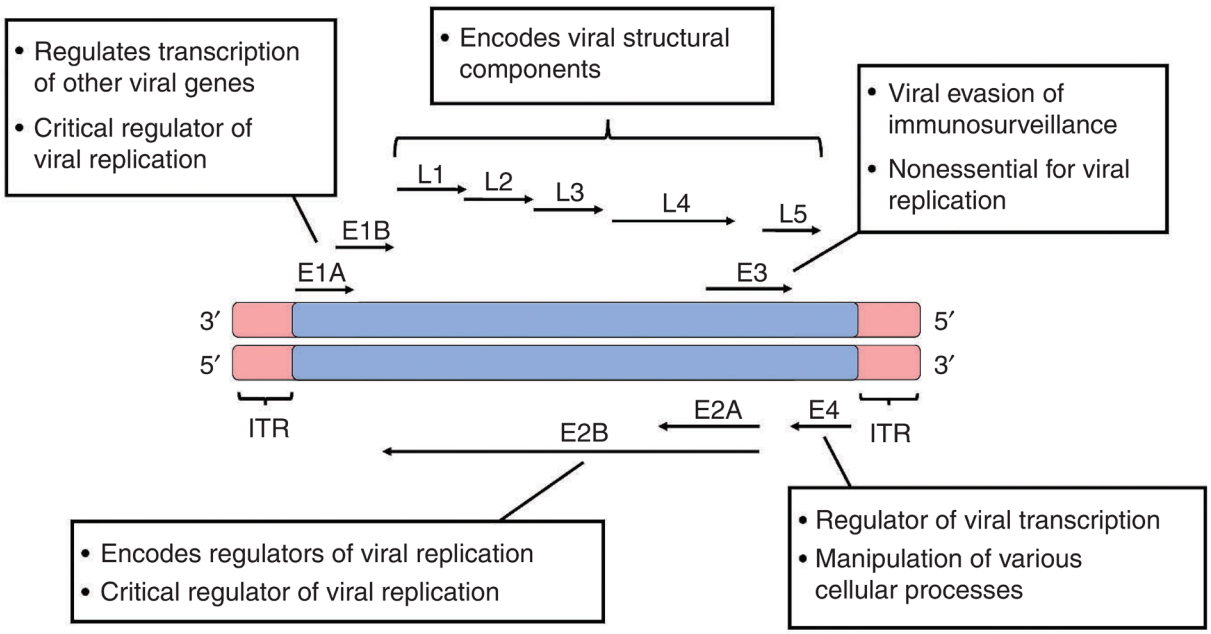

Figure 2: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).

70. The E1 gene is composed of E1A and E1B. The E1A gene controls transcription of viral genes and redirects host-cell gene expression machinery to enable virus replication. The proteins produced from the E1A genes are the first proteins expressed from the infecting virus, and are essential for the efficient expression of other viral genes (Roy et al., 2004; Saha and Parks, 2017). The E1B gene assists in viral replication and is mainly required for the export of viral late mRNA (L1 to L5) from the host-cell nucleus into the cytoplasm. Together, the E1A and E1B coding regions are essential for viral gene expression and replication (Roy et al., 2004; Saha and Parks, 2017).

71. The E2 gene consists of E2A and E2B, that encode E2 proteins. The E2 proteins are mainly involved in viral DNA replication and transcription of late genes (Roy et al., 2004; Saha and Parks, 2017). The E3 gene encodes viral proteins that aid the virus in evading the host immune response. The E4 gene modulates cellular function and assists with viral DNA replication and RNA processing.

72. Interactions of proteins encoded by the adenovirus genome are required to form a mature infectious particle. The 3 major proteins (hexon, penton and fiber) form the external capsid structure and "spikes" of the viral particle. The viral core proteins (V, VII and Mu) mediate the interactions between the core and the capsid, while the minor proteins (IIIa, VI, VIII and IX) contribute to the structure and stability of the virion by acting as cement proteins, connecting the major structural proteins with each other and with the viral core (see Figure 3) (Liu et al., 2010; Reddy et al., 2010; Reddy and Nemerow, 2014). These viral core and minor proteins are synthesised as precursors, then processed by adenovirus protease during assembly to form a mature infectious particle. The assembly of the final viral particle is thought to follow a sequential assembly pathway, whereby an empty capsid is formed prior to genome packaging (Ahi and Mittal, 2016; Ma and Hearing, 2011; Mangel and San Martin, 2014; San Martin, 2012).

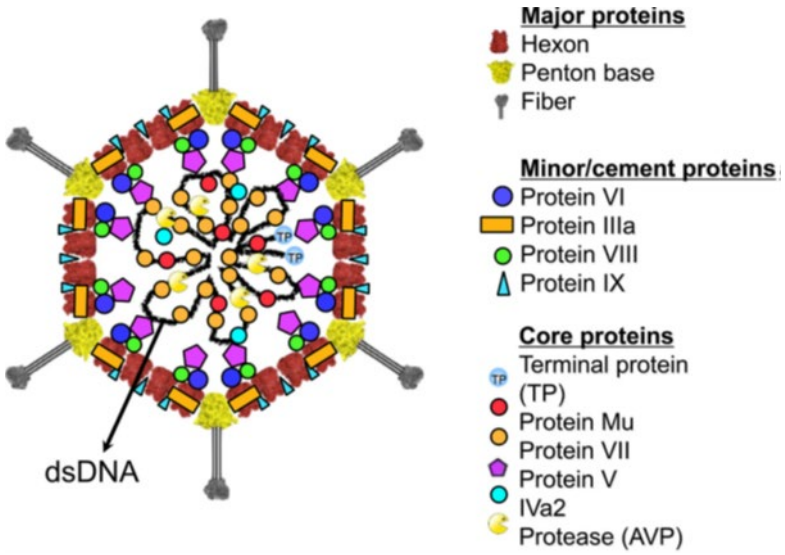

Figure 3: Structural model of human adenovirus (Benevento et al., 2014)

3.3 Viral infection and replication

73. Adenoviruses can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. AdVs most frequently infect epithelia of the upper or lower respiratory tract, eyes, gastrointestinal and urinary tract tissues. The tropism of AdVs is largely dependent on the species; species A, F and G infecting gastrointestinal cells, species C, E and some B species infecting the respiratory tract, the rest of species B infecting the urinary tract and species D infecting the conjunctiva of the eye (Leikas et al., 2023a).

74. Human adenoviruses use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins, CD46, CD80, CD86 and sialic acid to enter the host cells (Lion, 2019; Zhang and Bergelson, 2005). *In vitro* studies with HAdV-C also showed that vitamin K-dependent blood factors including Factor X (FX) increases the binding efficiency of HAdV-C to hepatocytes (Weaver et al., 2011).

75. Replication of AdVs occurs in the nucleus of the host cell, using the host cell nuclear machinery to make copies of itself (Figure 4). Following attachment to cell membrane receptors (steps 1-3), the AdV enters the host cell and is uncoated to release viral particles (step 4). The viral genome is transported into the nucleus (step 5) where the transcription of early phase genes occurs (step 6) (Charman et al., 2019). Viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made and new virus particles are assembled (steps 7-9). Finally, the host cell breaks apart releasing the viruses (step 10) (Waye and Sing, 2010).

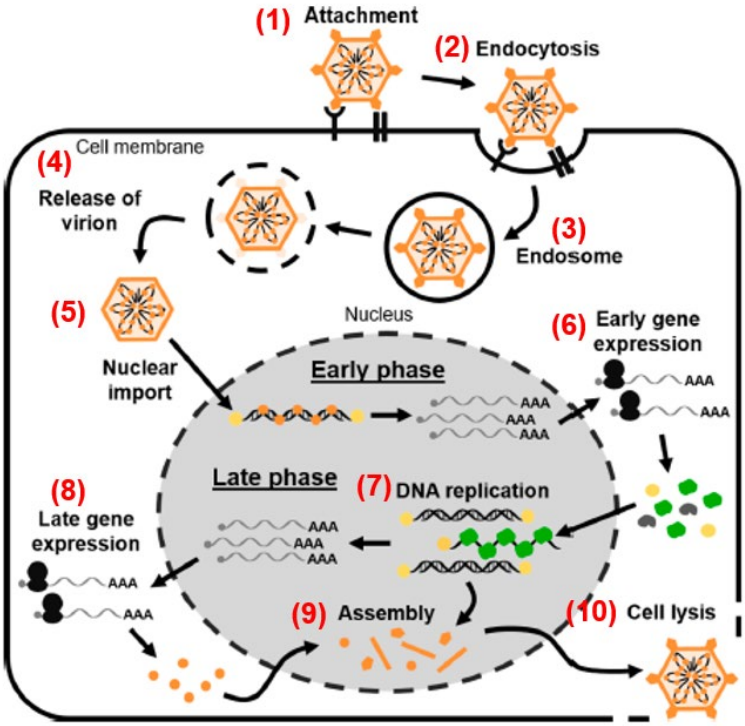

Figure 4: Overview of the adenovirus replication cycle (Charman et al., 2019). Virus entry and import of viral genomes into the nucleus lead to a program of early gene expression that includes the viral replication machinery. The onset of viral DNA replication marks progression from the early to the late phase of infection and is a prerequisite for both late gene expression and virion assembly.

3.4 Mutation and recombination

76. Adenovirus DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999) and AdVs do not have the machinery for efficient integration into the host genome. Instances of AdVs integration are considered rare, and random integration of virus DNA into the host genome has been observed only in very rare cases (Dehghan et al., 2019; Desfarges and Ciuffi, 2012; Harui et al., 1999; Hoppe et al., 2015a).

77. Where a cell is infected by multiple AdVs at the same time, exchange of genetic material can occur, which promotes the molecular evolution of AdVs through homologous recombination. Homologous recombination appears to be restricted to members of the same species and occurs in the regions of high sequence homology (Lukashev et al., 2008).

78. Bioinformatic analysis of HAdV-C suggests that homologous recombination in the capsid (hexon, penton and fiber) and E3 genes were not common and were not major contributors to the diversity seen in HAdV-C (Dhingra et al., 2019), although a more recent study using phylogenetic analyses demonstrated that the E3 region may act as recombination hotspots for HAdV-C (Fang et al., 2024). The hexon protein is a major constituent of the viral capsid and is suggested to be critical for the development of AdV vaccines or therapeutics by forming the serum neutralisation epitope; the penton and fiber proteins are responsible for host cell binding and internalisation; and the E3 proteins facilitate immune evasion by the virus (Ismail et al., 2018b; Robinson et al., 2011). The lack of homologous recombination in the capsid and E3 genes of HAdV-C reduces the likelihood of HAdV-C altering its cell tropism and of altering its ability to evade the immune system.

79. In addition, bioinformatic analysis also showed very low sequence diversity in the minor capsid proteins (IIIa, V, VI, VII, VIII and IX), suggesting that these proteins are well conserved between all HAdV-C serotypes (Dhingra et al., 2019). However, genome analysis of 51 circulating species HAdV-C

revealed that the evolution of HAdV-C may be the result of recombination events in the early genes (e.g. E1 and E4) (Dhingra et al., 2019). Bioinformatics analysis also suggested that HAdV-E4, a species E AdV, was a result of a recombination event between species B and C (Gruber et al., 1993).

3.5 Epidemiology

3.5.1 Host range and transmissibility

80. Humans are the natural host for HAdVs and most do not infect animals via natural routes (Liaci et al., 2025). Although there is evidence to suggest that AdVs have crossed the host species barrier especially between human and non-human primates, this is considered a rare event (Borkenhagen et al., 2019; Hoppe et al., 2015b). Experimentally, mice, cotton rats, hamsters, guinea pigs, tree shrews and rabbits can be infected with HAdVs (Bertzbach et al., 2021; Ismail et al., 2019). Whereas some animals such as hamsters can be permissive to HAdV replication in experimental conditions (Tollefson et al., 2017), in most animals, infections with HAdV are abortive even when they induce tissue pathology (Jogler et al., 2006). HAdV-11p was shown to undergo abortive infection in canine (MDCK), hamster (CHO) and mouse (McCoy and C127) cell lines (Gokumakulapalle et al., 2021) but could productively infect Vero cells (kidney epithelial) from African green monkey (Gokumakulapalle and Mei, 2016).

81. Transmission of HAdVs from an infected individual is primarily via direct contact with respiratory aerosols, conjunctival secretions or via the faecal-oral route (Allard and Vantarakis, 2017; CDC, 2019b; Gray and Erdman, 2018; Khanal et al., 2018; Leikas et al., 2023a). The virus can also be spread indirectly via contact with articles e.g. handkerchiefs, linens or utensils contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017). The infectious dose for AdV serotype 7 is more than 150 viral units, administered as nasal drops, but inhalation of as few as 5 AdV particles can cause disease in susceptible individuals (Musher, 2003; Public Health Agency of Canada, 2014).

3.5.2 Bio-distribution and shedding

82. The predominant natural tropism of HAdV-C is the respiratory tract and it causes a significant proportion of acute respiratory tract infections in children (Mennechet et al., 2019a). Following natural HAdV infection, virus particles are shed via respiratory secretions or in the faeces. Respiratory infections generate the highest viral load early post-infection with residual virus remaining for up to 2 months post-infection (Huh et al., 2019). The ease of transmission of HAdV is thought to be facilitated by very high levels of viral particles shed into sputum or oral secretions of the infected person (Allard and Vantarakis, 2017).

83. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing the HAdV-E4 and HAdV-B7 serotypes. Over 50% of the vaccine recipients tested positive for AdV faecal shedding between 7-28 days following vaccination. No faecal shedding was detected after 28 days following vaccination or at any time point in throat swabs (Allard and Vantarakis, 2017).

3.5.3 Prevalence

84. An estimation of the seroprevalence for different HAdV has been drawn from published literature. Seroprevalence in different countries ranges from 2%-96%. The highest worldwide seroprevalence is for HAdV4, 5 and 6 belonging to groups C and E (Hong et al., 2025). An estimation of the seroprevalance of HAdV-E4, -C5, -D26 and -B35 (serotypes commonly tested in the clinics or used in clinical/pre-clinical trials) is shown in Figure 5, based on approximately 30 studies published over the past 20 years (Mennechet et al., 2019a). HAdV-C5 is the most widely reported and has the highest seroprevalance globally.

85. In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health and Aged Care (1991-2000) showed an average of about 1400 reported cases of adenovirus

infection per year over 10 years (Spencer, 2002). It is important to note that the majority of reported AdV infections have not been serotyped and that testing for adenovirus infections may not be common in Australia. However, these numbers indicate that HAdVs are present in the Australian environment. In 2025, the Australian Respiratory Surveillance Report showed that adenovirus was identified in 4.7% of samples tested for respiratory pathogens among people with influenza-like illness attending general practice sites (Australian Respiratory Surveillance Report 2025, accessed November 2025).

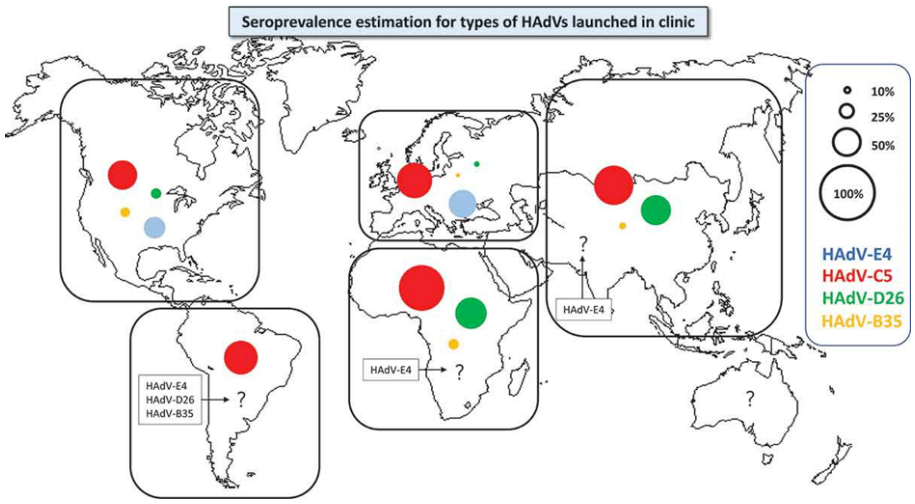

Figure 5: Seroprevalance for adenovirus types used in the clinic (Mennechet et al., 2019a)

3.5.4 Control, environmental stability and decontamination methods

86. Infection with HAdV is generally asymptomatic or associated with mild disease in healthy adults and is generally managed through a combination of supportive care and enhanced personal hygiene measures to limit transmission. Antiviral drugs may be used in immunocompromised patients or those with severe disease. Antiviral agents such as Cidofovir and Ribavarin are commonly used as first line adenoviral therapies (CDC, 2019a; Lion, 2019; Waye and Sing, 2010). There are currently no AdV-specific drugs to treat infection (CDC, 2019a; Waye and Sing, 2010).

87. Adenoviruses are resistant to most chemical or physical decontamination processes and agents (including lipid-disrupting disinfectants) as well as high or low pH conditions (Gray and Erdman, 2018; Public Health Agency of Canada, 2014; Rutala et al., 2006). They are also resistant to UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003), thus supporting survival in treated wastewater and sewage, rivers, oceans, swimming pools water and drinking water (Public Health Agency of Canada, 2014).

88. Adenoviruses are very stable in the environment at pH 6-8 and below 40˚C (Rexroad et al., 2006) and can survive for long periods in liquid or on surfaces in a desiccated state. For example, HAdV can survive up to 10 days on paper under ambient conditions and for 3-8 weeks on environmental surfaces at room temperature (Public Health Agency of Canada, 2014). Therefore, AdVs survival time depends on the relative humidity, temperature and on the type of surface (Abad et al., 1994).

89. Worldwide, HAdVs have been detected in water samples of different kinds including wastewater, river water, drinking water, ocean and swimming pools (Allard and Vantarakis, 2017). They are often detected in high concentrations in domestic sewage and sludge in various countries

and in some situations may be used in surveillance for faecal contamination (Allard and Vantarakis, 2017).

90. Adenoviruses are reported to be sensitive to 70% ethanol, 0.9% Virkon S (>5 min contact time), 0.2% chlorine, 0.55% ortho-phthalaldehyde and 2.4% glutaraldehyde (McCormick and Maheshwari, 2004; Rutala et al., 2006). AdVs can also be inactivated by contact with 1:5 dilution of bleach (sodium hypochlorite) (Public Health Agency of Canada, 2014). In addition, AdVs can be inactivated by heat e.g. heating to 56°C for 30 minutes or 60°C for 2 minutes or autoclaving (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Public Health Agency of Canada, 2014).

Section 4 The GMO - nature and effect of the genetic modification

4.1 The genetic modifications

91. Nadofaragene firadenovec is a replication-deficient recombinant HAdV carrying a gene encoding the human interferon alpha-2b (hIFN-α2b) protein.

92. This GM therapeutic was developed from HAdV-C5 by deleting specific gene sequences to improve safety and replacing a deleted DNA sequence with a *hIFN-α2b* gene expression cassette. The identities of the deletions have been declared Confidential Commercial Information (CCI). Under section 185 of the Act, the CCI is made available to the prescribed experts and agencies that are consulted on the RARMP for this application.

93. The GM therapeutic was generated through recombination between a plasmid containing the hIFN-α2b gene and a viral derivative, followed by *in vitro* co-transfection into a human cell line for viral production. The human cells provide necessary proteins during virus propagation. However, this production process may lead to the GM therapeutic containing a small percentage of replication-competent adenovirus (RCA) that is attenuated compared to the parent adenovirus. Information on how the GM therapeutic was generated and the identity of the human cell line have also been declared CCI.

4.2 Effects of the genetic modifications

4.2.1 Deletion of regions from HAdV-C5

94. The GM therapeutic was made safer due to the removal of specific DNA sequences from the HAdV-C5 genome. Details of the deletions have been declared CCI.

4.2.2 Insertion of the hIFN-α2b gene expression cassette

95. The GM therapeutic is intended as a treatment of BCG-unresponsive NMIBC. It contains an introduced *hIFN-α2b* gene expression cassette which produces the hIFN-α2b protein in patients receiving the therapeutic.

96. Interferons (IFNs) are produced by the innate immune system via Toll-like receptor (TLR) stimulation and other signalling cascades. There are 3 main classes of IFNs in humans: IFN-α, -β and -γ, with IFN-α and -β belonging to the type I IFNs (Shi et al., 2022).

97. IFN-α is a key cytokine produced primarily by monocytes/macrophages and can also be synthesised by B cells and fibroblasts. There are 13 different human IFN-α subtype proteins expressed from 14 human IFN-α genes (Shi et al., 2022).

98. IFN-α2b is one of 3 IFN-α2 variants sharing the same properties (Gibbert et al., 2013). The hIFN-α2b protein regulates expression of many genes involved in antiviral and antiproliferative activities and has been used in hepatitis and cancer treatments (Asmana Ningrum, 2014). It also plays a role in mediating an immune response and is involved in antigen recognition and processing, leading to T-cell, natural killer and dendritic cell activation (Martini et al., 2023). Therefore, the actions of the GM therapeutic are multi-fold and include direct cytotoxicity on cancer cells,

antiangiogenic effects, increased tumour cell immunogenicity and activation of key immune cells (Konety et al., 2024).

99. The *hIFN-α2b* gene expression is driven by a strong promoter and an associated enhancer sequence. Details of the hIFN-α2b protein, the promoter and the enhancer have been declared CCI. Under section 185 of the Act, the CCI is made available to the prescribed experts and agencies that are consulted on the RARMP for this application.

4.2.3 Toxicity or adverse response associated with the genetic modifications

100. The GM therapeutic is a GM HAdV intended for use as a therapeutic for patients with high-grade BCG-unresponsive NMIBC. The GM therapeutic functions to increase anticancer activity via immunostimulatory, antiangiogenic and apoptotic effects (Lee, 2023).

101. The GM therapeutic will produce the IFN-α2b protein, which has been used extensively in clinical applications for treatment of some viral infections and for treatment for various cancers (Xiong et al., 2022). In the past, treatments involving administration of the IFN-α2b protein have been through intramuscular, subcutaneous, intralesional, or intravenous routes, but not intravesical instillation. The commercially available IFN-α2b protein, registered in the USA as INTRON A, has been used to treat patients with hepatitis B and C, and various virus-induced tumours. According to the Product Information for INTRON A, most of the adverse reactions possibly related to INTRON A therapy during clinical trials were mild to moderate in severity and were manageable. Some were transient and most diminished with continued therapy. The most frequently reported adverse reactions were "flu-like" symptoms, particularly fever, headache, chills, myalgia, and fatigue. In nonclinical studies included in the product information, mice, rats and cynomolgus monkeys have been used for repeat-dose toxicity testing of INTRON A. The doses for mice (0.1, 1.0 million international units [IU]/kg/day) injected for 9 days, rats (4, 20, 100 million IU/kg/day) injected for 3 months and cynomolgus monkeys (0.25, 0.75, 1.1, 2.5 million IU/kg/day) injected for 1 month revealed no evidence of toxicity. However, high doses (20 and 100 million IU/kg/day) injected daily for 3 months in cynomolgus monkeys resulted in toxicity and mortality. Due to the known species-specificity of interferon, the effects in animals are unlikely to be predictive of those in humans.

102. According to information provided by the applicant, nonclinical studies of the GM therapeutic indicated that no unacceptable toxicities were seen in animals following intravesical administration of 5×10^{11} viral particles (vp)/mL. The predominant safety finding following the intravesical administration of the GM therapeutic to monkeys was a reversible exacerbation of local irritation produced by the dosing procedure.

103. The GM therapeutic was tested for adverse effects in cynomolgus monkeys following intravesical administration targeting the urothelium to treat urinary bladder cancer (Veneziale et al., 2011). Animals were repeatedly dosed with an interval of 90 days with either 2.5×10^{11} vp or 1.25×10^{13} vp. Adverse events, such as inflammation and ulceration of the bladder and irritation in the ureters, urethra and kidneys, were observed which resolved within 2 months after re-dosing.

4.3 Characterisation of the GMO

104. The GMO is engineered on the HAdV-C5 backbone except for the introduced transgene, thus the cell-host recognition in the GMO relies on the same mechanism as the wild-type HAdV-C5 and depends on the recognition of CAR for cell transduction, which are highly expressed on the surface of cancer cells.

105. Data obtained from pre-clinical and clinical studies using the proposed GMO has been used to characterise the GMO.

4.3.1 Genetic stability and molecular characterisation

106. Adenoviruses in general are genetically stable (Vujadinovic et al., 2018). As discussed in Section 4.1, due to the possible formation of RCA in the GM therapeutic during the manufacturing process,

the level of RCA in the final GM therapeutic product needs to be controlled. The presence of RCA contaminants constitutes a risk of unintended viral spread and host inflammation response when the viral products are used clinically. Therefore, the GM therapeutic product during manufacturing will be monitored to ensure that the level of RCA in the batches for clinical use meets the safety limit specification.

107. Adenovirus vectors are non-integrating and do not have a tendency to integrate or reactivate in a host (EMEA, 2007; FDA, 2020). The viral DNA is maintained as multiple episomal copies in the infected nuclei. Some studies in cell lines and mice have suggested plausible integration of AdV vectors into host genomes at very low frequencies (Hillgenberg et al., 2001; Stephen et al., 2010). However, a search of the scientific literature did not find any clinical or human studies that showed integration of an AdV vector into the host genome.

108. The entire vector genome of this GM therapeutic has been sequenced and aligns with the HAdV-C5 genome except for the intended modifications.

4.3.2 Stability in the environment and decontamination

109. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Methods of decontamination effective against the parent organism, HAdV-C5, are expected to be equally effective against the GMO (see Chapter 1, Section 3.5.4).

4.3.3 Pre-clinical studies using the GMO

110. The GM therapeutic has been evaluated in pre-clinical studies *in vitro* using cancer cell lines and *in vivo* in various animal models.

111. *In vitro* pharmacology data from several cancer cell lines, including urothelial cancer cell lines, has shown that transduction with the GMO produces biologically active IFN-α2b protein in a time and dose-dependent manner (Adam et al., 2007; Benedict et al., 2004; Iqbal Ahmed et al., 2001). Treatment of a human liver cancer cell line with the GMO resulted in inhibition of cell growth and potent cellular toxicity, with an increase in caspase 3 induction and DNA fragmentation and resulted in apoptosis (Benedict et al., 2004).

112. The anti-tumour efficacy of the GMO has been demonstrated in several animal species. Intra-tumoral or intravenous administration of the GMO was found to prolong survival and suppression of tumour growth was demonstrated in a dose dependent manner (Iqbal Ahmed et al., 2001). In a mouse orthotopic xenograft tumour model for NMIBC, high concentrations of IFN-α2b were expressed in bladders of mice following intravesical administration of the GMO formulated with the excipient Syn3 and bladder tumours significantly regressed (Benedict et al., 2004). Syn3 has been identified as an excipient that can increase AdV-mediated gene transfer and expression in the bladder epithelium (Connor et al., 2001).

113. According to information provided by the applicant, in a pilot study, cynomolgus monkeys following intravesical administration of 2.5 x 10^{13} vp GMO with Syn3 showed peak urinary IFN-α2b protein concentrations >10,000 - 50,000 pg/mL and concentrations remained above background levels for 14 days. IFN-α2b expression was mainly localised and confined to the bladder and urine. IFN-α2b expression was attenuated after re-dosing, possibly due to neutralising antibodies to the adenovirus and/or IFN-α2b protein. Similar results of attenuated IFN-α2b expression following re-dosing were also observed in the rat model (Connor et al., 2005).

114. The systemic exposure of the GMO, as measured by copies of GMO-specific DNA/mL in blood and plasma in the different toxicology studies in monkey and rat, was low and close to the low level of quantification for all doses and for both species (Information provided by the applicant).

115. In a different study, biodistribution and shedding of the GMO were analysed in cynomolgus monkeys by real-time quantitative PCR (qPCR) assay following intravesical administration of the GMO with the doses of 2.5 x 10^{11} or 1.25 x 10^{13} vp (Veneziale et al., 2011). Urine, blood and tissue samples

(liver, kidney, bladder and gonads) were collected at various time points from Day 1 to Day 148. Most urine samples tested positive for the GMO DNA-fragments that were amplified (GMO-specific DNA) in the first two days after each dose. On Day 15 and Day 105 (15 days post-second dose), urine from only one and two of the 32 monkeys tested positive, respectively. None of the urine samples tested positive on week 12, prior to the second dose. As expected, due to the route of administration, GMO-specific DNA was detected in bladder tissue on Day 8 post-first dose and Day 98 (8 days post-second dose) in both the low and high-dose group. In blood samples, GMO-specific DNA was detected at low levels in the low-dose group during the first 24 hours in a limited number of monkeys (2/16 post-first dose and 1/10 post-second dose). In the high-dose group, two-thirds of the monkeys (11/16 for first dose and 7/10 for repeat dose) tested positive during the first 24 hours. Detection was below quantifiable levels in all monkeys for the remaining samples collected on Days 8, 15, 98 and 148. Low levels of GMO-specific DNA were detected in kidney (1/16 at Day 148) and liver (2/16 at Day 8) in the low dose group. For the high dose group, higher levels of GMO-specific DNA were detected in kidney (3/16 at Day 98) and liver (5/16 at Day 8). In the high dose group, GMO-specific DNA was also detected in gonads of one male and one female on Day 8. These monkeys also had the highest level of GMO-specific DNA in their blood samples. GMO-specific DNA was not detected in gonads beyond Day 8.

116. The applicant stated that the potential of the GMO for genotoxicity or carcinogenicity, or for toxicity to reproduction and development, has not been studied.

4.3.4 Clinical trials of the GMO

117. The GM therapeutic has been studied in 4 clinical trials from Phase 1 to 3 in the USA for intravesical recombinant AdV mediated IFN-α2b gene therapy formulated with Syn3 in patients with high-grade BCG-unresponsive NMIBC (Table 1).

Table 1. Summary of previous clinical trials using the GMO

No.	Clinical study	No. treated	Adverse events (AE)*	References
1	A Phase 1 study of the safety and tolerability of intravesical administration of SCH 721015 in patients with transitional cell carcinoma of the bladder	17	All patients had at least one AE of grade 1 or 2. Common treatment-related AEs included micturition urgency (88%), headache (59%), fatigue (47%) and nausea (35%). No dose-limiting changes in laboratory parameters were reported, but transient decreases in total white blood cell counts, neutrophil counts, and lymphocyte counts were observed.	NCT00536588 (Dinney et al., 2013)
2	Phase 1b intravesical administration of SCH 721015 (Ad-IFNa) in admixture with SCH 209702 (Syn3) for the treatment of BCG refractory superficial bladder cancer	7	One AE reported as a non-serious worsening of lower urinary tract symptoms from one patient.	NCT01162785 (Navai et al., 2016)
3	A Phase 2, randomized, open label, parallel arm study to evaluate the safety and efficacy of rAd-IFN/Syn3 following intravesical administration in subjects with high grade, BCG	40	97.5% patients experienced at least one AE, with slightly more AEs in the 3×10^{11} vp/mL dose group compared to the 1×10^{11} vp/mL dose group. Most AEs were Grade 2 or lower, while 9 patients (22.5%) had AEs of Grade 3. There were no Grade 4 or 5 events.	NCT01687244 (Shore et al., 2017)

No.	Clinical study	No. treated	Adverse events (AE)*	References
	refractory or relapsed superficial bladder cancer			
4	A Phase III, open label study to evaluate the safety and efficacy of INSTILADRIN® (rAd-IFN)/Syn3) administered intravesically to patients with high-grade, BCG unresponsive non-muscle invasive bladder cancer (NMIBC)	157	93.0% patients experienced an AE. Most AEs were Grade 2 or lower, while 31 patients (19.7%) and 3 patients (1.9%) had AEs of Grade 3 and 4, respectively. GMO-related AEs occurred in 70.7% of patients; 6 (3.8%) patients had a GMO-related Grade 3 AE. No GMO-related Grade 4 or 5 AEs were reported.	NCT02773849 (Boorjian et al., 2021)

*Based on Common Terminology Criteria for Adverse Events (CTCAE): Grade 1 - Mild; Grade 2 - Moderate; Grade 3 - Severe or medically significant but not immediately life-threatening; Grade 4 - Life-threatening consequences; Grade 5 - Death.

118. The Phase 1 trial assessed the safety, tolerability, and maximum tolerated dose (MTD) of the intravesical administered GMO in patients with transitional cell carcinoma of the bladder. No dose limiting toxicity was identified, and no significant GMO-related adverse events were observed. Therefore, the MTD was not reached in this trial and therefore the 2 highest doses (1×10^{11} vp/mL and 3×10^{11} vp/mL) were selected for the Phase 2 trial. qPCR analysis of blood samples showed no GMO-specific DNA detected in any samples collected at 2, 6 and 72 hours post dose from the 17 patients. The presence of GMO-derived DNA was also assessed in urine using qPCR. Generally, a higher frequency of detection of samples positive for GMO-derived DNA and persistence of presence correlated with increase in dose level with correspondingly more quantifiable samples at higher doses. At the highest dose concentration of 3×10^{11} vp/mL, quantifiable DNA in urine was noted up to Day 3 in 3 of 4 patients, with detectable levels of DNA in urine persisting up to Day 14. Detection of DNA by qPCR does not necessarily indicate the presence of intact GMO in urine. Infectivity assessment of qPCR-positive samples was not performed.

119. The Phase 1b trial assessed safety and tolerability of 2 intravesical administrations of the GMO (dose of 3×10^{11} vp/mL) in patients with BCG-refractory NMIBC. It showed that treatment was generally well tolerated and a second instillation on Day 4 did not have any notable benefits for sustained IFN-α2b protein synthesis.

120. The Phase 2 trial evaluated safety and efficacy in patients with high-grade BCG-refractory or relapsed NMIBC at two dose levels (1×10^{11} vp/mL and 3×10^{11} vp/mL). The 3×10^{11} vp/mL dose, administered every 3 months, showed numerically higher efficacy and was well tolerated. None of the 40 patients that received their initial dose had measurable GMO DNA in their blood samples collected 2, 4 and 12 days post dose. Of the 23 patients receiving a second dose at month 4 day 1, one patient had a positive test result for the GMO DNA in blood at day 2 following the second dose. All 40 patients had measurable amounts of the GMO DNA in urine after their initial dose. The number of patients with GMO DNA in urine slightly declined to 33 patients (84.6%) at month 1 day 12. Of 23 patients receiving dose 2, pre-dose levels of 20 patients (87.0%) were negative for the GMO DNA and 3 patients (13.0%) had measurable GMO DNA in urine resulting from the first dose. At month 4 day 4, 19 patients (90.5%) receiving dose 2 had GMO DNA in urine but this dropped to 6 patients (28.6%) by month 4 day 12.

121. The Phase 3 trial focused on confirming the safety and efficacy of the 3×10^{11} vp/mL dose of intravesical administered GMO in high-grade BCG-unresponsive NMIBC. It measured the complete response rate in patients with CIS and secondary outcomes such as duration of complete response and high-grade recurrence-free survival or patients with papillary disease.

122. The safety of the GMO was also evaluated in the Phase 2 and Phase 3 trials with AEs recorded as shown in Table 1. The most frequently reported AEs (occurring in ≥10% of patients overall) in these trials were micturition urgency, dysuria, fatigue, pollakiuria, haematuria, nocturia, urinary tract infection, pyrexia, chills, nausea, diarrhoea, and urinary incontinence. No GMO-related Grade 4 or 5 AEs were reported.

123. Immunogenicity was evaluated through the measurement of anti-AdV 5 antibody levels in serum following the intravesical administrations of the GMO in the clinical trials. Five patients (29.4%) in the Phase 1 trial, 22 patients (55.0%) in the Phase 2 trial and 97 patients (72.4%) in the Phase 3 trial revealed a significant anti-AdV antibody response.

Section 5 The receiving environment

124. The receiving environment forms part of the context for assessing risks associated with dealings with the GMO (OGTR, 2013). It informs the consideration of potential exposure pathways, including the likelihood of the GMO spreading or persisting outside the site of release.

5.1 Site of administration

125. The intended primary receiving environment will be the bladder of participants with NMIBC, administered via intravesical instillation by experienced clinicians in a hospital.

126. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and waste disposed of, however none of the procedures are expected to generate aerosols. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance with institutional policies based on Standard Precautions for handling potentially infectious substances and the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

127. The principal route by which the GMO may enter the wider environment following administration is via shedding. As discussed in Sections 4.3.3 and 4.3.4, the GMO may be shed in minimal quantities in urine after the administration of the GMO for several days. Further, GMO may also enter the environment via accidental spills of unused GMO. Another route by which the GMO may enter the wider environment is via accidental spills of the GMO during or after administration, or during transport or storage, or following disposal of the vials or syringes contaminated with the GMO.

5.2 Presence of related viral species in the receiving environment

128. The presence of related viruses may offer an opportunity for introduced genetic material to transfer between the GMO and other organisms in the receiving environment.

129. AdVs belong to five genera: *Aviadenoviruses* (infecting birds), *Mastadenovirus* (infecting mammals), *Atadenovirus* (infecting a broad range of hosts including reptiles, lizards and some mammals), *Siadenovirus* (infecting one species of frog and one species of tortoise and multiple species of domestic, wild and captive birds) and *Ichtadenovirus* (infecting fish) (Lange et al., 2019; Tong et al., 2010; Vaz et al., 2020). As such, they are a common cause of infection in humans and animals, and can be found in all environments where humans or animals congregate in groups (Usman and Suarez, 2020). A more detailed description of AdVs presence in the environment is in Section 3.5.4.

130. The prevalance of HAdVs in Australia based on the reported cases and seroprevalance is low, as mentioned in Section 3.5.3.

5.3 Presence of similar genetic material in the environment

131. The balance of a system could be perturbed by the introduction of new genetic material through horizontal gene transfer or through release of GMO into the environment. However, the effect of perturbation would be relatively small if the genetic material was already present in the system and did not confer any selective advantage to an organism that gained this genetic material.

132. All the viral genes in the GM therapeutic are the same or similar to those present in naturally occurring HAdVs. The *hIFN-α2b* gene introduced into the GM therapeutic was derived from humans, and so similar genetic material would already be present in the environment.

Section 6 Previous authorisations

6.1 Australian approvals

133. In October 2025, the Regulator issued a licence for the commercial supply of nadofaragene firadenovec for bladder cancer treatment (DIR 217). This licence covers dealings only related to the commercial supply of the GMO, being import, transport, disposal and possession, but not experimentation (i.e. clinical trials).

134. As nadofaragene firadenovec is manufactured overseas, a permit from DAFF will be required for its import into Australia.

6.2 International approvals

135. Nadofaragene firadenovec was approved by the Food and Drug Administration in the USA in December 2022 for the treatment of high-risk BCG-unresponsive NMIBC under the tradename ADSTILADRIN.

136. Clinical trials of nadofaragene firadenovec are being conducted in the USA and Japan.

Chapter 2 Risk assessment

Section 1 Introduction

137. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by or as the result of gene technology (Figure 7). Risks are identified within the established risk assessment context (Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

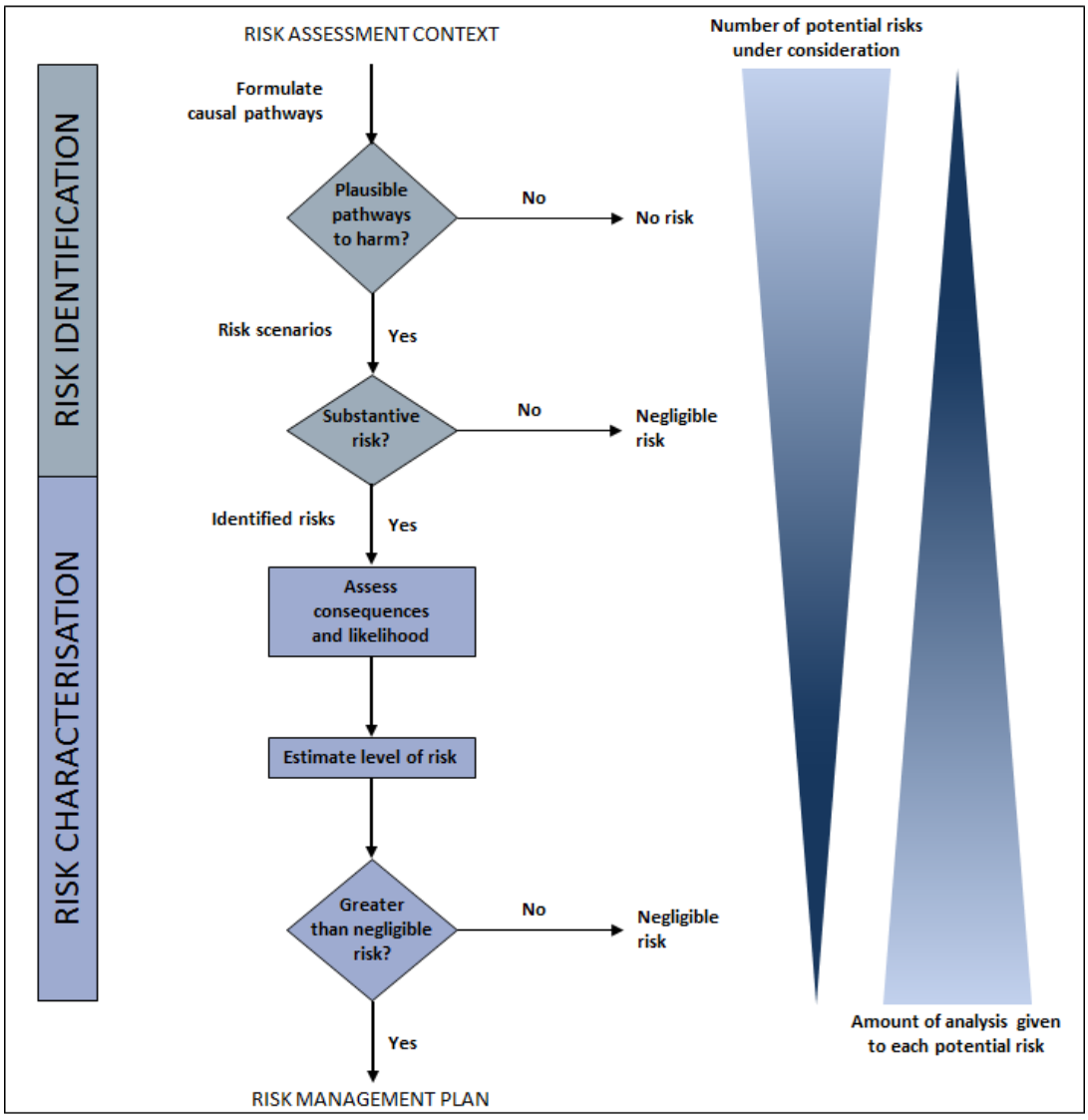

Figure 7: The risk assessment process

138. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013). Risk scenarios examined in RARMPs prepared for licence applications for the same or similar GMOs, are also considered.

139. Risk identification first considers a wide range of circumstances in which the GMO, or the introduced genetic material, could come into contact with people or the environment. This leads to postulating causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are called risk scenarios.

140. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the short and long term, do not advance in the risk assessment process (Figure 8), i.e. the risk is considered no greater than negligible.

141. Risk scenarios identified as substantive risks are further characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The consequence and likelihood assessments are combined to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk identification

142. Postulated risk scenarios are comprised of three components (Figure 8):

i. The source of potential harm (risk source)

ii. A plausible causal linkage to potential harm (causal pathway), and

iii. Potential harm to people or the environment.

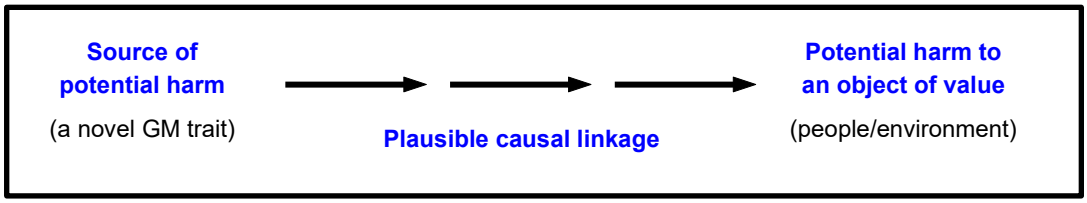

Figure 8: Components of a risk scenario

143. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Chapter 1:

- the proposed dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO and
- the characteristics of the parent organism(s).

2.1 Risk source

144. The parent organism is a HAdV-C5. Details of the pathogenicity and transmissibility of HAdV is discussed in Chapter 1. Infection is generally the result of inhalation of aerosolised droplets excreted from respiratory or ocular secretions containing the virus or mucosal exposure to the virus or via faecal-oral transmission. HAdV infects humans and causes common cold-like symptoms, eye infections or diarrhoea.

145. As discussed in Chapter 1, Section 4.1, the GMO has been modified by deleting specific gene sequences and replacing a deleted DNA sequence with the *hIFN-α2b* gene expression cassette. This introduced gene and its encoded protein are considered further as a potential source of risk.

2.2 Causal pathway

146. The following factors are taken into account when postulating plausible causal pathways to potential harm:

- the proposed dealings, which are conducting experiments with the GMO, and transport or disposal of the GMO and possession (including storage) in the course of any of these dealings (excluding any dealings already covered by licence DIR 217);

- restrictions placed on the import, transport or disposal of the GMO by other regulatory agencies, the States and Territories;
- characteristics of the parent organism;
- routes of exposure to the GMO, the introduced gene(s) and gene product(s);
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism;
- potential exposure of other organisms to the introduced gene(s) and gene product(s) from other sources in the environment;
- potential exposure of other organisms to the GMO in the environment;
- the release environment;
- spread and persistence of the GMO (e.g. dispersal pathways and establishment potential);
- environmental stability of the organism (tolerance to temperature, UV irradiation and humidity);
- gene transfer by horizontal gene transfer;
- unauthorised activities; and
- practices before and after administration of the GMO.

147. As discussed in Chapter 1 Section 1.1, the TGA, the trial sponsor, the Investigators and HREC all have roles in ensuring the safety of trial participants under the *Therapeutic Goods Act 1989*, and human clinical trials must be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council et al., 2018). Therefore, risk scenarios in the current assessment focus primarily on risks posed to people other than the intended GMO recipient, and to the environment, including long term persistence of the GMO, which may arise from the import, transport, storage or disposal of the GMO.

148. The Act provides for substantial penalties for unauthorised dealings with GMOs or non-compliance with licence conditions, and also requires the Regulator to have regard to the suitability of an applicant to hold a licence prior to the issuing of the licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities. Therefore, unauthorised activities will not be considered further.

149. As mentioned in Chapter 1, Section 3.4, adenoviruses remain episomal throughout the infection and do not integrate into the host DNA. Similarly, the vectors derived from these adenoviruses are considered as non-integrating vectors which do not have a propensity to integrate or reactivate following latency in a host (EMEA, 2007; FDA, 2020). Further, adenoviral vectors (such as HAdV-C5) have been used extensively in clinical studies as a vaccine and as a gene therapy for almost 30 years (Crystal, 2014) and there is no evidence of integration of viral DNA into the host genome. Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

150. Recombination between different GMOs using adenovirus platforms is highly unlikely because it is improbable that two or more adenovirus-based therapies are administered at the same time with the same route (intravesical) and the lack of homology between adenoviral vectors further reduces the possibility of recombination. Thus, the potential of recombination between adenoviral therapies will not be further discussed.

151. Potential sources of harm can be due to the intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology. Unintended effects can arise through horizontal gene transfer (HGT) which is the stable transfer of genetic material from one organism to another without sexual reproduction. All genes within an organism, including those introduced by gene technology, can be transferred to another organism by HGT. A gene transferred through HGT could confer a novel trait to the recipient

organism. The novel trait may result in negative, neutral or positive effects on the fitness of the recipient organism. HGT commonly occurs from cells to viruses but rarely occurs from viruses to their host cells, with the exception of retroviruses and some DNA viruses. This pathway is further considered as a potential source of risk.

2.3 Potential harms

152. The following factors are taken into account when postulating relevant risk scenarios for this licence application:

- harm to the health of people or desirable organisms, including disease in humans or animals or adverse immune response to the GMO
- the potential for establishment of a novel virus that could cause harm to people or the environment

153. Toxicity and allergenicity of the introduced genes and their protein products have not been directly considered, but are taken into account in the context of their contribution to ill health.

2.4 Postulated risk scenarios

154. Three risk scenarios were postulated and screened to identify substantive risks. These hypothetical scenarios are summarised in Table 2 and discussed in depth in Sections 2.4.1-2.4.3 (this chapter).

155. In the context of the activities proposed by the applicant and considering both the short and long term, none of the 3 risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 2. Summary of hypothetical risk scenarios from dealings with the GMO

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of people to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events: (a) Preparation and administration of the GMO (b) During import, transport or storage of the GMO (c) Handling of samples containing the GMO (d) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇	Adverse immune reactions; illness, local inflammation, flu-like symptoms	No	• Import and transport of the GMO would be in accordance with IATA 3373 and/or the Regulator's *Guidelines for Transport, Storage and Disposal of GMOs*. • Only trained and experienced personnel would conduct dealings with the GMO, using personal protective equipment to minimise potential exposure. • GMO and contaminated waste disposed of as infectious clinical waste. • The dose received through accidental exposure during preparation or administration would be substantially less than that administered to trial participants and would not

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		Post infection immune response due to the presence of the virus and/or Expression of the IFN-α2b protein			be sufficient to result in a serious adverse reaction in exposed persons. • At risk people (e.g. immunosuppressed) would be excluded from handling the GMO. • The GMO is replication incompetent and will not produce further viral particles to sustain an infection. • The GMO has a good safety profile at doses higher than would be expected through accidental exposure. • IFN-α2b protein has been extensively used in clinical applications for treatment of some viral infection and various cancers with manageable adverse reactions. • People are regularly exposed to HAdVs and the genetic modifications do not confer any pathogenic advantage over the wild type. • Most of the population has pre-existing immunity to HAdVs. • The immune system is expected to clear the GMO quickly.
2	GMO	GMO release into the environment (e.g. sewerage, spills, shedding of the GMO from participants) ⬇ Exposure to people or animals ⬇ As per Risk scenario 1	Adverse immune reactions; disease in people or animals	No	As discussed in Risk Scenario 1 and: • GMO not known to naturally infect non-human hosts and does not infect aquatic species. • The trial participants are required to disinfect voided urine in the toilet for 2 days following treatment, minimising the amount of the GMO entering the sewerage. • There are a large number of HAdVs in the sewage or water systems.

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
					• GMO cannot replicate inside or outside the host, hence GMO is only available for one infection cycle.
3	GMO	Exposure of other people and animals to the GMO as mentioned in Risk Scenarios 1 and 2 Or Exposure of trial participants during treatment ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ⬇ (a) Complementation of genes responsible for viral replication and immune-evasion properties by AdV (b) Homologous recombination with AdV ⬇ Production of other recombinant GMOs including with increased virulence and/or host range	Adverse immune reactions; disease in people or animals	No	As for risk scenario 1 and 2 and: • Co-infection of the same cell with both GMO and HAdV at the same time is a rare event. • A large proportion of the population have a pre-existing immunity to HAdV-C5 reducing the likelihood of HAdV infection. • There is a low probability of continuous complementation of GMO by HAdV because HAdV infection is self-limiting. • Recombination among AdVs is usually restricted to the same species. • Homologous recombination in HAdV-C is more likely to occur in E1 and E4 regions, which are not involved in virus tropism. • Multiple recombination events would be required to produce a replication competent HAdV with altered tropism and immune evasion properties.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of people to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events: (a) Preparation and administration of the GMO (b) During import, transport or storage of the GMO (c) Handling of samples containing the GMO (d) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Post infection immune response due to the presence of the virus and/or Expression of the IFN-α2b protein
Potential harm	Adverse immune reactions; illness, local inflammation, flu-like symptoms

Risk source

156. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

157. People (other than the intended recipient) could be directly or indirectly exposed to the GMO in a number of ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO or during preparation of the GMO. It could also be transmitted during administration by needlestick injury. There is likely to be transient and low-level shedding of the GMO in urine due to the method of administration. The collection of samples from trial participants could pose another route of exposure. These exposures could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

158. As discussed in Chapter 1, Section 2.1, preparation and administration of the GMO will be carried out in clinical trial sites. The GMO is intended to be administered through intravesical installation performed by trained healthcare professionals. The risk of needle stick injuries is eliminated as the applicant stated that vented vial adapters will be used to transfer the GMO from the vial to the syringe (Chapter 1 Section 2.3.6). There is potential for exposure of people involved in the preparation or administration of the GM therapeutic through aerosol formation during preparation and/or due to breakage/spillage of the GM therapeutic or urine from patients onto surfaces.

159. The GMO will be prepared and administered by authorised, experienced and trained health professionals. All personnel working in settings where healthcare is provided, including clinical trial services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and the *Australian Immunisation Handbook.*

160. Caregivers and healthcare personnel who are in close contact with people treated with the GMO may be inadvertently exposed to the GMO during administration via spillage or after patient use of bathrooms. Caregivers and others exposed to the GMO in this way will only be expected to be exposed to low levels of the GMO.

161. The compliance with the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and the *Australian Immunisation Handbook* and existing work practices will minimise the potential exposure of people to the GMO during preparation and administration of the GMO.

Exposure during import, transport and storage of the GMO

162. Import, transport and storage of the GMO have been considered under licence application DIR 217 for the commercial supply of the GMO in Australia. To avoid duplication, for this licence only dealings with the GMO occurring at the clinical trial site or downstream dealings such as collection and handling of samples from participants, and transport and disposal of clinical waste containing the GMO will be assessed, while import of the GMO and any transport or storage of the GMO before reaching the clinical trial site is not included.

Exposure through the collection of samples

163. Clinical trial staff collecting samples from trial participants could also be exposed to the GMO in the samples. However, as via the shedding route, the exposure via clinical sample collection is expected to be very low. Furthermore, only trained staff will collect the samples and any samples that may contain the GMO will be handled according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs) (Chapter 1, Section 2.2).

Exposure during disposal of waste containing the GMO

164. Individuals may be inadvertently exposed to GMOs while disposing of used or unused vials of the GMO. The two locations where this is most likely to occur are at:

- locations where stocks of the GMO are stored;
- locations where the GMO is administered.

165. As discussed above, any transport, storage or disposal of the GMO before reaching the clinical trial site is covered by licence DIR 217.

166. If waste containing the GMO was spilled during transport or storage, this could result in exposure to people in the area via aerosol or liquid contact with eyes, mucous membranes or skin. Further, people could be inadvertently exposed to the GMO via contact with materials contaminated with the GMO and subsequent hand to mouth transmission.

167. As discussed in Chapter 1, Section 2.3, unused vials of the GMO, as well as the vials with residual GMO, syringes and waste contaminated with the GMO would be treated as clinical/medical waste and disposed of in accordance with the waste disposal methods approved by the Environmental Protection Agency or Health Department in the relevant State or Territory (ACT, 2017; NSW, 2018; NT, 2014; QLD, 2019; SA, 2020; TAS, 2007; VIC, 2020; WA, 2016). Waste containing the GMO will also be handled according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs) (Chapter 1, Section 2.2). Adherence to these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

168. Antiviral disinfectants would be used for decontamination and disinfection in the case of accidental spills of waste containing the GMO.

169. Taken together, the disposal and decontamination procedures discussed above would minimise likelihood of exposure that could be associated with conducting these dealings with the GMO.

170. For a productive infection to occur, individuals must be exposed to an infectious dose. Residual liquid in used vials and used syringes would not contain a sufficient titre to cause a productive infection. The same would apply to secondary waste such as gloves that may be contaminated with the GMO. Thus, the dose received through accidental exposure would be far smaller than that

administered during the clinical trial and lower than that required for productive infection. Therefore, even if an individual is inadvertently exposed to the GMO, they are unlikely to develop an adverse immune reaction.

Potential harm

171. If people are exposed to the GMO, they could develop flu-like symptoms, eye infections or local inflammation for a short period of time before the virus is cleared by the immune system. It is plausible that exposed people could experience an adverse immune response or disease.

172. As the GMO is replication incompetent, it is unable to produce further viral particles which are required to sustain an infection. This would also mean that the IFN-α2b expression would be limited to cells transduced by initial exposure to the GMO and the protein expressed would be unable to accumulate other than the cells originally transduced, and any reactions to the protein would be transient and only persist until the point of clearance of the GMO, limiting the magnitude of toxic effect and any immune response.

173. As discussed in Chapter 1, Section 4.2.3, the purified IFN-α2b protein has been extensively used in clinical applications for treatment of hepatitis B and C infection and various virus induced cancers. Most of the adverse reactions related to the IFN-α2b therapy were mild to moderate and were manageable, and most diminished with continued therapy. As discussed in Chapter 1, Section 4.3.4, in the Phases 2 and 3 clinical trials of the GMO, no Grade 4 or 5 adverse events related to the GMO treatment were reported.

174. As discussed in Chapter 1, Section 3.1, immunocompromised individuals and children are high-risk groups for development of severe disease following HAdV infection. In the event of accidental exposure via mucosa/broken skin, the amount of GMO transferred would be far smaller than that administered during treatment. As the GMO cannot replicate, the minimal exposure and transient nature of infection would be expected to result in very mild or negligible symptoms and would also minimise the potential for an adverse immune response to the GMO. Therefore, the accidental exposure to the GMO is not expected to result in an infection and would not result in an increased disease burden.

175. As discussed in Chapter 1, Section 4.3.1, a very low level of RCA may also be present in the GM therapeutic product. This RCA differs from the wild-type RCA as it is a recombinant virus that is unable to evade the host immune system. Therefore, it is unlikely to infect immune-competent people but could potentially infect immunosuppressed individuals. Clinical data regarding the effect of the GM therapeutic on immunosuppressed individuals are lacking as this group has been excluded from the clinical trials. If an immunosuppressed individual was to be accidentally exposed to the RCA in the therapeutic product, the number of RCA particles would be extremely low and it is unlikely that they would develop severe symptoms or the risk for disseminated HAdV infection would be significantly increased, although this is an area of some uncertainty as adults who lack antibody could be infected by as few as 5 AdV particles (see Chapter 1, Section 3.5.1). The RCA is attenuated compared to the wild type organisms and would be able to be cleared faster than the wild type HAdv5. Even if an immunosuppressed person is exposed to the RCA, a productive infection would be likely to be transient and mild in nature as a result of the attenuation.

176. As per the US Package Insert for ADSTILADRIN, individuals who are immunosuppressed or immune-deficient, should not prepare, administer, or come into contact with ADSTILADRIN. The applicant has also proposed that a similar precaution be implemented for the clinical trials in this application. This would reduce the chance of immunosuppressed persons coming into contact with the GMO, becoming infected and potentially developing severe disease.

Conclusion

177. The potential for an unintentional exposure of people and animals to the GMO to cause harm via a serious adverse immune reaction in humans is not identified as a risk that could be greater than

negligible. The main reasons are that the GMO is not expected to infect or replicate in healthy people and any infection resulting from potential exposure is expected to be rapidly cleared and unlikely to cause disease. Therefore, this risk scenario does not warrant further detailed assessment.

2.4.2 Risk Scenario 2

Risk source	GMO
Causal pathway	Release of GMO into the environment via accidental spill/unused residues (e.g. sewerage, spills, shedding of the GMO from participants) ⬇ Exposure of people or animals ⬇ As per Risk scenario 1
Potential harm	Adverse immune reactions; disease in people or animals

Risk source

178. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

179. The GMO could be released in the environment through a spill during transport, storage or disposal where people or animals, including marine or aquatic animals could be exposed to the GMO. It is also possible that the GMO will be shed from participants post administration, potentially contaminating toilets, shared household items and exposing non-participants. The GMO could also be released to the environment through sewerage from a toilet bowl used by a treated patient but not appropriately decontaminated. It could also be released to the environment, such as the hospital or patient home, via patient incontinence/urine. This could result in exposure of people and animals to the GMO and could potentially result in adverse immune reactions and/or disease in people and animals.

180. As discussed in Risk Scenario 1, accidental spills associated with import, transport, storage and disposal have been considered, including the range of measures that are in place that would reduce the chances of GMO being released into the environment.

181. Although shedding of live viral particles was not tested, based on the preclinical studies of shedding of the GMO following intravesical administration in cynomolgus monkeys (Chapter 1, Section 4.3.3) and the clinical trials (Chapter 1, Section 4.3.4), the trial participants are expected to shed the GMO in the urine for a few days post instillation, as quantifiable GMO-specific DNA was noted for up to 3 days, while GMO-specific DNA could be detected for about 15 day. As per the Package Insert for ADSTILADRIN, patients in the US receiving the treatment and their carers are informed that transient and low-level shedding of the GMO may occur in urine and that they must add half cup of bleach to the toilet bowl before urinating and disinfect voided urine for 15 min before flushing the toilet for 2 days following treatment. Such urine treatment was also included as a condition in licence DIR 217 for commercial supply of the GMO in Australia and would be relevant for clinical trials of the GMO. This would reduce the chance of the GMO being released into sewerage. The TGA is responsible for reviewing any instructions for use of the GMO by the patient, including what information is included in the Product Information regarding precautions to take after GMO administration.

182. In the event of a spill or unused vials or urine without correct decontamination with suitable disinfectants, the GMO could potentially survive on surfaces for up to 8 weeks at low humidity (see Chapter 1, Section 3.5.4). In cold water or dark sediments, survival could be up to a few months (see Chapter 1, Section 3.5.4). As AdVs are resistant to UV treatment in wastewater and can survive for a

long time, this could lead to the persistence of the GMO and/or recombinant adenoviruses in the environment. However, due to its non-replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods and is unlikely to spread and would eventually degrade.

183. In the event that the GMO is released into sewage water, it would be markedly diluted due to the small quantity of GMO present in a large volume of liquid waste or water. Water quality studies have shown that sewerage treatment does not kill adenovirus (Fong et al., 2010), however the GMO is not able to replicate and would be unlikely to be present in high enough amounts for an infectious dose. Therefore, it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source.

184. There are no data on transmission of the GMO to babies via breastfeeding or to foetuses if a woman is pregnant and to non-participants through sexual activities. However, transmission of the GMO to babies via breastfeeding or to foetuses can be prevented as pregnant and breastfeeding women will be excluded from the clinical trials. The transmission of the GMO to non-participants through sexual activities can be minimised by the use of effective barrier methods. One of the inclusion criteria is for participants to agree to use a barrier method for the duration of the trial.

185. As mentioned in Chapter 1, Section 3.5.1, HAdVs, including HAdV-C serotypes, are adapted to infect humans and their ability to infect and replicate in certain mammals were only demonstrated under experimental conditions. Infections in other mammals are considered less likely under natural conditions. Given that the GMO is replication incompetent, exposure to the GMO to other mammals could only result in infection but not the replication and multiplication of the GMO.

186. HAdV infection is not known to infect insects, birds and other non-mammalian aquatic organisms. Therefore, the likelihood of HAdVs infecting other species in the Australian environment in highly unlikely.

Potential harm

187. Potential harms to people in this risk scenario would be the same as considered in Risk Scenario 1. As it is highly unlikely to infect or replicate in animals, animals are not expected to be harmed.

Conclusion

188. The potential for the GMO to be released into the environment and result in adverse immune reactions or disease in people or other animals is not identified as a risk that could be greater than negligible. This is for the reasons described in Risk Scenario 1. The main reasons are that the GMO is not expected to infect or replicate in healthy people or in animals, and any infection resulting from potential exposure is expected to be rapidly cleared and unlikely to cause disease. Therefore, this risk scenario does not warrant further assessment.

2.4.3 Risk scenario 3

<table>
<tr><td>Risk source</td><td>GMO</td></tr>
<tr><td>Causal pathway</td><td>Exposure of people and animals to the GMO as mentioned in Risk Scenarios 1 and 2
Or
Exposure of trial participants during treatment
⬇
Transduction of cells by GMO
⬇
Transduced cells co-infected with AdV
↙ ↘
Complementation of gene sequences responsible for viral replication and immune-evasion properties by AdV
⬇
Production of more replication incompetent GMOs with immune-evasion properties

Homologous recombination with AdV in gene sequences responsible for viral replication and immune-evasion properties or other regions of high homology
⬇
(i) Formation of more replication incompetent AdV expressing IFN-α2b protein with immune evasion properties
AND
Replication competent GMO without IFN-α2b expression cassette
OR
(ii) Replication competent AdV with defective immune evasion properties
AND
Replication incompetent GMO with immune evasion properties
OR
(iii) Replication competent AdV or replication incompetent GMO with altered tropism</td></tr>
<tr><td>Potential harm</td><td>Adverse immune reactions; disease in people or animals</td></tr>
</table>

Risk Source

189. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

190. Transmission of GMO can occur by the pathways mentioned in Risk Scenarios 1 and 2 which could potentially result in transduction of host cells. If the person or animal exposed to the GMO has an existing infection of AdVs at the time or acquired an AdV infection while the GMO is present, this co-infection could potentially result in complementation or recombination of the GMO with wild-type AdVs and cause adverse immune reactions and/or disease in people or animals

Complementation of gene sequences responsible for viral replication and immune-evasion properties by AdV

191. HAdV infects a very large portion of the human population, and HAdV-C is the most widely reported serotype and has the highest seroprevalence globally (Chapter 1, Section 3.5.3). The HAdV genome sequences are largely conserved from isolate to isolate of the same type, and the genome of HAdV-C is highly conserved with over 95% nucleotide identity among the serotype (Ismail et al., 2018a). Therefore, it is plausible that the gene sequences for viral replication and immune-evasion properties could be provided *in trans* from a pre-existing or acquired HAdV infection in persons accidentally exposed to the GMO if a co-infection in the same cell occurs. This could result in complementation by the HAdV leading to replication of the GMOs with immune evasion properties in the host. As discussed in Chapter 1, Section 3.5.3, the reported prevalence of HAdV infection in Australia is very low, although this may be an underestimation of actual prevalence, as HAdV infection is not a reportable illness. However, HAdV infections are also self-limiting, decreasing the probability of continuous complementation of GMO by HAdV (Leikas et al., 2023b; Lichtenstein and Wold, 2004). Thus, the likelihood that a person has a HAdV-C infection that could continuously complement the missing gene sequences for viral replication and defective gene sequences for immune-evasion properties in the GMO is very low.

192. As mentioned in Chapter 1, Section 3.5.1, spontaneous infection of animals with HAdV-C in the wild is considered unlikely and no natural infections of non-human hosts have been reported so far. Therefore, it is considered highly unlikely that the GMO could replicate in animals as a result of complementation.

Homologous recombination with AdV

193. Recombination is common among circulating wild-type adenoviruses in nature. It is seen as a key driver for adenoviral evolution. Similar to complementation, homologous recombination requires the person or animals exposed to the GMO to be infected with a wild-type AdV at the same time. Adenoviruses are prevalent in respiratory, gastrointestinal or ocular tissue. Co-infection could also occur from contact with GMO contaminated surfaces or spills. Licence conditions will be in place to limit and control the exposure of the GMO to people or animals via inhalation or contact with mucus tissue via requirements to use PPE and through transport and disposal procedures, and for the participants to decontaminate their urine for 2 days after administration of the GMO.

194. As mentioned in Chapter 1, Section 3.4, homologous recombination is restricted to members of the same species. However, homologous recombination with closely related adenoviruses species has been observed where high sequence homology occurs (Hoppe et al., 2015; Dehghan et al., 2019). The DNA homology between HAdV species is less than 20% (Ghebremedhin, 2014) and is more than 95% in HAdV-C species (Ismail et al., 2018a). Therefore, there is a potential for homologous recombination between the GMO and HAdV-C as they belong to the same species. If it was to occur, co-infection and recombination processes could potentially result in the generation of different GM recombinants, as described in Table 3.

Table 3. Theoretical recombinants of GMO and wild-type (WT) adenoviruses

Recombinant region	Resultant recombinant	Outcome	Likelihood
Gene sequences for viral replication between • GMO • WT AdV	• Replication competent GMO without functional gene sequences for immune-evasion properties • Replication incompetent AdV	• Replication competent GMO that is still less immune evasive than WT • Replication incompetent AdV expressing hIFN-α2b protein	Unlikely

Recombinant region	Resultant recombinant	Outcome	Likelihood
	with *hIFN-α2b* gene cassette		
Gene sequences for immune-evasion properties between • GMO • WT AdV	• Replication incompetent GMO with functional gene sequences for immune-evasion properties • Replication competent AdV without functional gene sequences for immune-evasion properties	• Replication incompetent GMO with modified immune-evasive properties • Replication competent AdV without immune-evasive properties (a wild type adenovirus unable to evade the host immune system)	Unlikely
Capsid genes (hexon, penton and fibre) between • GMO • WT AdV	• Replication incompetent GMO with different hexon, penton or fibre • Replication competent AdV without the *hIFN-α2b* gene cassette but with different hexon, penton or fibre	• Altered tropism and host range of GMO • Altered tropism and host range of AdV	Highly unlikely

195. In the event of homologous recombination in the gene sequences responsible for viral replication, the GMO could regain its gene sequences for viral replication, or the corresponding region of the WT-AdV, and become replication competent, but lose the expression cassette encoding the hIFN-α2b protein. The WT-AdV could receive the hIFN-α2b expression cassette but lose the gene sequences for viral replication, making it replication-incompetent. This would result in a replication competent GMO without the hIFN-α2b expression cassette and functional gene sequences for immune-evasion properties; and a replication incompetent AdV expressing the hIFN-α2b protein. The resulting viruses are unlikely to be more pathogenic than a WT-AdV strain.

196. Alternatively, in the event of homologous recombination in the gene sequences responsible for immune-evasion properties, the GMO could regain its gene sequences for immune-evasion properties but remain replication incompetent due to still lacking the genes for viral replication. The recombinant virus would not be able to replicate and would eventually be cleared by the immune system of the host. As an HAdV, the recombinant virus is not expected to cause disease in animals.

197. As discussed in Chapter 1, Section 3.4, recombination is an important source of genetic variation in viruses. Recombination of genes encoding structural proteins, such as hexon, penton and

fibre regions of AdV can result in altered cell tropism. Recombination in HAdV-C occurs most frequently in the E1 and E4 regions. The likelihood of homologous recombination at the hexon, penton and fibre regions of AdV, resulting in the GMO with an altered cell tropism is very low. In the event of recombination, the resulting AdV would remain replication incompetent.

198. If a recombinant replication competent HAdV is produced, it could be shed from the original host and transmitted to other hosts (human or animals) in the environment. These replication competent viruses would not contain the hIFN-α2b expression cassette and would be similar to a WT-AdV. In addition, for a full reversion into a WT virus, multiple recombination events would need to occur, and this is highly unlikely.

Potential harm

199. If complementation were to occur, the number of replication incompetent GMO produced in the host cells would increase, resulting in increased expression of the IFN-α2b protein in the host. This is not expected to cause harm to affected individuals for reasons as discussed in Risk Scenario 1. Also, if the person exhibits any symptoms of AdV infection, effective antiviral treatments can be used to treat the infection.

200. If homologous recombination were to occur it could result in the formation of replication competent HAdV-C5. The person exposed could potentially experience mild respiratory or eye infections depending on the route of exposure as described in Chapter 1, Section 3.1. These infections are self-limiting and rarely need medical intervention. If needed, first line adenoviral antiviral therapies could be used (Chapter 1, Section 3.5.4). Theoretically, if homologous recombination in the major capsid proteins (HAdV-C) or other AdV regions with high homology occurs, it could alter the tropism and host range of the virus. However, occurrence of increased harm is unlikely as AdV do not usually cause severe disease and the resultant recombinants are unlikely to be more pathogenic than a WT-AdV strain.

Conclusion

201. The exposure of people or animals to a GMO which has acquired the gene sequences responsible for viral replication, transferred the hIFN-α2b protein to other AdVs or other recombinant viruses resulting in adverse immune response or disease in people or animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

Section 3 Uncertainty

202. Uncertainty is an intrinsic property of risk analysis and is present in all aspects of risk analysis. This is discussed in detail in the Regulator's Risk Analysis Framework document.

203. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk, the Regulator will take this uncertainty into account in making decisions.

204. Uncertainty can also arise from a lack of experience with the GM therapeutic itself. For DIR-223, while the potential for harm due to the RCA contamination following accidental exposure has been noted as an area of uncertainty (Risk Scenario 1), the GM therapeutic has been approved for commercial supply in Australia by the Regulator and commercial clinical use in the USA by the FDA (Chapter 1, Sections 6.1 and 6.2) and overall, treatment with the GM therapeutic was considered to be safe (Steinmetz et al., 2024).

205. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

Section 4 Risk evaluation

206. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

207. Factors used to determine which risks need treatment may include:

- risk criteria,
- level of risk,
- uncertainty associated with risk characterisation, and
- interactions between substantive risks.

208. Three risk scenarios were identified whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people can be exposed to the GMO while conducting the dealings and whether there is a potential for complementation and recombination of the GMO with other adenoviruses. The potential for GMO to be released into the environment and its effects was also considered.

209. A risk is substantive only when the risk scenario may, because of gene technology, have some chance of causing harm. Risk scenarios that do not lead to harm, or could not reasonably occur, do not represent an identified risk and do not advance in the risk assessment process.

210. In the context of the range of measures already in place, including the operating guidelines and requirements of the other regulatory agencies, and considering both the short and long term, none of these scenarios was identified as representing a substantive risk requiring further assessment. The principal reasons for this include:

- the GMO is replication incompetent which will prevent it from multiplying in other cells; and
- the likelihood of accidental exposure to the GMO in people not being treated or animals would be minimised due to well-established clinical, import, transport, storage and disposal procedures; and
- the dose received through accidental exposure would be far smaller than that administered; and
- complementation and recombination of GMO with other adenoviruses is highly unlikely to lead to adverse effects; and
- survival and persistence of the small amount of GMO in the Australian aquatic and terrestrial environment is highly unlikely.

211. Therefore, any risks to the health and safety of people, or the environment, from the proposed clinical trial using the GMO are considered to be negligible. The *Risk Analysis Framework* (OGTR 2013), which guides the risk assessment and risk management process, defines negligible risks as insubstantial with no present need to invoke actions for their mitigation. No controls are required to treat these negligible risks. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment.[4]

[4] As none of the proposed dealings are considered to pose a significant risk to people or the environment, Section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP.

Chapter 3 Risk management plan

Section 1 Background

212. 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 addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through proposed licence conditions.

213. Under section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

214. All licences are subject to 3 conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings: Section 64 requires the licence holder to provide access to premises to OGTR inspectors and Section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder are also required to be reported to the Regulator.

215. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in Section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under Section 152 of the Act.

Section 2 Risk treatment measures for substantive risks

216. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed clinical trial with the GMO. These risk scenarios were considered in the context of the scale of the proposed clinical trial (Chapter 1, Section 2.1), the proposed controls (Chapter 1, Section 2.2), the proposed receiving environment (Chapter 1, Section 5), and considering both the short and long term effects of the GMO. Limits and controls proposed by the applicant and other general risk management measures are discussed below.

Section 3 General risk management

217. The limits and controls proposed in the application were important in establishing the context for the risk assessment and in reaching the conclusion that the risks posed to people and the environment are negligible. Therefore, to maintain the risk context, draft licence conditions have been imposed to limit the number of trial participants, location limited to hospitals and clinical trial sites, limits on the duration of the trial, as well as a range of controls to restrict the spread and persistence of the GMOs and their genetic material in the environment. The conditions are discussed and summarised in this Chapter and listed in detail in the draft licence.

3.1 Limits and controls on the clinical trial

218. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Ferring. Many of these are discussed in the 3 risk scenarios considered in Chapter 2. The appropriateness of the limits and controls is considered further in the following sections.

3.1.1 Consideration of limits and controls proposed by Ferring

219. The proposed clinical trial would involve a maximum of 13 participants within Australia, and dealings with the GMO would take place in medical facilities such as clinical trial facilities or hospitals. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMO. The applicant has proposed to complete dealings with the GMO within 5 years of commencement. A proposed licence condition limits the period when the GMO may be administered under the licence to 5 years from the date of issue of the licence. Other conditions maintaining the risk context and proposed limits of the trial such as a maximum of 13 trial participants and requirements for dealings related to preparation and administration of the GMO to be conducted at a clinical trial site have been included in the draft licence.

220. Import and transport of the GMO is covered under licence DIR 217. The applicant advised that transport and disposal of the waste containing the GMO would be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. These are standard protocols for the handling and minimising exposure to the GMO. These proposed transport conditions are suitable for the GMO. Therefore, the draft licence details the minimum requirements for packaging and labelling waste contaminated with the GMO for transport and storage within a clinical trial site, as well as transport of the samples that may contain GMO for analysis. These measures would limit the exposure of people and the environment to the GMO.

221. There are proposed inclusion and exclusion criteria for both trial participants and staff as listed in Chapter 1, Section 2.3.5. The inclusion and exclusion criteria for trial participants would be subject to approval by a HREC, who would consider the safety of the individuals involved in the trial.

222. The relevant inclusion criteria proposed by the applicant include that the trial participants must agree to use effective forms of contraception during treatment and for 6 months (female) or 3 months (male) after the last dose.

223. Shedding in semen has not been assessed for this GMO. Due to the non-replicating nature of the GMO, sexual transmission of the GMO from the trial participants is unlikely, however the preclinical studies with the GMO show the presence of GMO-specific DNA in the gonads of monkeys 8 days after intravesical administration of the GMO (Chapter 1 Section 4.3.3). Therefore, as a precaution, the participants should use effective barrier methods to prevent pregnancy and potential exposure to the GMO during sexual activities, and not donate gametes for a period after GMO administration. Regarding donation of blood and other tissues, the Phase 2 clinical trial of the GMO showed GMO-specific DNA in the blood of 1/23 participants 2 days after the second intravesical administration of the GMO (Chapter 1 Section 4.4.4), therefore blood and organ donation after GMO administration should also be avoided as a precaution. Using the conservative timeframe of 60 days after GMO administration, as is standard in similar clinical trial licences, this use of effective barrier method as well as abstaining from blood, gamete or organ donation would further minimise the potential for transmission of infectious viral particles. Therefore, the criteria included in the draft licence are that the licence holder must obtain written agreement from the trial participant that they will use an effective barrier method for 60 days after each administration of the GMO and will not donate blood, gametes or organs for the duration of the trial and 60 days after the last dose of the GMO.

224. The relevant exclusion criteria proposed by the applicant include pregnant or breastfeeding women, and immunocompromised or immunodeficient people.

225. The risk context is maintained provided the GMO can be cleared by the immune system, therefore a precautionary condition is included in the licence to exclude participants with an immunosuppressive disorder or an illness that impairs immune function.

226. The potential transmission to babies via breastfeeding and to foetuses if pregnant women are included in the trial is minimal. However, this risk would be minimised further by excluding

breastfeeding and pregnant women and a condition to exclude pregnant and breastfeeding women from participating in the clinical trial has been included in the draft licence.

227. For the context of this RARMP, persons who have immunosuppressive disorders or who are pregnant are considered persons at higher risk of a serious adverse event when exposed to the GMO. To manage risk and to maintain the context of the risk assessment, a condition in the draft licence requires persons preparing or administering the GMO must be informed of the risks associated with the GMO (including risks in people suffering from immunosuppressive disorder or pregnant individuals).

228. In addition, the clinical staff handling the GMO would wear PPE including gown, gloves, mask and eye protection/face shield. These practices would minimise exposure of people handling and administering the GMO (Risk scenario 1) and have been included in the draft licence conditions.

229. While recombination with other adenoviruses is considered unlikely to occur, a precautionary condition is included in the licence to exclude participants who have recently received a different adenovirus-based therapy.

230. Due to the intravesical mode of administration, shedding of infectious viral particles from urine of the trial participants following the bladder installation is expected to last for a few days. To maintain the risk context of minimising the amount of the GMO entering the sewerage, a requirement has been included in the draft licence for the licence holder to instruct the patients to add bleach to the toilet bowl before urinating and disinfect voided urine for 15 min before flushing the toilet for 2 days following treatment, consistent with the requirements as per the Package Insert for ADSTILADRIN.

231. Conditions are included in the draft licence requiring the licence holder to ensure that all GMOs, including material or waste that has been in contact with the GMO, within the clinical trial site, are decontaminated by autoclaving, chemical treatment or by high-temperature incineration. Draft licence conditions require that the licence holder must ensure that the GMO, or material or waste that has been in contact with the GMO, that is to be destroyed by external service providers, is through a clinical waste stream. This is considered satisfactory, provided that the licence holder is only permitted to engage persons who can adhere to appropriate standards to conduct the dealings.

232. The Industry Code of Practice for the Management of Clinical and Related Wastes details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability (Biohazard Waste Industry, 2010). The clinical waste stream typically involves destruction of infectious waste by incineration or autoclaving, which are considered appropriate for disposal of the GMO. Given that AdV can persist in the environment, disposal measures such as burial or maceration would not ensure containment. Therefore, the draft licence requires waste disposal by external service providers to be by autoclaving or high-temperature incineration. These measures would limit the exposure of people or other animals to the GMO.

233. A standard condition is included in the draft licence requiring the licence holder to ensure that dealings are conducted so as to ensure containment of the GMO, not compromise the health and safety of people and minimise unintentional exposure to the GMO. A note to the condition explains that compliance may be achieved by only engaging persons who are required to adhere to appropriate standards to conduct the dealings.

234. Other standard conditions included in the draft licence state that only people authorised by the licence holder are covered by the licence, and that the licence holder must inform all people dealing with the GMO, other than external service providers, of applicable licence conditions.

235. Further conditions to be implemented in the draft licence is to ensure that a compliance management plan is in place for each clinical trial site before administration of the GMO commences at that site. The compliance management plan must detail how the licence holder intends to comply

with the licence conditions, including listing persons responsible for site management, proposed reporting structures, staff training procedures and transport and disposal processes.

3.1.2 Summary of licence conditions to be implemented to limit and control the clinical trial

236. A number of licence conditions have been drafted to limit and control the proposed clinical trial, based on the above considerations. These include requirements to:

- limit the trial to 13 trial participants;
- the trial must be conducted at suitable clinical trial sites;
- limit the time when the GMO can be administered to 5 years from issue of the licence;
- restrict access to the GMO;
- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements;
- ensure appropriate PPE is used;
- restrict personnel permitted to administer the GMO;
- requiring appropriate decontamination of the GMO and materials and equipment that have been in contact with the GMO;
- Instructing the patients to disinfect voided urine in the toilet bowl before flushing the toilet for 2 days following treatment;
- transport and store the GMO and samples from GMO-treated participants in accordance with IATA shipping classification UN 3373 [Category B] and/or the minimum requirements for packaging, and labelling as detailed in the draft licence;
- clinical waste stream to be used by external service providers to destroy untreated GMO and GMO-related waste.

3.2 Other risk management considerations

237. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- contingency plans
- identification of the persons or classes of persons covered by the licence
- reporting requirements
- access for the purpose of monitoring for compliance.

3.2.1 Applicant suitability

238. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under Section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country
- the capacity of the applicant to meet the conditions of the licence.

239. If a licence were issued, the conditions would include a requirement for the licence holder to inform the Regulator of any information that would affect their suitability.

240. In addition, the applicant organisation must have access to an IBC and be an accredited organisation under the Act.

3.2.2 Contingency plans

241. Should a licence be issued, Ferring is required to submit a contingency plan to the Regulator before commencing dealings with the GMO. This plan will detail measures to be undertaken in the event of:

- the unintended release of the GMO, including spills
- exposure of, or transmission to persons other than trial participants
- a person exposed to the GMO developing a serious adverse response.

3.2.3 Identification of the persons or classes of persons covered by the licence

242. If issued, the persons covered by the licence would be the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by the licence. Prior to dealings with the GMO, Ferring is required to provide a list of people and organisations that are covered by the licence, or the function or position where names are not known at the time.

3.2.4 Reporting requirements

243. If issued, the licence would require the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the clinical trial.

244. A number of written notices are also required under the licence regarding dealings with the GMO, to assist the Regulator in designing and implementing a monitoring program for all licensed dealings. The notices include:

- identification of the clinical trial sites where administration of the GMO to trial participants would take place
- expected date of administration with the GMO for each clinical trial site
- cease of administration with the GMO for each clinical trial site.

3.2.5 Monitoring for compliance

245. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow inspectors and other persons authorised by the Regulator to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

246. If monitoring activities identify changes in the risks associated with the authorised dealings, the Regulator may also vary licence conditions, or if necessary, suspend or cancel the licence.

247. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Issues to be addressed for future releases

248. As noted in Chapter 2, Section 3, the level of uncertainty in this risk assessment is considered low and the commercial release of the GMO has been approved under the DIR 217 licence, and

therefore no further issues have been identified that may be required to assess any future applications.

Section 5 Conclusions of the consultation RARMP

249. The risk assessment concludes that the proposed clinical trial of the GMO poses negligible risks to the health and safety of people or the environment as a result of gene technology. These negligible risks do not require specific risk treatment measures.

250. If a licence is issued, conditions are imposed to limit the trial to the proposed scale, location and duration, and to restrict the spread and persistence of the GMO and its genetic material in the environment, as these were important considerations in establishing the context for assessing the risks.

Chapter 4 Draft licence conditions

Section 1 Interpretations and Definitions

1. In this licence:

   (a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Gene Technology Regulations 2001;

   (b) words importing a gender include every other gender;

   (c) words in the singular number include the plural and words in the plural include the singular;

   (d) expressions used to denote persons generally (such as “person”, “party”, “someone”, “anyone”, “no one”, “one”, “another” and “whoever”), include a body politic or corporate as well as an individual;

   (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

   (f) where any word or phrase is given a particular meaning, other grammatical forms of that word or phrase have corresponding meanings;

   (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

‘Act’ means the *Gene Technology Act 2000* (Commonwealth) or the corresponding State Law under which this licence is issued.

‘Analytical facility’ means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC).

‘Clinical trial site’ means a medical facility in Australia such as a clinical trial facility and associated Pharmacy, which are notified in writing to the Regulator for the purposes of conducting this clinical trial.

‘Decontaminate’ (or ***‘Decontamination’***) means, as the case requires, kill the GMOs by one or more of the following methods:

   (a) chemical treatment;

   (b) autoclaving;

   (c) high-temperature incineration; or

   (d) a method approved in writing by the Regulator.

   Note: 'As the case requires' has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.

‘External service provider’ means a person engaged by the licence holder solely in relation to transport, storage and/or disposal of the GMOs, or Sample analysis other than at a Clinical trial site, and who is not undertaking any dealings with the GMOs that are not for those purposes.

‘GM’ means genetically modified.

‘*GMO*’ means the genetically modified organisms that are the subject of the dealings authorised by this licence.

'Immunosuppressive disorder' means a condition characterised by a weakened immune system due to underlying disease (e.g. HIV), medications (excluding anti-cancer medications) or treatment (e.g. organ transplant).

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

'OGTR' means the Office of the Gene Technology Regulator

'Personal information' has the same meaning as in the *Privacy Act 1988*. Personal information means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

(a) whether the information or opinion is true or not; and

(b) whether the information or opinion is recorded in a material form or not.

'Pharmacy' means a location within the Clinical trial site, where authorised staff stores, prepares, and dispenses medications in a medical environment.

'*Regulations*' means the *Gene Technology Regulations 2001* (Commonwealth) or the corresponding State Law under which this licence is issued.

'Regulator' means the Gene Technology Regulator.

'Sample' means any biological material collected from a treated trial participant for analysis as part of the trial.

'Storage facility' means a third-party facility offering logistical services and distribution of clinical supplies.

Section 2 General conditions and obligations

Holder of licence

3. The licence holder is Ferring Pharmaceuticals Pty Ltd.

Remaining an Accredited Organisation

4. The licence holder must, at all times, remain an accredited organisation.

Validity of licence

5. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension, or after the licence has been cancelled or surrendered.

Note: Although this licence has no expiry date, the duration of preparation and administration of the GMO is restricted in accordance with Condition 23.

Persons covered by this licence

6. The persons covered by this licence are:

(a) the licence holder, and any employees, agents or External service providers engaged by the licence holder; and

(b) the project supervisor(s); and

(c) other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.

7. To the extent that any activity by a trial participant may be considered to be a dealing with the GMO as described in **Attachment A** for purposes of the Act, that dealing is authorised by this licence.

8. The licence holder must keep a record of all persons covered by this licence, and must keep a record of the contact details of the project supervisor(s) for the licence.

Note: Where External service providers are used, it is sufficient to record the company name and the position or job title of the person(s) conducting the dealing.

9. The licence holder must provide information related to the persons covered by the licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Description of GMOs covered

10. The licence authorises specific dealings in respect of the GMO identified and described in **Attachment A**.

Dealings authorised by this licence

11. The licence holder and persons covered by this licence may conduct the following dealings with the GMO:

(a) conduct the following experiments with the GMO:

i) prepare the GMO for administration;

ii) administer the GMO to clinical trial participants by intravesical instillation;

iii) collect Samples from trial participants;

iv) analyse the Samples described in 11(a)iii);

(b) transport of Samples or waste containing the GMO; and

(c) dispose of Samples or waste containing the GMO;

and may possess, supply, use or store the GMO for the purposes of, or in the course of, any of these dealings.

12. This licence does not apply to dealings with the GMO conducted pursuant to another authorisation under the Act.

Note: The import, transport and disposal of the GMO are authorised under the DIR-217 licence. Therefore, this licence is limited to the dealings described above, and to the supply and storage of Samples and waste containing the GMO for the purpose of these dealings, taking place at Clinical trial sites and Analytical facilities.

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

13. The licence holder must inform any person covered by the licence, to whom a particular condition of the licence applies, of the following:

(a) the particular condition, including any variations of it; and

(b) the cancellation or suspension of the licence; and

(c) the surrender of the licence.

Note: No particular conditions of this licence apply to trial participants; therefore, Condition 13 does not apply to trial participants.

Monitoring and audits (section 64)

14. If a person is authorised by this licence to deal with the GMO and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Additional information to be given to the Regulator (section 65)

15. The licence holder must inform the Regulator, if they become aware of:

(a) additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

(b) any contraventions of the licence by a person covered by the licence; or

(c) any unintended effects of the dealings authorised by the licence.

Note 1: For the purposes of this Condition:

(a) The licence holder is taken to have become aware of additional information if they were reckless as to whether such information existed; and

(b) The licence holder is taken to have become aware of contraventions, or unintended effects, if they were reckless as to whether such contraventions had occurred, or such unintended effects existed.

Note 2: Contraventions of the licence may occur through the action or inaction of a person.

Note 3: Additional information includes any changes at a Clinical trial site, which might increase the likelihood of unintentional exposure of people or release of the GMO into the environment.

Note 4: As example of informing immediately is contact made at the time of the incident via the OGTR free call phone number 1800 181 030 or email to OGTR.M&C@health.gov.au.

Informing the Regulator of any material changes of circumstance

16. The licence holder must immediately, by notice in writing, inform the Regulator of:

(d) any relevant conviction of the licence holder occurring after the commencement of this licence;

(b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country, being a law relating to the health and safety of people or the environment;

(c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

17. The licence holder must provide information related to the licence holder's ongoing suitability to hold a licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Further conditions with respect to informing persons covered by the licence

18. If a particular condition, including any variation of it, applies to an External service provider covered by this licence, the licence holder must not permit that person to conduct any dealings unless the person has been informed of the condition, including any variation to it.

Note: Information required under Condition 18 may be provided to External service providers who are engaged solely for storage and transport of the GMO through labelling of the outermost container of the GMO in accordance with Condition 35(a).

19. If a particular condition, including any variation of it, applies to a person with respect to any dealing, other than to an External service provider, the licence holder must not permit a person covered by this licence to conduct that dealing unless:

(a) the licence holder has obtained from the person a signed and dated statement that the person:

i) has been informed by the licence holder of the condition and, when applicable, its variation; and

ii) has understood and agreed to be bound by the condition, or its variation; and

iii) has been trained in accordance with sub-condition 19(b) below; and

(b) the licence holder has trained that person in a manner which enables them to conduct the dealings in accordance with the conditions of this licence.

20. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

21. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence, other than External service providers, who are conducting dealings with the GMO.

Note: The licence may be made available electronically.

Section 3 Limits and control measures

Limits on clinical trials conducted under this licence

22. The GMO may be administered to a maximum of 13 trial participants.

23. The preparation and administration of the GMO must be completed within 5 years from the date of issuing of the licence.

Preparation and administration of the GMO

24. Administration of the GMO to trial participants must not commence prior to approval by a Human Research Ethics Committee.

25. The following activities must occur within a Clinical trial site:

(a) preparation of the GMO for administration to trial participants; and

(b) administration of the GMO to trial participants.

Note: Before any of these activities take place, the details of each Clinical trial site must have been notified to the Regulator in accordance with Condition 41(a).

Conditions relating to trial participants

26. The licence holder must notify each trial participant, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

27. The licence holder must ensure that exclusion criteria in selecting trial participants include (though are not limited to):

(a) pregnant and breastfeeding women;

(b) any people suffering from an Immunosuppressive disorder;

(c) those having received a prior treatment with adenovirus-vector based therapies within 60 days of participating in the trial;

(d) those intending to become pregnant during the trial or during the first 60 days following each treatment with the GMO.

28. Before inoculating any trial participant with the GMO, the licence holder must obtain written agreement from the trial participant that they would:

(a) use barrier method(s) to prevent pregnancy and exposure to the GMO during any sexual activities for 60 days following each administration of the GMO; and

(b) not donate blood, sperm, ova, tissues or organs while participating in the trial and for 60 days after the final administration of the GMO; and

(c) follow the instructions provided by the licence holder for the treatment of urine (Condition 29).

Preventive practices required post-administration

29. Before inoculating a trial participant with the GMO, the licence holder must provide instructions to the trial participant to disinfect voided urine for two days following treatment with the GMO by adding half a cup of household bleach to the toilet bowl prior to urinating and wait 15 minutes before flushing.

Conditions related to the conduct of the dealings

30. Conditions that apply to dealings with GMOs do not apply to Samples collected from trial participants, or other materials, or waste, that are reasonably expected not to contain the GMO. The licence holder must provide to the Regulator upon request, a written justification for this expectation.

31. The licence holder must ensure that dealings are only conducted in a manner which:

(a) does not compromise the health and safety of people; and

(b) minimises the exposure of persons conducting the dealings to the GMO, other than intended exposure of trial participants.

Note: The licence holder may do this by only engaging or otherwise authorising persons to conduct dealings who are required to adhere to appropriate standards and guidelines. For example, standards developed by the National Pathology Accreditation Advisory Council for pathology practices, the Australian Guidelines for the Prevention and Control of Infection in Healthcare, Guidelines for Good Clinical Practice and the National Safety and Quality Health Service (NSQHS) Standards.

32. The licence holder must ensure that procedures are in place to account for the GMO from import to destruction/export, and records must be made available to the Regulator on request.

Work practices at Clinical trial sites

33. For the purposes of Condition 31, the work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) preparation of the GMO must be conducted in a Class II biosafety cabinet (Class II BSC), a negative pressure pharmaceutical isolator, or alternative containment equipment approved in writing by the Regulator;

(b) persons preparing the GMO must wear personal protective equipment (PPE), including gowns, gloves and eye protection. In addition to this, persons administering the GMO must also wear a P2 facemask or equivalent facemask;

(c) persons preparing or administering the GMO must be informed of the risks associated with the GMO (including risks in people suffering from an Immunosuppressive disorder or

pregnant individuals) and have provided a signed statement to that effect in accordance with Condition 19;

(d) any broken skin (e.g. cuts, scratches, dermatitis) of persons conducting dealings not covered by PPE or clothing must be covered with a waterproof dressing;

(e) all work surfaces must be decontaminated after they have been used for conducting dealings authorised by this licence;

(f) equipment used for dealings with the GMO must be decontaminated after use;

(g) preparation and administration of the GMO must be conducted by suitably qualified and trained staff.

Transport, storage and disposal of the GMO

34. Unless covered by an NLRD, the licence holder must ensure that transport of the GMO is conducted only for the purposes of, or in the course of, another dealing permitted by this licence.

35. The licence holder must ensure that transport and storage of the GMO follow these sub-conditions:

(a) The GMO must be contained within sealed, unbreakable primary and secondary containers, with the outer packaging labelled to indicate at least:

i) that it contains GMOs; and

ii) that it contains biohazardous material as designated by a biohazard label; and

iii) the contact details for the licence holder; and

iv) instructions to notify the licence holder in case of loss or spill of the GMO; and

(b) the external surface of the primary and secondary containers must be decontaminated prior to and after transport; and

(c) procedures must be in place to ensure that the GMO can be accounted for and that a loss of GMOs during transport or storage or failure of delivery can be detected; and

(d) access to the GMO is restricted to authorised persons for whom Condition 18 or Condition 19 has been met (i.e. the GMO is within a locked unit or an area which has restricted access). This includes situations where containers are left for collection in a holding area, or left unattended prior to Decontamination; and

Note: All stored GMOs remain the responsibility of the licence holder.

(e) if the GMO is being transported or stored with a coolant (e.g. dry ice, liquid nitrogen or any other coolant) which will release a gas, a mechanism to allow the escape of the gas must be included. If water ice is used as a coolant then the outer packaging should be constructed so as to prevent any leakage. All containers must be able to withstand the temperatures to which they will be subjected; and

Note: When transporting and storing with coolants, it is preferable for coolants to be used outside of the secondary container.

(f) a consolidated record of all GMOs being stored under this condition is maintained and made available to the Regulator upon request; and

(g) for the purposes of transport entirely within a building, where the GMO is accompanied by an authorised person for whom Condition 19 has been met, Conditions 35(a)iii), 35(a)iv) and 35(c) do not apply.

36. The licence holder must ensure that all GMOs and waste reasonably expected to contain the GMO are Decontaminated:

(a) prior to disposal, unless the method of disposal is also a method of Decontamination; and

(b) before or upon suspension, cancellation or surrender of the licence, unless covered by another authorisation under the Act, or exported; and

(c) by autoclaving, chemical treatment, high-temperature incineration or any other method approved in writing by the Regulator.

37. Where transport is conducted by External service providers for the purposes of destruction, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, enters the clinical waste stream for Decontamination via autoclaving or high-temperature incineration.

Note: In the event of a spill during transport by an External service provider, compliance with relevant State or Territory legislation and regulations to manage clinical or biohazardous spills is sufficient.

Contingency plans

38. The licence holder must ensure that any person (other than a trial participant) exposed to the GMO is offered prompt medical advice. The clinician must be provided with any relevant information about the GMO.

39. If there is a spill or an unintentional release of GMO at a Storage facility or Clinical trial site, the following measures must be implemented:

(a) the GMO must be contained to prevent further dispersal; and

(b) persons cleaning up the GMO must wear appropriate PPE; and

(c) the exposed area must be decontaminated with an appropriate chemical disinfectant effective against the GMO; and

(d) any material used to clean up the spill or PPE worn during clean-up of the spill must be Decontaminated; and

(e) the licence holder must be notified as soon as reasonably possible.

Section 4 Reporting and Documentation

Note: The following licence conditions are imposed to demonstrate compliance with other conditions and facilitate monitoring of compliance by staff of the OGTR. Notices and reports may be by email to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at ***Attachment B****.*

40. The licence holder must notify the Regulator, in writing, of the name and address of each storage facility before commencement of dealings at that location.

41. At least 14 days prior to first administering the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

(a) the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities;

(b) the role and contact details for key persons responsible for the management of the trial at the site;

(c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures;

(d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Condition 15, 16, 42 and 43;

(e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;

(f) the person(s) or class of persons administering the GMO;

(g) where, within the site, the GMO is expected to be administered;

(h) the expected date of first administration; and

(i) how compliance with Condition 31 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.

Note: For the purpose of finding out whether the Act has been complied with, an OGTR inspector may, if entry is at a reasonable time, enter a facility occupied by the licence holder or a person covered by the licence and exercise monitoring powers.

42. For each Clinical trial site, the licence holder must notify the Regulator, in writing, of the end of the clinical trial, no later than 30 days after:

(a) the final dose being administered; or

(b) the decision that no further participants will be treated at the site.

43. The licence holder must inform the Regulator as soon as reasonably possible:

(a) in the event of a loss or spill of the GMO;

(b) in the event of the exposure of a person other than a trial participant to the GMO; and

(c) if a trial participant has not followed the procedures described in the instructions provided by the licence holder under Conditions 28 and 29.

44. Upon request from the Regulator, the licence holder must provide any signed records or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.

Attachment A

DIR No: 223

Full Title: Clinical trials of a genetically modified adenovirus for treatment of bladder cancer

Licence Holder: Ferring Pharmaceuticals Pty Ltd

GMO Description

GMOs covered by this licence:

Human adenovirus C serotype 5 modified by deleting specific gene sequences to improve safety and replacing a deleted gene sequence with a human interferon alfa-2b (*hIFN-α2b*) gene expression cassette. The identities of the deleted gene sequences and the regulatory elements included in the *hIFN-α2b* gene expression cassette have been declared Confidential Commercial Information (CCI) under s185 of the Act.

Parent Organisms:

Common Name: Human adenovirus

Scientific Name: Human adenovirus C serotype 5

Modified traits:

Categories: Human therapeutic

Description: The adenovirus has been modified to be replication incompetent and carries a *hIFN-α2b* gene for the treatment of adult patients with high-grade Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) or intermediate risk (IR) NMIBC.

Attachment B Summary of reporting requirements*

Prior to the commencement of the trial	Condition	Timeframe for reporting
The name and address of each Storage facility	40	Before commencement of dealings at that location
A written Compliance Management Plan for each Clinical trial site: • the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; • the role and contact details for key persons responsible for the management of the trial at the site; • that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures; • the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events; • details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; • the person(s) or class of persons administering the GMO; • where, within the site, the GMO is expected to be administered; • expected date of first administration; and • how compliance with Condition 29 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.	41	At least 14 days prior to the first administration of the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator
Information to be provided at any time during the Clinical trial		
Any additional information related to the health and safety of people and the environment associated with the dealing covered by the licence, or any unintended effect of the dealing authorised by the licence	15(a), (c)	Immediately
Information related to any contravention of the licence by a person covered by the licence	15(b)	Immediately
Any relevant conviction of the licence holder	16(d)	Immediately

Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	16(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately
Provide notification to the Regulator, in writing, of the final GMO administration of the last trial participant at each Clinical trial site	42(a)	Within 30 days of the decision to cease GMO administration at that particular Clinical trial site
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	43(a), (b)	As soon as reasonably possible
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	43(c)	As soon as reasonably possible
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
A consolidated record of all GMOs being stored	35(f)	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	44	Within a timeframe stipulated by the Regulator

*Notifications and documents to be sent to OGTR.M&C@health.gov.au

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