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

October 2025

Risk Assessment and Risk Management Plan

for

DIR 217

Commercial supply of nadofaragene firadenovec for bladder cancer treatment

Applicant: Ferring Pharmaceuticals Pty Ltd

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

Decision

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

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

A Risk Assessment and Risk Management Plan (RARMP) for this application has been prepared by the Regulator in accordance with the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation, and finalised following consultation with a wide range of experts, agencies and authorities, and the public. The RARMP concluded that the proposed commercial supply of the GM therapeutic poses negligible risks to human health and safety and the environment, and no specific risk treatment measures are required. However, general licence conditions have been imposed to ensure that there is ongoing oversight of the release.

The application

Application number	DIR 217
Applicant	Ferring Pharmaceuticals Pty Ltd
Project Title	Commercial supply of nadofaragene firadenovec for bladder cancer treatment[1]
Parent organism	Human adenovirus C serotype 5 (HAd5)
Modified trait	Replication incompetent HAd5 expressing a human interferon alpha-2b (*hIFN-α2b*) gene
Genetic modification	• deletion of gene sequences[2] to improve safety • insertion of the *hIFN-α2b* gene to produce the protein with anticancer activities
Proposed locations	Australia-wide
Principal purpose	Commercial supply of the GM therapeutic
Previous approvals	The GM therapeutic has not previously been approved in Australia. Internationally, the GM therapeutic has been approved by the Food and Drug Administration (FDA) in the USA.
Proposed period of release	Ongoing from issue of licence

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

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

Risk assessment

The risk assessment process considers how the genetic modification and proposed activities conducted with the GM therapeutic in the context of import, transport, storage, and disposal might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application, relevant previous approvals, current scientific knowledge and advice received from a wide range of experts, agencies and authorities consulted on the preparation of the RARMP. Both the short and long term risks were considered.

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

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

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

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

Risk management

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

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

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

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Abbreviations

AdV	Adenovirus
AICIS	Australian Industrial Chemicals Introduction Scheme
AIDS	Acquired immunodeficiency syndrome
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARTG	Australian Register of Therapeutic Goods
BCG	Bacillus Calmette-Guérin
CAR	Coxsackie-adenovirus receptor
DAFF	Department of Agriculture, Fisheries and Forestry
DIR	Dealings involving intentional release
DNIR	Dealings not involving intentional release
FSANZ	Food Standards Australia New Zealand
GM(O)	Genetically modified (organism)
GM-CSF	Granulocyte macrophage colony-stimulating factor
GTTAC	Gene Technology Technical Advisory Committee
HAdV	Human adenovirus
IFN-α	Interferon alpha protein
IFN-α2b	Interferon alpha-2b protein
IU	International unit
kb	Kilobase
mL	Millilitre
MTD	Maximum tolerated dose
NMIBC	Non-muscle invasive bladder cancer
OGTR	Office of the Gene Technology Regulator
PCR	Polymerase chain reaction
PFU	Plaque forming units
pg	Picogram
PRR	Post release review
qPCR	Real-time quantitative polymerase chain reaction
RARMP	Risk Assessment and Risk Management Plan
TGA	Therapeutic Goods Administration
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
vp	Viral particle
WT	Wildtype

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 (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, in establishing the risk assessment context. This information is specific for each application. Potential risks to the health and safety of people or the environment posed by the proposed release are assessed within this context. Chapter 1 provides the specific information for establishing the risk assessment context for this application.

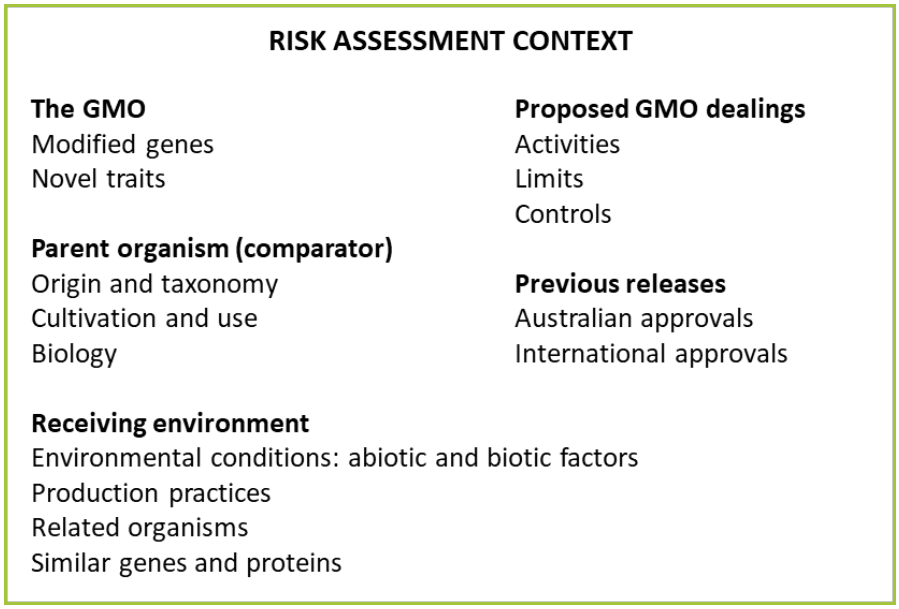

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR, and the Risk Analysis Framework

6. Since this application is for commercial purposes, it does not meet the criteria for a limited and controlled release application under section 50A of the Act. Therefore, under section 50(3) of the Act, the Regulator was required to seek advice from prescribed experts, agencies and authorities on

matters relevant to the preparation of the RARMP. This first round of consultation included the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities and agencies prescribed in the Regulations and the Minister for the Environment. A summary of issues contained in submissions received is provided in Appendix A.

7. Section 52 of the Act requires the Regulator, in a second round of consultation, to seek comment on the RARMP from the experts, agencies and authorities outlined above, as well as the public. Advice from the prescribed experts, agencies and authorities in the second round of consultation, and how it was taken into account, is summarised in Appendix B. Two public submissions were received, and their consideration is summarised in Appendix C.

1.1 Interface with other regulatory schemes

8. 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). Proposed dealings may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

9. To avoid duplication of regulatory oversight, risks that will be considered by other regulatory agencies would not be assessed or managed by the Regulator.

10. For the commercial supply of a live GM therapeutic, dealings regulated under the Act include the import, transport, storage, and disposal of GMOs. The Regulator has assessed risks to people as a consequence of these activities and risks from persistence of the GMOs in the environment and has considered the necessity of risk management for these risks.

11. The DAFF regulates products imported into Australia to protect Australia from biosecurity risks. Under the *Biosecurity Act 2015*, the importation of biological material such as live GM therapeutics requires a permit from the DAFF.

12. The TGA provides a national system of controls for therapeutic goods. It administers the provisions of the *Therapeutic Goods Act 1989* which specifies the standard that must be met before a therapeutic product can be included on the Australian Register of Therapeutic Goods (ARTG). Inclusion in the ARTG is required before a live biological therapeutic product can be lawfully supplied in Australia. As part of this process, the TGA would assess the quality, safety, and efficacy of the therapeutic product. Quality aspects could include batch-to-batch consistency in product composition, purity, and potency. Safety aspects could include the toxicological and allergenicity profiles, including any excipients, by-products, and impurities from manufacture.

13. The administration/use of GMOs as therapeutics is not regulated under gene technology legislation. The Regulator does not assess excipients and would not assess manufacturing by-products and impurities unless they are GM products.

14. The labelling, handling, sale and supply of scheduled medicines is regulated through the Scheduling Policy Framework for Medicines and Chemicals (AHMAC, 2018). Guidelines for the safe handling, storage and distribution of Schedule 4 medicines such as biological medicines like the GMO are specified through the Australian Code of good wholesaling practice for medicines in schedules 2, 3, 4 and 8 (NCCTG, 2011). The provisions of this Code, which ensure that quality is maintained during wholesaling, are applied through applicable State and Territory therapeutic goods/drugs and poisons legislation, and/or State or Territory wholesaler licensing arrangements.

Section 2 The proposed dealings

15. Ferring Pharmaceuticals Pty Ltd (Ferring) is seeking authorisation for the commercial supply of an adenoviral vector-based therapeutic product, nadofaragene firadenovec (also known as nadofaragene firadenovec-vncg, rAd-IFN/Syn3 and Adstiladrin), in Australia. This GM therapeutic has been developed as a therapy for the treatment of adult patients with high-grade Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC). The GM therapeutic is administered by intravesical (bladder) instillation.

16. For the ongoing commercial supply of nadofaragene firadenovec, the dealings assessed by the Regulator are to:

(a) import the GMO

(b) transport the GMO

(c) dispose of the GMO

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

2.1 Details of the proposed dealings

17. Nadofaragene firadenovec is manufactured by FinVector Oy (FinVector) in Finland. Ferring proposes to import the GM therapeutic into Australia from FinVector.

18. 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.

19. Once the GM therapeutic has entered Australia, storage, transport, and handling would be conducted in accordance with local regulations, the *World Health Organization Good storage and distribution practices for medical products* (World Health Organization, 2020), and the *Australian Code of Good Wholesaling Practice for Medicines in schedules 2, 3, 4 and 8* (NCCTG, 2011), which includes maintenance of the cold chain and security arrangements to prevent unauthorised access to the medicines.

20. 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. On receipt at the clinic, the unit-dose will be stored in a freezer until it is unsealed when needed for a patient.

21. If approved by both the Regulator and the TGA, Ferring intends to supply nadofaragene firadenovec Australia-wide for treatment of adult patients with high-grade BCG-unresponsive NMIBC. The clinic sites to be involved in the commercial supply of the GM therapeutic would be the urology and oncology departments of hospitals.

22. Disposal of the GM therapeutic and any associated material contaminated with the GMO would be in accordance with the requirements of the *Work Health and Safety Act 2011* (Commonwealth of Australia, 2011) and related State and Territory legislation.

23. At the clinic sites where the administration of the GM therapeutic occurs, vented vial adapters will be used to transfer the drug from the vial to the syringe to eliminate the risk of needle stick injuries. Unused drug, and used vials, syringes, vented vial adapters, any disposable instruments or other consumable materials such as gowns, dressings, gauze and bandages used during the procedure will be disposed of in a manner consistent with the standard practice of the institution for biohazardous materials. This will involve temporary containment in sharps bins or clearly marked bags

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

(e.g. biohazard, medical waste) prior to autoclaving and/or incineration either onsite or offsite as per local institutional guidelines for handling infectious material.

Section 3 The parent organism

24. 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.

25. 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., 2023). 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., 2023).

26. 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., 2019; 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., 2023; Sato-Dahlman et al., 2020; Shaw and Suzuki, 2019).

3.1 Pathology

27. Human adenoviruses can 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., 2023; Public Health Agency of Canada, 2014). 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).

28. Outbreaks of HAdV-associated respiratory disease are more common in late winter, spring and early summer, however infections can occur throughout the year. After natural HAdV infection, the incubation period 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.

29. Infections with HAdVs are generally mild and self-limiting, but can be more severe or lethal in certain risk groups (Leikas et al., 2023; Mennechet et al., 2019). The most critical risk groups are neonates and immunocompromised individuals, in which the HAdVs may cause severe pneumonia and diseases affecting organ systems other than the respiratory tract, depending on the level of immunocompetency (Leikas et al., 2023). Children and immunocompromised people with either congenital or acquired immunodeficiency (e.g. resulting from immunosuppressive therapy, radiation therapy, use of corticosteroids and acquired immunodeficiency syndrome (AIDS)) can develop acute or persistent infections, leading to high morbidity or even mortality (Echavarría, 2008). For example, mortality rates of 2 to 70% were reported for paediatric and adult bone marrow or stem cell transplant patients (Echavarría, 2008). Infection of infants with HAdVs can also result in serious

bronchiolitis (irritation and swelling of the small airways in the lung) and intussusception (a form of bowel obstruction where a part of the intestine folds into the adjacent intestine) (Shieh, 2022). HAdVs account for approximately 5% - 18% of bronchiolitis in infants (Shieh, 2022) and up to 41% of intussusception in children (Guarner et al., 2003).

30. The parental species, HAdV-C, has been mainly associated with acute respiratory tract infections in children and is the most common species reported in most populations, with anti-HAdV-C5 antibodies detected in almost 85% of the population (Leikas et al., 2023; Mennechet et al., 2019). HAdV-C has been shown to be associated with mortality in immunocompromised individuals, particularly in paediatric liver transplant recipients (Echavarría, 2008).

3.2 Structure and genome organisation

31. Adenoviruses are non-enveloped, double-stranded DNA viruses with an icosahedral capsid comprising of major (hexon, penton base and fibre) and 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).

32. The HAdV genome consists of early and late genes which are organised into transcription units (Figure 2). The early genes (E1 to E4) are involved in directly activating transcription of other viral regions, altering the host cellular environment to enhance viral replication, and coordination 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.

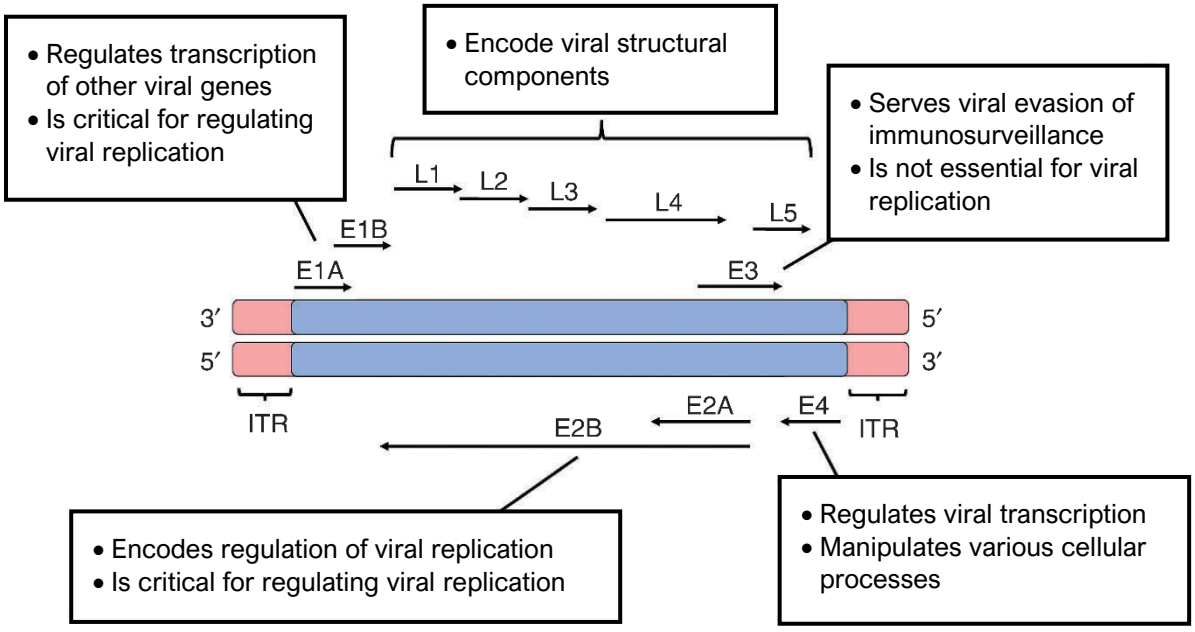

Figure 2. Functions, organisation and structure of HAdV genome. Image modified from Afkhami et al. (2016).

33. The E1 region is composed of the E1A and E1B regions. The E1A region controls transcription of viral genes and redirects host-cell gene expression machinery to enable virus replication. The two proteins produced from the E1A region 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 region 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).

34. The E2 region consists of E2A and E2B which 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 region encodes viral proteins which aid the virus in evading the host immune response. The E4 region modulates cellular function and assists with viral DNA replication and RNA processing.

35. Interactions of proteins encoded by the AdV genome are required to form a mature infectious particle. The 3 major proteins (hexon, penton and fibre) form the external capsid structure and "spikes" of the viral particle. The viral core proteins (V, VII and μ) 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 AdV 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).

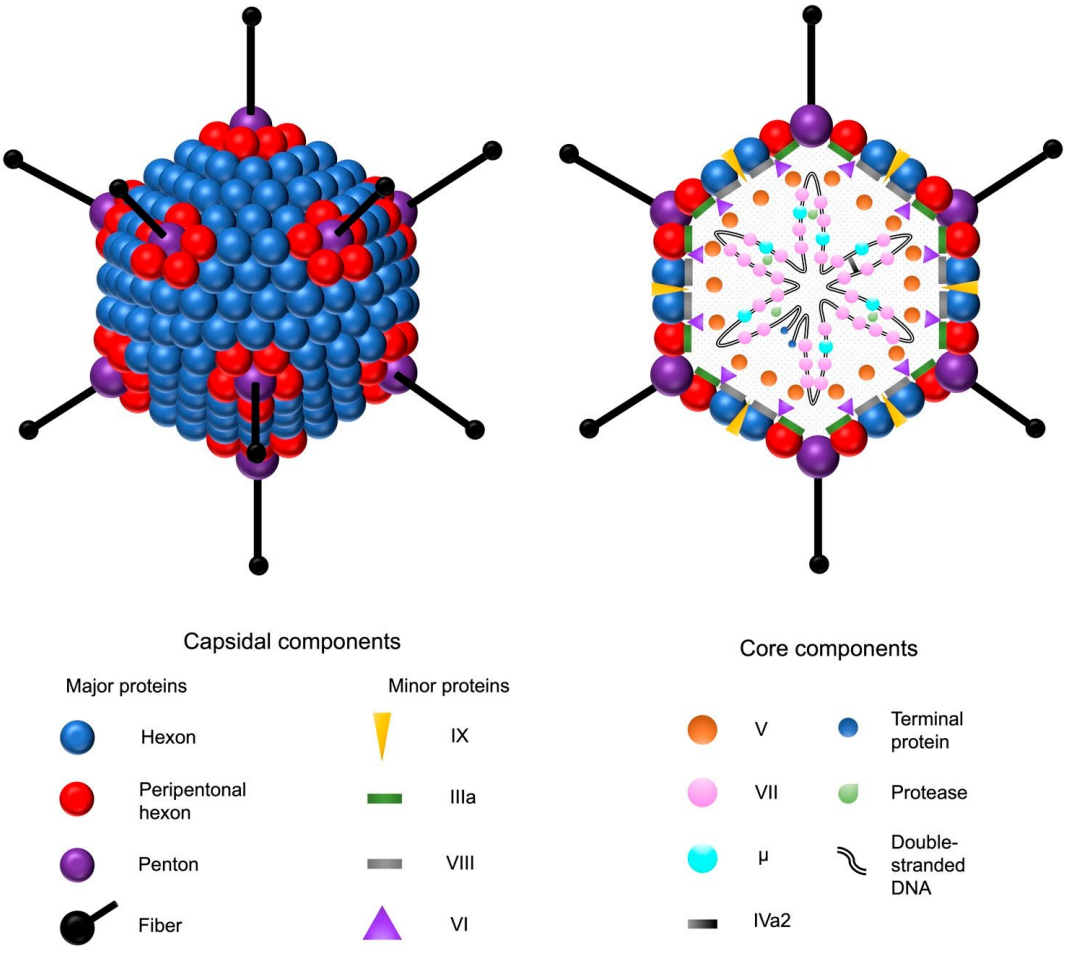

Figure 3. Structural model of human adenovirus. Image source: Leikas et al. (2023)

3.3 Viral infection and replication

36. Human adenoviruses can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. Human adenoviruses most frequently infect epithelia of the

upper or lower respiratory tract, eyes, gastrointestinal and urinary tract (see paragraph 25 for the tropism of different species in the infected tissue types).

37. HAdVs use the Coxsackie-adenovirus receptor (CAR) transmembrane protein, and other receptors including CD46, CD80 and CD86, and sialic acid to enter the host cells (Lion, 2019; Zhang and Bergelson, 2005). HAdV-C5 enter cells by binding to CAR present in heart, brain, and more generally, epithelial and endothelial cells (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).

38. Replication of HAdVs occurs in the nucleus of the host cell. HAdV uses the host cell nuclear machinery to make copies of itself (see Figure 4). Following attachment to cell membrane receptors (steps 1-3), the HAdV enters the host cell and is uncoated to release viral particles (step 4). The viral genome is transported into the nucleus (step 5) where transcription of early phase genes occurs (Charman et al., 2019). The transcripts from the early genes are transported into the cytoplasm where early proteins for viral DNA replication (step 6) are produced. These early proteins are transported back into the nucleus and DNA replication can occur (step 7). Late phase transcripts are also transported into the cytoplasm where viral structural proteins are made (step 8). These viral structural proteins are also transported back into the nucleus where new virus particles are assembled (step 9). Finally, the host cell breaks apart releasing the new virus particles (step 10) (Waye and Sing, 2010).

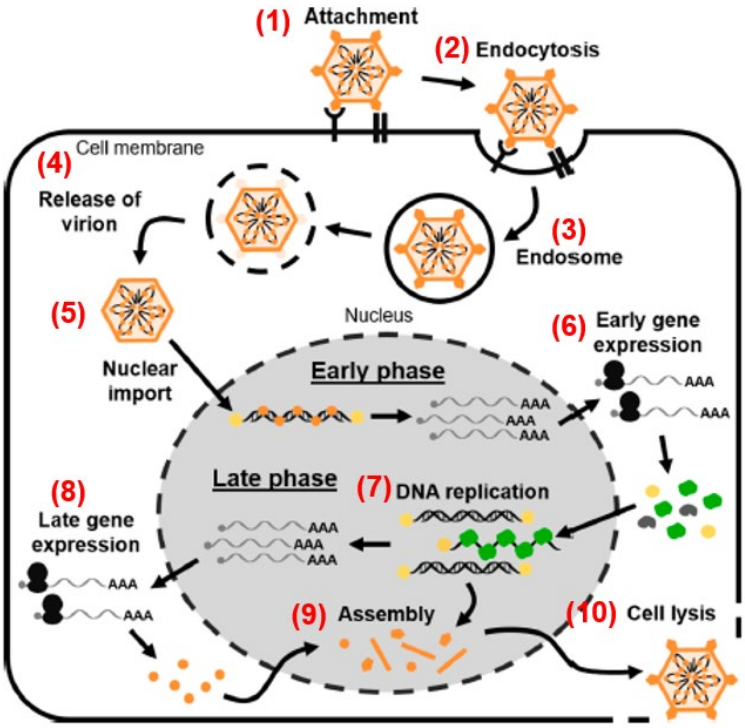

Figure 4. Overview of the adenovirus replication cycle (Charman et al., 2019). Virus entry and import of viral genomes into the nucleus lead to a program of early gene expression that includes the viral replication machinery. The onset of viral DNA replication marks progression from the early to the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

3.4 Mutation and recombination

39. 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., 2015).

40. 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).

41. Bioinformatic analysis of HAdV-C suggests that homologous recombination in the capsid (hexon, penton and fibre) and E3 genes were not common and were not major contributors to the diversity seen in HAdV-C (Dhingra et al., 2019). 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 fibre 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 these regions of HAdV-C reduces the likelihood of HAdV-C altering its cell tropism and of altering its ability to evade the immune system.

42. 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 genotypes of 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

43. Humans are the natural host for HAdVs (Custers, 2020). In general, HAdVs do not cause disease in animals, and animal AdVs are only pathogenic to the species in which they originated. Companion animals such as dogs and cats are unlikely to be infected with HAdVs (Borkenhagen et al., 2019). Experimentally, hamsters, mice, cotton rats, rabbits and tree shrews have been used as animal models to study HAdV-induced disease in animals (Bertzbach et al., 2021). Replication of various HAdV serotypes have been found difficult in some animal models (mice, cotton rats and rabbits) (Ismail et al., 2019). While HAdVs, including HAdV-C serotypes, are adapted to infect humans, experimental studies have demonstrated their ability to infect and replicate in certain mammals in a dose dependent manner (Bertzbach et al., 2021). However, infections in animals are considered less likely under natural circumstances and no natural infection of non-human hosts has been reported so far.

44. 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., 2023). The virus can also be spread indirectly via contact with surfaces or articles such as handkerchiefs, linens or utensils that have been contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017). According to the Pathogen Safety Data Sheet produced by the Public Health Agency of Canada, 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).

3.5.2 Bio-distribution and shedding

45. 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., 2019). 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 (100,000-1,000,000/mL) of viral particles shed into sputum or oral secretions of the infected person (Allard and Vantarakis, 2017).

46. 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

47. An estimation of the seroprevalence of HAdV-E4, -C5, -D26 and -B35 (serotypes commonly tested in clinics) is shown in Figure 5, based on approximately 30 studies published over the 20 years (Mennechet et al., 2019). HAdV-C5 is the most widely reported and has the highest seroprevalence globally.

48. In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health and Aged Care (1991-2000) showed an average of about 1,400 reported cases of AdV infection per year over 10 years (Spencer, 2002). From 1 January to 20 May 2023, New South Wales registered 5,724 cases of HAdV infections (NSW Health, 2023). It is important to note that the majority of reported HAdV infections have not been serotyped and that testing for HAdV infections may not be as common in Australia compared to other regions internationally. However, these numbers indicate that HAdVs are present in the Australian environment.

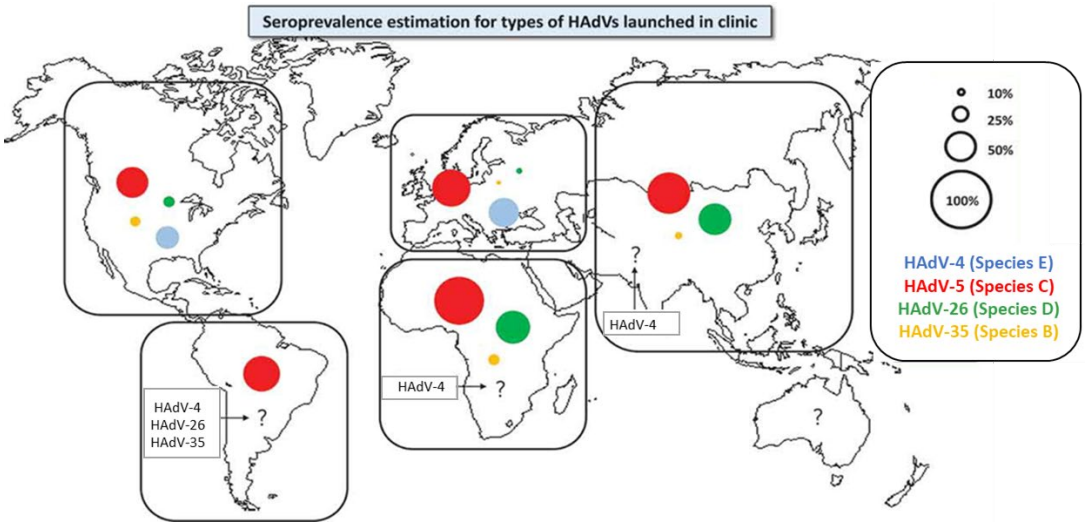

Figure 5. Estimation of seroprevalance for HAdV types used in clinics (adapted from Mennechet, 2019)

3.5.4 Control, environmental stability and decontamination methods

49. 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 off-label in immunocompromised patients, babies 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). Cidofovir is among the most potent of antivirals for DNA viruses. It inhibits viral replication by mimicking the monophosphate form of nucleotides. Its efficacy has been confirmed in all HAdV types. Ribavirin is a broad-spectrum antiviral with a similar mode of action to Cidofovir. However, ribavirin was shown to be active against HAdV-C isolates and has variable activity in other species (Hoeben and Uil, 2013; Waye and Sing, 2010). There are no AdV-specific drugs to treat infection (CDC, 2019a; Waye and Sing, 2010). There is no AdV vaccine approved for use in Australia. In the United States, a live (non-attenuated) AdV vaccine is available to military personnel but not to the public (CDC, 2020).

50. 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). They can survive in treated wastewater and sewage, rivers, oceans, water in swimming pools, drinking water and groundwater (Public Health Agency of Canada, 2014; Takuissu et al., 2024).

51. 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 (Allard and Vantarakis, 2017). 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). 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). Certain types of HAdVs were shown to be stable in surface waters and groundwater at 10°C for at least 160 days (Rigotto et al., 2011). Therefore, AdVs survival time depends on the relative humidity, temperature and the type of surface (Abad et al., 1994).

52. 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). In addition, AdVs can be inactivated by heat, for example 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

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

54. 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.

55. 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). 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

56. 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

57. 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.

58. 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).

59. IFN-α is a key cytokine produced primarily by monocytes/macrophages and can also be synthesized 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).

60. 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).

61. 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.

4.2.3 Toxicity or adverse response associated with the genetic modifications

62. The GM therapeutic is a genetically modified 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).

63. 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 with the IFN-α2b protein have been intramuscular, subcutaneous, intralesional, or intravenous, 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 produced toxicity and mortality. Due to the known species-specificity of interferon, the effects in animals are unlikely to be predictive of those in humans.

64. 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.

65. 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 repeat 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

66. 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 which are highly expressed on the surface of cancer cells.

67. 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

68. 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.

69. 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.

70. 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

71. 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 on the GMO

72. The GM therapeutic has been evaluated in preclinical studies *in vitro* using cancer cell lines and *in vivo* in various animal models.

73. *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).

74. 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).

75. 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).

76. The systemic exposure of the GMO as measured by copies of the 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).

77. 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.

78. 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 studies of the GMO

79. 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	7	One AE reported as a non-serious worsening of lower urinary tract symptoms from one patient.	NCT01162785

No.	Clinical study	No. treated	Adverse events (AE)*	References
	of BCG refractory superficial bladder cancer			(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 refractory or relapsed superficial bladder cancer	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)
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.

80. 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 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.

81. 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.

82. 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. 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 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 the 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 the GMO DNA in urine but this dropped to 6 patients (28.6%) by month 4 day 12.

83. The Phase 3 trial was focusing 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.

84. 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.

85. 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

86. The receiving environment forms part of the context for assessing risks associated with dealings with the GM therapeutic (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 release

87. The GM therapeutic is intended to be administered by experienced urologists in the urology and oncology departments in hospitals.

88. Hospitals are regulated by State and Territory governments and must be accredited to the National Safety and Quality Health Service (NSQHS) Standards to ensure minimum standards for 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.

89. As the GMO is administered to the patients by instillation into the bladder, the principal route by which the GMO may enter the wider environment following administration is via shedding through urine. Another route by which the GMO may enter the wider environment is via accidental spills of the GM therapeutic during or after administration or during transport or storage, or a sharps injury occurring following disposal of the vials or syringes contaminated with the GM therapeutic.

5.2 Related viral species in the receiving environment

90. 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.

91. Adenoviruses belong to 5 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.

92. The prevalence of HAdVs in Australia based on the reported cases and seroprevalence is low, as mentioned in Section 3.5.3.

5.3 Similar genetic material in the environment

93. The balance of an ecosystem could be perturbed by the introduction of new genetic material through horizontal gene transfer or through release of a 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.

94. 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 Relevant Australian and international approvals

6.1 Australian approvals

6.1.1 Approvals by the Regulator

95. The Regulator has not previously approved any licences in relation to this GM therapeutic.

96. Recent approvals of dealings with GM HAdVs by the Regulator are shown in Table 2.

Table 2. Recent licences issued by the Regulator for dealings with GM human adenovirus

Application reference	Title (GMO)	Organisation
DNIR-599	A phase 3, open-label, randomized, parallel group study to evaluate the efficacy and safety of intrapleural administration of adenovirus-delivered interferon alpha-2b (rAd-IFN) in combination with celecoxib and gemcitabine in patients with malignant pleural mesothelioma (GM adenovirus expressing human IFN-α2b)	Medpace Australia Pty Ltd
DIR-177	Clinical trial of genetically modified human adenovirus for bladder cancer treatment (GM adenovirus expressing human GM-CSF)	Novotech (Australia) Pty Limited
DIR-195	Trial of a genetically modified vaccine against devil facial tumour disease in Tasmanian devils (GM adenovirus expressing antigen genes)	University of Tasmania
DIR-213	Clinical trial of a genetically modified human adenovirus for treatment of melanoma (GM adenovirus expressing human CD40L)	Novotech (Australia) Pty Ltd
DIR-214	Trial of a genetically modified (GM) vaccine for the prevention of respiratory disease in horses (GM adenovirus expressing VapA from *Rhodococcus equi*)	University of Queensland

6.1.2 Approvals by other government agencies

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

98. Assessment by the TGA and inclusion on the ARTG are required before a GM therapeutic can be lawfully supplied in Australia.

6.2 International approvals

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

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

Chapter 2 Risk assessment

Section 1 Introduction

101. 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 6). 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.

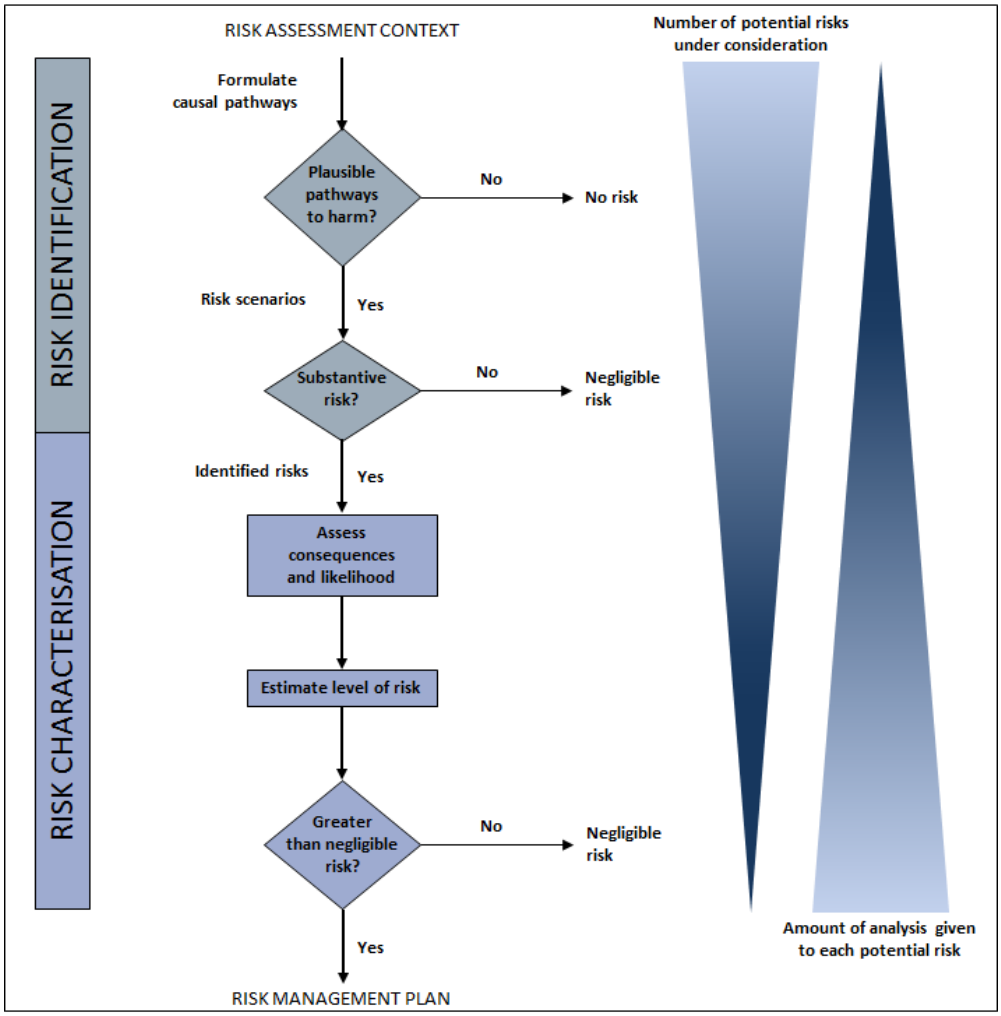

Figure 6. The risk assessment process

102. The Regulator uses several techniques to identify risks, including checklists, brainstorming, 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.

103. 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 plausible causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are called risk scenarios.

104. Risk scenarios are screened to identify substantive risks, which 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 7), i.e. the risk is considered no greater than negligible.

105. 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

106. Postulated risk scenarios are comprised of three components (Figure 7):

I. the source of potential harm (risk source)

II. a plausible causal linkage to potential harm (causal pathway)

III. potential harm to people or the environment.

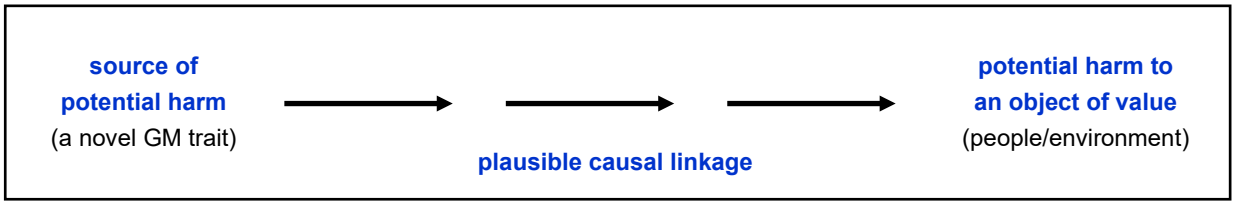

Figure 7. Risk scenario

107. 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

108. The parent organism is a HAdV-C5. Details of pathogenicity and transmissibility of HAdV is discussed in Chapter 1, Section 3.1. Infection is generally the result of inhalation of aerosolised droplets excreted from respiratory or ocular secretions containing the virus, mucosal exposure to the virus, or via faecal-oral transmission. When infecting humans, HAdV-C5 may cause common cold-like symptoms, as well as eye infections or diarrhoea.

109. The specific risk source in this application is the introduced gene in the GM therapeutic. 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.

110. The GM therapeutic formulation also contains several excipients. The excipients are not GMOs and will not be considered in the risk assessment.

2.2 Causal pathway

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

- the proposed dealings, which are the import, transport and disposal of the GMO and possession (including storage) in the course of any of these dealings
- restrictions placed on 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 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 (e.g. tolerance to temperature, UV irradiation and humidity)
- gene transfer by horizontal gene transfer
- practices before and after administration of the GMO
- potential for unauthorised activities.

112. The current assessment focuses on risks posed to people or the environment, including long term persistence of the GMO, which may arise from the import, transport, storage, or disposal of the GM therapeutic, and the possession, supply, or use of the GMO for the purposes of, or in the course of, any of these dealings.

113. The TGA regulates quality, safety, and efficacy of therapeutic goods under the *Therapeutic Goods Act 1989*, as mentioned in Chapter 1, Section 1.1. This includes:

- assessment of patient safety, therapeutic quality and efficacy prior to inclusion on the ARTG
- recommended practices for the transport, storage, and disposal of the GM therapeutic under the *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (NCCTG, 2011)
- requirements for the scheduling, labelling, and packaging under the *Poisons Standard* (Therapeutic Goods Administration, 2023).

114. Use of GMOs is not a dealing under the *Gene Technology Act 2000.* Consequently, the Regulator does not assess risks from the use of GMO therapeutics, such as risks to the intended treatment recipients from the GM therapeutic. Therefore, this assessment focuses primarily on risks posed by accidental exposure of people and other organisms and to the environment from the GMO, and not the intended treatment recipients.

115. As discussed in Chapter 1, Section 3.4, AdVs remain episomal throughout the infection and have not been reported to integrate into the host DNA. Similarly, the vectors derived from these AdVs 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, AdV 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.

116. The Act provides for substantial penalties for unauthorised dealings with GMOs or noncompliance 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.

2.3 Potential harms

117. Potential harms from the GM therapeutic include:

- harms to the health of people or other organisms following accidental exposure to the GMO, including disease or an adverse immune response to the GMO
- the potential for establishment of a novel virus in the environment (discussed in Section 2.2).

2.4 Postulated risk scenarios

118. Three risk scenarios were postulated and screened to identify any substantive risks. These scenarios are summarised in Table 3 and examined in detail in Section 2.4.1.

119. In the context of the activities proposed by the applicant and considering both the short and long term, the risk scenarios did not give rise to any substantive risks.

Table 3. Summary of risk scenarios from the proposed dealings with the GM therapeutic

Risk scenario	Risk source	Causal pathway	Potential harm	Substantive risk?	Reasons
1	GMO	Exposure of people and animals to the GMO via aerosols, fomites, contact with abraded skin or mucous membranes during (a) Import, transport or storage of the GMO (b) Preparation and administration of the GMO (c) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the IFN-α2b protein	Toxicity or adverse immune reactions	No	• The GMO is replication incompetent and will not produce further viral particles to sustain an infection • The dose received through accidental exposure would be far smaller than that intentionally administered. • 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 • Import, transport, storage, and disposal will follow well established procedures.
2	GMO	Exposure of people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ 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	Toxicity/adverse immune reactions; disease in people or animals	No	• 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.

Risk scenario	Risk source	Causal pathway	Potential harm	Substantive risk?	Reasons
		(b) Homologous recombination with AdV ⬇ Formation of other recombinant AdVs as described in Table 4			• 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.
3	GMO	Release of GMO into the environment via accidental spill/unused residues or urine from treated patients (sewerage) ⬇ Exposure to people or animals ⬇ As per Risk Scenario 1-2	Toxicity/adverse immune reactions; disease in people or animals	No	• As discussed in Risk Scenarios 1 and 2. • HAdVs are not known to infect species outside mammals. • GMO cannot replicate inside or outside the host, hence GMO is only available for one infection cycle.

2.4.1 Risk Scenario 1

Risk source	GMO
Causal pathway	Exposure of people and animals to the GMO via aerosols, fomites, contact with abraded skin or mucous membranes during (a) Import, transport or storage of the GMO (b) Preparation and administration of the GMO (c) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the IFN-α2b protein ⬇
Potential harm	Toxicity or adverse immune reactions

Risk source

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

Causal pathway

121. People (other than the intended recipient) and animals could be directly or indirectly exposed to the GMO in several ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO, or contact with urine, or during handling of the GMO via a breakage or leakage of the GMO from its container (e.g. vial/syringe) and ingestion or splashing to the mucous membranes of the eyes, nose and mouth. This exposure could result in infection with the GMO that could lead to ill health. 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 2.1).

Exposure during import, transport and storage of the GMO

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

123. The applicant proposes to import the GMO from overseas in sealed containers with tamper proof seals in secondary packaging. Each unit-dose of the ready-to-use pack contains 4 single-dose vials with absorbent material under the vials (Chapter 1, Section 2.1). When ordered from a clinic, a unit-dose pack that is not repackaged will be distributed directly to medical facilities with a smaller shipper in a bio-hazard bag surrounded by dry ice. This would lower the likelihood of unintended dispersal of the GMO.

124. The GM therapeutic would be classified as a Schedule 4 (prescription only) medicine if approved by the TGA. The *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (NCCTG, 2011) recommends that:

- upon arrival at the wholesaler, packaging should be removed, and stock should be examined for the absence of damage or evidence of tampering. Damaged stock should be quarantined.
- packaging of cold chain medicines should alert the receiver of its contents and that the receiver should place the medicines in appropriate storage facilities as soon as possible.
- wholesalers should ensure that persons supplied with medicines are authorised appropriately under State or Territory legislation to be supplied with those medicines.

125. Additionally, storage, handling and transport would be in accordance with both the *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (NCCTG, 2011) and the *World Health Organization's Good storage and distribution practices for medical products* (World Health Organization, 2020). These guidelines require that:

- written procedures for dealing with spillage of items of special hazard are available and training is provided to responsible staff.
- in the event of a spill, the spill should be cleaned up promptly and rendered safe as quickly as practicable in accordance with the material safety data sheet (MSDS).
- spills kits should be conveniently located within the storage area.
- access to the medical product is restricted to individuals with the appropriate training.

126. These practices would minimise the likelihood of damaged and leaking stock going unnoticed and ensure the GM therapeutic is being handled by individuals who are trained in procedures required to decontaminate a spill, thus minimising the likelihood of unintended dispersal of the GMO.

127. Should the GMO be unintentionally released, it is highly unlikely to infect and result in disease in people and animals as it is replication incompetent. Further, the presence of animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

128. Decontamination agents and methods, suitable for HAdV vectors would be used in accordance with local requirements and legislation, for decontamination and disinfection measures after administration of the GMO or in the case of accidental spills during the commercial supply of the GMO.

129. The import, transport and storage procedures discussed above meet the requirements of *the Regulator's Guidelines for the Transport, Storage and Disposal of GMOs* and would mitigate exposure due to spills of the GMO during these dealings.

Exposure during preparation and administration of the GMO

130. As discussed in Chapter 1, Section 5.1, the GM therapeutic is intended to be administered through intravesical installation performed by trained healthcare professionals at urology and oncology departments in hospitals. 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.

131. The GMO would be prepared and administered by authorised, experienced and trained health professionals. All personnel working in settings where healthcare is provided 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 (National Health and Medical Research Council, 2019). This includes hand hygiene, sharps safety, wearing of appropriate personal protective equipment (including protective gown or laboratory coat, gloves, and safety glasses and surgical mask), and covering cuts and abrasions on exposed skin with water-proof dressings. Compliance with these behavioural practices at clinical sites will limit unintended exposure of people to the GMO.

Exposure during disposal of the GMO and any contaminated waste

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

- a storage/distribution centre where stocks of the GM therapeutic is held
- locations where the GM therapeutic is administered.

133. There is also potential for family members or caregivers of patients to be exposed to the GMO or RCA in urine after administration of the GM therapeutic.

134. The *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (NCCTG, 2011) requires:

- specific training for personnel handling medicines that pose a high risk to personnel if package integrity is breached or spillage occurs
- waste medicines be collected and destroyed by a person who is licensed or permitted to do so under relevant State or Territory legislation
- medicines for destruction be enclosed in sealed packaging or in a container.

135. As discussed in Chapter 1, Section 2.1, at the sites of administration, unused vials of the GMO and used vials with residue GMO, syringes, vented vial adapters, any disposable instruments and waste contaminated with the GMO would be treated as clinical waste and disposed of in accordance with the waste disposal methods approved by the States and Territories. Also, patients and their caregivers would be instructed to properly prepare for decontamination of voided urine before urinating. Adherence with these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

136. 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.

Potential harm

137. If people or animals 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 or animals could experience an adverse immune response or disease.

138. 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 inoculum and the protein expressed would be unable to accumulate 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.

139. 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.

140. 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. However, as discussed in Chapter 1, Section 4.3.1, a very low level of RCA may 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).

141. 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 would be implemented for commercial release of the GMO in Australia. This would reduce the chance of immunosuppressed persons coming into contact with the GMO, becoming infected and potentially developing severe disease. The TGA is responsible for reviewing any instructions for use of the GM therapeutic, including warnings and precautions.

Conclusion

142. The potential for an unintentional exposure of people and animals to the GMO during transport, storage, and disposal resulting in toxicity or adverse immune reactions is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

2.4.2 Risk Scenario 2

Risk source	GMO
Causal pathway	Exposure of people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ 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
Potential harm	Toxicity/adverse immune reactions and/or disease in people or animals

Risk source

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

Causal pathway

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

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

145. 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 over time and the genome of HAdV-C is highly conserved with over 95% nucleotide identity (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., 2023; Lichtenstein and Wold, 2004). Thus, the likelihood that a person with 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.

146. 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 unlikely that the GMO could replicate in animals as a result of complementation.

Homologous recombination with AdV

147. Recombination is common among circulating wild-type AdVs in nature. It is seen as a key driver for AdV evolution and viruses in general. Similar to complementation, homologous recombination also requires the person or animals exposed to the GMO to be infected with a wild-type AdV at the same time. Exposure to the GMO by people or animals via inhalation or contact with mucus tissue is plausible but unlikely as detailed in Risk Scenario 1. Therefore, the likelihood of the GMO to be present simultaneously with a resident Adv in the same cell is highly unlikely.

148. AdV infections are common in humans and are present in other species. Therefore, there is a potential that a person or animal exposed to the GMO is co-infected with AdV. As mentioned in Chapter 1, Section 3.4, homologous recombination is generally restricted to members of the same species but 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 of 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 result in the generation of different GM recombinants. These GM recombinants are described in Table 4.

Table 4. Plausible theoretical recombinants of GMO and wild-type 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 with *hIFN-α2b* gene cassette	• Replication competent GMO that is still less immune evasive than WT • Replication incompetent AdV expressing hIFN-α2b protein	Unlikely
Gene sequences for immune-evasion properties between • GMO • WT AdV	• Replication incompetent GMO with functional gene sequences for immune-evasion properties • Replication competent AdV	• Replication incompetent GMO with modifed immune-evasive properties • Replication competent AdV without immune-evasive properties (a wild type adenovirus unable to	Unlikely

Recombinant region	Resultant recombinant	Outcome	Likelihood
	without functional gene sequences for immune-evasion properties	evade the host immune system)	
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

149. 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 X1 region, 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.

150. 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.

151. 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.

152. 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

153. 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.

154. 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, 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

155. The exposure of people or animals to a GMO which has acquired the gene sequences 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.

2.4.3 Risk Scenario 3

Risk source	GMO
Causal pathway	Release of GMO into the environment via accidental spill/unused residues or urine from treated patients (sewerage) ⬇ Exposure to people or animals ⬇ As per scenario 1-2
Potential harm	Toxicity/adverse immune reactions and/or disease in people or animals

Risk Source

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

Causal Pathway

157. 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. 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 toxicity or adverse immune reactions and/or disease in people and animals.

158. As discussed in Risk Scenario 1, the 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 the GMO being released into the environment. 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. The applicant has proposed that such urine treatment would also occur if the GM therapeutic was approved in Australia. 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.

159. In the event of a spill 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). Accidental spillage or urine that is not decontaminated could result in the release of the GMO and/or recombinant viruses into the environment. 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.

160. 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.

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

162. Similar to the parent organism, the GMO could persist 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. Further, accidental spill/unused vials if not decontaminated appropriately could result in the survival of the GMO and their presence in waste in landfill, or the sewerage and subsequently GMO dispersal in the aquatic environment. The impact of survival of the GMO in landfill or an aquatic environment is likely to be very low as the GMO is replication incompetent and would eventually degrade.

163. If the GMO is released into sewage water, it will be markedly diluted due to the small quantity of GMO present in a large volume of liquid waste or water, and it is replication-incompetent. Therefore, it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source.

164. Complementation and recombination could occur in the cells of co-infected animals in a similar way to the host as discussed in Risk Scenario 2.

Potential harm

165. Potential harms in this risk scenario would be the same as considered in the risk scenario 1 and 2 presented above.

Conclusion

166. The potential of 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. Therefore, it does not warrant further assessment

Section 3 Uncertainty

167. 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.

168. 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 estimate the level of risk, the Regulator will take this uncertainty into account in making decisions.

169. Uncertainty can also arise from a lack of experience with the GM therapeutic itself. For DIR-217, 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 clinical use by the FDA (Chapter 1, Section 6.2) and overall, treatment with the GM therapeutic was considered to be safe (Steinmetz et al., 2024).

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

171. Post release review (PRR; Chapter 3, Section 4) will be used to address uncertainty regarding future changes to knowledge about the GMO. This is typically used for commercial releases of GMOs, which generally do not have fixed duration.

Section 4 Risk evaluation

172. 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.

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

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

174. Three risk scenarios were postulated whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people and animals can be accidentally 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.

175. 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.

176. 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 the risk 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
- exposure to the GM therapeutic would be minimised by well-established clinical, import, transport, storage, and disposal procedures
- the dose received through accidental exposure would be far smaller than that administered
- the likelihood of severe disease as a result of complementation and recombination of GMO with other AdVs is highly unlikely and the impact of persistence of the small numbers of GMO in the Australian aquatic and terrestrial environment is negligible.

177. Therefore, any risks to the health and safety of people, or the environment, from the proposed commercial supply of the GM therapeutic 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.

Chapter 3 Risk management plan

Section 1 Background

178. 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 licence conditions.

179. 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 can be managed in a way that protects the health and safety of people and the environment.

180. All licences are subject to three 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 must also be reported to the Regulator.

181. 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 and to manage risk to people or the environment. 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

182. The risk assessment of the risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed supply of the GM therapeutic. These risk scenarios were considered in the context of the proposed receiving environment and the Australia-wide release. The risk evaluation concluded that no specific risk treatment measures are required to treat these negligible risks. However, to maintain the risk context of minimising the amount of the GMO entering the sewerage, a requirement has been included in the 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. General risk management measures are discussed below.

Section 3 General risk management

183. All DIR licences issued by the Regulator contain several conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- testing methodology
- identification of the persons or classes of persons covered by the licence
- reporting structures
- access for the purpose of monitoring for compliance.

3.1 Applicant suitability

184. 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.

185. On the basis of information submitted by the applicant and records held by the OGTR, the Regulator considers Ferring suitable to hold a licence. The licence includes a requirement for the licence holder to inform the Regulator of any circumstances that would affect their suitability.

3.2 Testing methodology

186. Ferring is required to provide a method to the Regulator for the reliable detection of the GMO, and the presence of the introduced genetic materials in a recipient organism. This is required prior to conducting any dealings with the GMO.

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

187. Any person, including the licence holder, could conduct any permitted dealing with the GMO.

3.4 Reporting requirements

188. The licence obliges 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 release.

189. The licence holder is also obliged to submit an Annual Report containing any information required by the licence.

190. There are also provisions that enable the Regulator to obtain information from the licence holder relating to the progress of the commercial release (see Section 4, below).

3.5 Monitoring for compliance

191. 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 the Regulator, inspectors or other person authorised by the Regulator, to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

192. 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 Post release review

193. Regulation 10 requires the Regulator to consider the short and the long term when assessing risks. The Regulator takes account of the likelihood and impact of an adverse outcome over the

foreseeable future and does not disregard a risk on the basis that an adverse outcome might only occur in the longer term. However, as with any predictive process, accuracy is often greater in the shorter rather than longer term.

194. The Regulator has imposed conditions that require ongoing oversight in order to provide feedback on the findings of the RARMP and ensure the outcomes remain valid for future findings or changes in circumstances. This ongoing oversight will be achieved through post release review (PRR) activities. The three components of PRR are:

- adverse effects reporting system (Section 4.1)
- requirement to monitor specific indicators of harm (Section 4.2)
- review of the RARMP (Section 4.3).

195. The outcomes of these PRR activities may result in no change to the licence or could result in the variation, cancellation or suspension of the licence.

4.1 Adverse effects reporting systems

196. Any member of the public can report adverse experiences/effects resulting from a GMO to the OGTR through the Free-call number (1800 181 030), mail (MDP 54 – GPO Box 9848, Canberra ACT 2601) or via email to the OGTR inbox (ogtr@health.gov.au). Reports can be made at any time on any DIR licence. Credible information would form the basis of further investigation and may be used to inform a review of a RARMP (see Section 4.3 below) as well as the risk assessment of future applications involving similar GMOs.

4.2 Requirement to monitor specific indicators of harm

197. Collection of additional specific information on an intentional release provides a mechanism for 'closing the loop' in the risk analysis process and for verifying findings of the RARMP, by monitoring the specific indicators of harm that have been identified in the risk assessment.

198. The term 'specific indicators of harm' does not mean that it is expected that harm would necessarily occur if a licence was issued. Instead, it refers to measurement endpoints which are expected to change should the authorised dealings result in harm. The licence holder is required to monitor these specific indicators of harm as mandated by the licence.

199. The triggers for this component of PRR may include risk estimates greater than negligible or significant uncertainty in the risk assessment.

200. The characterisation of the risk scenarios discussed in Chapter 2 did not identify any risks greater than negligible. Therefore, they were not considered substantive risks that warranted further detailed assessment. Uncertainty is considered to be low. No specific indicators of harm have been identified in this RARMP for application DIR 217. However, specific indicators of harm may also be identified during later stages, through either of the other components of PRR.

201. Conditions have been included in the licence to allow the Regulator to request further information from the licence holder about any matter to do with the progress of the release, including research to verify predictions of the risk assessment.

4.3 Review of the RARMP

202. The third component of PRR is the review of RARMPs after a commercial/general release licence is issued. Such a review would consider any relevant new information, including any changes in the context of the release, to determine if the findings of the RARMP remained current. The timing of the review would be determined on a case-by-case basis and may be triggered by findings from either of the other components of PRR or be undertaken after the authorised dealings have been conducted for some time. If the review findings justified either an increase or decrease in the initial risk

estimate(s) or identified new risks to people or to the environment that require management, this could lead to changes to the risk management plan and licence conditions.

Section 5 Conclusions of the RARMP

203. The risk assessment concludes that the proposed commercial release of this GM therapeutic poses negligible risks to the health and safety of people or the environment as a result of gene technology.

204. The risk management plan concludes that these negligible risks do not require specific risk treatment measures. However, general conditions are imposed to ensure that there is ongoing oversight of the release.

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Appendix A: Summary of submissions on RARMP preparation from experts, agencies and authorities

The Regulator received several submissions from prescribed experts, agencies, and authorities[4] on matters relevant to preparation of the RARMP. All issues raised in submissions relating to risks to the health and safety of people and the environment were considered. These issues, and where they are addressed in the consultation RARMP, are summarised below.

Submission	Summary of issues raised	Comment
1	Agrees that the following should be included in the RARMP: • the potential for the GMO to be persistent in the environment • the potential for harm due to exposure of people or animals to the GMO • the potential for recombination with wild type virus resulting in novel human adenovirus with altered characteristics.	Noted. The risks for the GMO to be persistent in the environment are discussed in Chapter 2, Section 2.4.3 (Risk Scenario 3). The potential for accidental exposure to people or animals leading to harm is discussed in Chapter 2, Section 2.4.1 (Risk scenario 1). The potential for reversion and recombination resulting in harm is discussed in Chapter 2, Section 2.4.2 (Risk Scenario 2).
	Advises that the Regulator should further consider the effectiveness of the decontamination process following patient urination.	Discussion of urination is included in Chapter 2, Section 2.4.3 (Risk Scenario 3).
2	Has no comment in relation to the application.	Noted.
3	Does not have any advice or comments.	Noted.
4	Does not have specific advice on risks to the health and safety of people and the environment.	Noted.

[4] Prescribed experts, agencies and authorities include GTTAC, State and Territory Governments, relevant local governments, Australian government agencies and the Minister for the Environment.

Appendix B: Summary of submissions from prescribed experts, agencies and authorities on the consultation RARMP

The Regulator received a number of submissions from prescribed experts, agencies and authorities on the consultation RARMP. All issues raised in submissions that related to risks to the health and safety of people and the environment were considered in the context of the currently available scientific evidence and were used in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence. Advice received is summarised below.

Submission	Summary of issues raised	Comment
1	No advice or comments on the RARMP.	Noted.
2	Agrees that the risk assessment identifies all plausible risk scenarios by which the proposed dealings could potentially give rise to risks relating to the health and safety of people or the environment.	Noted.
	Recommends that the information on the prevalence and serotyping of HAdV in Australia be clarified.	Text in Paragraph 145 under Risk Scenario 2 has been amended for clarification.
	Recommends that clarity be sought about the testing method from the applicant.	Noted. The Regulator only requires the licence holder to provide a testing method that can reliably detect the GMO without being prescriptive. The text in Paragraph 186 and the relevant licence condition are considered suitable.
	Recommends that the Regulator consider providing advice to the TGA on the matter of potential risks to personnel involved with the commercial supply of this GMO, including the low potential for integration by adenovirus.	Noted.
	Agrees with the overall conclusion of the RARMP.	Noted.
3	Overall, accepts that the application has negligible risks to the health and safety of people and the environment. Satisfied that the measures taken to manage the short- and long-term risks from the proposal are adequate.	Noted.
4	Agree with the conclusion that risks to the health and safety of people or the environment from the proposed dealings are negligible, given that: - the adenoviral vector-based therapeutic is replication incompetent, susceptible to clearance by the host immune system and unlikely to infect humans and cause disease; and	Noted. Please note that administration of the GM therapeutic is not regulated under gene technology legislation and is not considered in this RARMP. It considers risks to people and the environment from import, transport, storage and disposal of the therapeutic as part of its commercial supply.

Submission	Summary of issues raised	Comment
	- treatment will be administered by experienced urologists in the urology and oncology departments in hospitals; and - transport, storage, and disposal will follow established procedures. Notes the RARMP considers relevant risks, uncertainty is low, and post-release review ensures ongoing oversight.	
5	Supports the Regulator's conclusion that the proposed dealings pose negligible risk of harm to human health and safety and the environment. Agreed with the inclusion of the post-release review as a licence condition to ensure continued oversight of the supply of this therapeutic and to verify the RARMP's findings, as this application is considered to be the first application of a GM therapeutic in Australia.	Noted. The Regulator has previously issued many licences for dealings with GM therapeutics in Australia, either as clinical trials or for commercial supply. Post-release review is a key part of general risk management measures included in all commercial releases.
6	Satisfied with the RARMP. Notes that although the TGA is the main evaluator of this product, the Regulator specifying that there will be a post-release review of any untoward effects is a good proposal as the virus used in the treatment may possibly migrate into unpredicted associations.	Noted. Post-release review is a key part of general risk management measures included in all commercial releases.

Appendix C: Summary of submissions from the public on the consultation RARMP

The Regulator received 2 submissions from the public on the consultation RARMP. The issues raised in the submissions are summarised in the table below. All issues that related to risks to the health and safety of people and the environment were considered in the context of currently available scientific evidence in finalising the RARMP that formed the basis of the Regulator's decision to issue the licence.

Submission	Summary of issues raised	Comment
1	Provides suggestions regarding improving future wording/documentation regarding the role of the licence holder and the role of the therapy deliverer (i.e. hospital) in terms of workforce, infrastructure, reporting and other OGTR requirements.	Noted.
	Points out that potential therapy providers want to deliver such therapies but are often unaware of the regulatory requirements regarding GMOs, and this RARMP does not include such information for potential providers in understanding such requirements. Suggests that making these requirements clear would expedite patient access.	OGTR's website has information about the regulatory requirements for GMOs under the gene technology scheme, including GMOs used for therapies. Licence holders and therapy providers are required to comply with the conditions of the licence specific to their GMO(s). The use/administration of this GM therapeutic is regulated by the Therapeutic Goods Administration (TGA). Furthermore, clinical practice and patient access is outside the remit of the Regulator. It is the responsibility of the users of GM therapeutics to be aware of, and comply with, any other requirements/restrictions/guidelines that apply.
	Points out that a nationally agreed and consistent approach regarding licence holder general and specific obligations (e.g. AE reporting, monitor harm indicators, annual report) needs to be in place. Suggests that the RARMP should provide such information to better inform a nationally agreed and consistent approach to meeting OGTR requirements.	
	States that the RARMP has no mention of Advanced Pharmacy Australia guidelines that are relevant to pharmacists at an administering site who would be responsible for dealings with the therapy. Suggests including information about the role of pharmacists in supporting delivery of this therapy. Considers that the current wording implies 'anyone' can order and handle the therapy, is inaccurate and misleading.	
	Also states that there is no reference to workforce training or hospital infrastructure to address OGTR compliance and peak body requirements, and suggests inclusion of such information for the licence holder or as information for potential providers.	
	Concerns about funding mechanisms and impact on sites for therapy delivery and therefore patient access to the therapy. Suggests including a reference to the 'funding mechanisms' in the RARMP to manage risks such as backlash from the	Noted. Funding issues are outside the legislative responsibility of the Regulator. These are matters for States and Territories, and industry.

Submission	Summary of issues raised	Comment
	private sector resulting in negative media interest.	
2	Human health, safety and the environment should be protected as much as possible.	Noted. The RARMP prepared for this application concludes that there is negligible risk to people and the environment from the dealings with the GMO.