



Australian Government

Department of Health

Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan for

DIR 180

Commercial supply of a genetically modified COVID-19 vaccine

Applicant: AstraZeneca Pty Ltd

February 2021

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Summary of the Risk Assessment and Risk Management Plan for Licence Application DIR 180

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for application (DIR 180) for the import, transport, storage and disposal of a genetically modified (GM) COVID-19 vaccine, as part of its commercial supply as a human vaccine.

Before the GM vaccine can be used, AstraZeneca must also obtain regulatory approval from the Therapeutic Goods Administration (TGA). Therapeutic goods for sale in Australia must be included in the Australian Register of Therapeutic Goods (ARTG) under the *Therapeutic Goods Act 1989*. The TGA would assess patient safety and the quality and efficacy of the vaccine prior to including the GM vaccine on the ARTG. In addition, approval from the Department of Agriculture, Water and the Environment will be required for import of the GM vaccine.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed supply of the GM vaccine poses negligible risks to human health and safety and the environment and no specific risk treatment measures are imposed. However, general licence conditions have been imposed to ensure that there is ongoing oversight of the proposed supply.

The application

Application number	DIR-180
Applicant	AstraZeneca Pty Ltd
Project title	Commercial supply of a genetically modified COVID-19 vaccine ¹
Parent organism	Chimpanzee adenovirus Y25
Introduced gene and modified trait	<ul style="list-style-type: none"> • Deletion of: <ul style="list-style-type: none"> ○ E1 gene (renders virus unable to multiply) ○ E3 gene (increases immune response to virus and virus production during manufacture) • Partial substitution of E4 gene with the corresponding gene from the human adenovirus 5 (improves virus yield during manufacture) • Insertion of a gene encoding codon-optimised full length SARS-CoV-2 spike protein (expresses spike protein)
Previous clinical trials	Phase 1/2 clinical trial with the GM vaccine ChAdOx1-S [recombinant] (also known as AZD1222, ChAdOx1 nCoV-19) was conducted and completed in the United Kingdom (UK) to test the safety of the vaccine in adults aged 18-55 years.
Current approvals	<ul style="list-style-type: none"> • Clinical trials with the GM vaccine ChAdOx1-S [recombinant] (also known as AZD1222, ChAdOx1 nCoV-19) are approved and are currently ongoing in several overseas jurisdictions including the UK, the United States (US),

¹ The title of the licence application submitted by AstraZeneca is “Commercial release of a COVID-19 vaccine AstraZeneca to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)”.

	<p>Brazil, South Africa, Argentina, Chile, Colombia, Japan, Peru and the Russian Federation.</p> <ul style="list-style-type: none"> • The GM vaccine may be manufactured in Australia under a licence for Dealings Not involving Intentional Release (DNIR) of a GMO into the environment (DNIR-630 and DNIR-632) or imported under a Notifiable Low Risk Dealing authorisation. • The GM vaccine is currently approved for emergency use in several countries including the UK, Argentina, Brazil, El Salvador, India, Dominican Republic, Mexico, Morocco and Pakistan. • The GM vaccine has been approved for commercial use in the European Union.
Proposed locations	Australia-wide
Primary purpose	Commercial supply of the GM COVID-19 vaccine

Risk assessment

The risk assessment concluded that risks to the health and safety of people or the environment from the proposed supply, either in the short or long term, are negligible. No specific risk treatment measures are required to manage these negligible risks.

The current assessment focused on risks posed to people other than the intended vaccine recipient and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO. The risk assessment process considered how the genetic modification and activities conducted with the GM vaccine in the context of import, transport, storage and disposal might lead to harm to people or the environment. Risks were 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 included: whether people and animals can be exposed to the GMO and whether there is a potential for the GMO to recombine with other similar viruses or to get genes from those viruses. The potential for the GMO to be released into the environment and its effects was also considered.

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

- The GMO is replication incompetent which will prevent it from multiplying in other cells;
- The GMO would be restricted to the site of injection and/or draining lymph nodes and would not be shed from the vaccine recipients;
- The likelihood of complementation and recombination of GMO with other adenoviruses is very low;
- The GMO does not cause disease in humans and other organisms other than great apes;
- The likelihood of accidental exposure to the GMO in people not being vaccinated would be minimised due to implementation of well-established import, transport, storage and disposal 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 activities can be managed so that people and the environment are protected by imposing general conditions to ensure that there is ongoing oversight of the vaccine 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 COVID-19 vaccine and to allow the collection of ongoing information to verify the findings of the RARMP. The licence also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects from activities with the vaccine.

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Abbreviations

AICIS	Australian Industrial Chemicals Introduction Scheme
AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARTG	Australian Register of Therapeutic Goods
BAC	Bacterial artificial chromosome
CAR	Coxsackie and adenovirus receptor
ChAd	Chimpanzee adenovirus
ChAdOx1	Chimpanzee adenovirus type Oxford University 1
COVID-19	Coronavirus disease 2019
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
FSANZ	Food Standards Australia New Zealand
g	gram
GM	Genetically modified
GMO	Genetically modified organism
GTTAC	Gene Technology Technical Advisory Committee
HAdV	Human adenovirus
HGT	Horizontal gene transfer
IATA	International Air Transport Association
IM	Intramuscular
kb	Kilobase pair of DNA
ml	Milli litre
NSW	New South Wales
OGTR	Office of the Gene Technology Regulator
Orf	Open reading frame
PCR	Polymerase chain reaction
QLD	Queensland
RARMP	Risk Assessment and Risk Management Plan
RNA	Ribonucleic acid
S	Spike
SAdV	Simian adenovirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
the Act	The <i>Gene Technology Act 2000</i>
the Regulations	The Gene Technology Regulations 2001

the Regulator	The Gene Technology Regulator
tPA	Tissue plasminogen activator
UK	United Kingdom
USA	United States of America
WA	Western Australia
WHO	World Health Organization

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.
2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia’s national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.
3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.
4. The *Risk Analysis Framework* (RAF) (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator ([OGTR website](#)).
5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Risks to the health and safety of people or the environment posed by the proposed supply were assessed within this context. Chapter 1 provides the specific information for establishing the risk assessment context for this application.

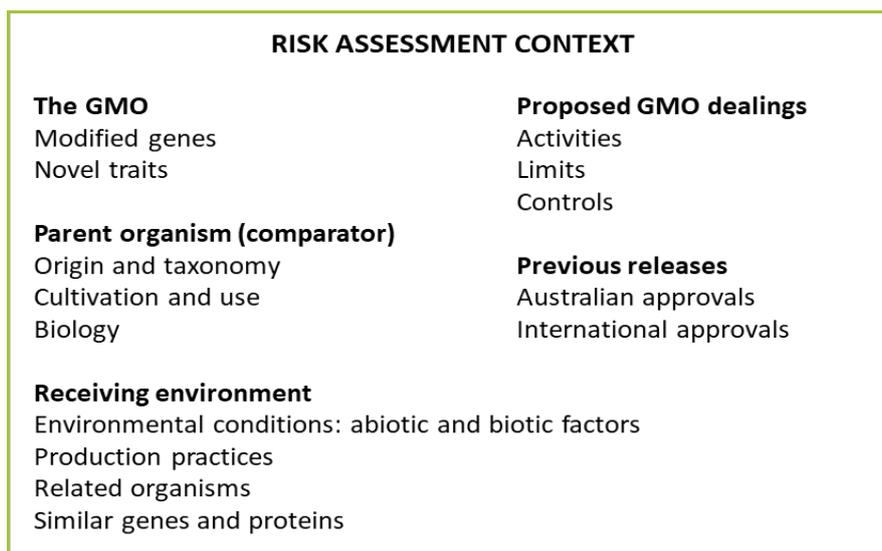


Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. This application did 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 or 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. Under Section 52 of the Act the Regulator was required to conduct a second round of consultation, to seek comment on the RARMP from the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities or agencies prescribed in the Regulations, and the Minister for the Environment, as well as the public. A summary of the advice from the prescribed experts, agencies and authorities in the second round of consultation, and how it was taken into account, is presented in Appendix B. Forty-four 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, Water and the Environment (DAWE).

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

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

11. 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 vaccines are specified through the *Australian Code of good wholesaling practice for medicines in schedules 2, 3, 4 & 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.

12. To avoid duplication of regulatory oversight, risks that have been considered by other regulatory agencies would not be re-assessed by the Regulator.

13. For the commercial supply of a GM COVID-19 vaccine, 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 conducting these activities and risks from persistence of the GMOs in the environment.

Section 2 The proposed dealings

14. SARS-CoV-2 is a novel coronavirus discovered in December 2019 in Wuhan, Hubei province of China and is the cause of the COVID-19 disease. As this virus quickly spread around the world, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern (PHEIC) on the 30th January 2020 and ultimately a pandemic on 11th March 2020 (WHO - Timeline of WHO's response to COVID-19, 2020).

15. The most common symptoms of COVID-19 are fever, tiredness and a dry cough, although some patients develop aches and pains, nasal congestion, runny nose, sore throat or diarrhoea. Symptoms are usually mild with gradual onset and about 80% of infected people recover without specific treatment. However, COVID-19 can cause complications such as severe pneumonia, acute respiratory distress syndrome, and multiple organ failure and in some cases, death. Complications are particularly severe in older patients and others with pre-existing respiratory or cardiovascular conditions. There is currently one COVID-19 vaccine available for general use in Australia but as of 26th January 2021, 63 candidate vaccines are in clinical evaluation around the world (WHO -Draft landscape of COVID-19 candidate vaccine, 2020). These vaccines are based on a variety of platforms such as lipid nanoparticles mRNA, DNA, adjuvant protein, inactivated virus particles and non-replicating viral vectors.

16. AstraZeneca Pty Ltd (AstraZeneca) is seeking authorisation of the commercial supply of a genetically modified (GM) COVID-19 vaccine (ChAdOx1-S [recombinant], also known as AZD1222 and ChAdOx1 nCoV19) to occur Australia-wide.

17. The proposed vaccine is to prevent coronavirus disease - 2019 (COVID-19) caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals.

18. For the ongoing commercial supply of the GM vaccine, the dealings assessed by the Regulator are:

- (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

19. The GM vaccine would be distributed to a variety of facilities which offer vaccination services in all Australian States and Territories. The GM vaccine would be administered by intramuscular injection.

20. The vaccine would be supplied as a multi-dose vial with up to 10 doses per vial (volume up to 5 ml). These vials will be packed into cartons followed by packaging into shipping boxes for distribution.

21. The GM vaccine may be manufactured overseas, in Australia or a combination of both to meet the target supply. An import permit from the DAWE would be required for the vaccine manufactured overseas.

22. The storage and handling of both imported and Australian manufactured GM vaccine would be in accordance with the *Australian Code of Good Wholesaling Practice for Medicines in schedules 2, 3, 4 and 8* (TGA, 2011) and the WHO *Good distribution practices for pharmaceutical products* (WHO, 2010). Further, the Australian manufactured GM vaccine is subject to the storage and transport requirements of the DNIR licence approved by the Regulator (DNIR-632).

23. The transport within Australia (i.e., distribution to vaccination centres) for both imported and Australian manufactured GM vaccine would be conducted by a commercial courier company experienced in the transportation of pharmaceutical products such as vaccines.

24. Storage of the GM vaccine at vaccination centres and other facilities will be conducted according to the National Vaccine Storage Guidelines (Department of Health, 2019) and the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2020) which includes maintenance of the 'cold chain' and restriction of access to pharmacy and other authorised personnel.

25. The GM vaccine would be administered as an intramuscular injection at vaccination centres. Following administration, all residual vaccine and associated waste which has come in to contact with GM vaccine (such as syringes and swabs) will be discarded into clinical and related waste. Similarly, unused expired vaccine would be disposed of at vaccination centres or storage facilities in accordance

with the relevant State and Territory legislation procedures for clinical/medical waste disposal methods such as high temperature incineration.

Section 3 Parent organism

26. The GM vaccine contains a chimpanzee adenovirus type Oxford University 1 (ChAdOx1) vaccine vector which was derived from modified chimpanzee adenovirus isolate Y25 (ChAd Y25). ChAd is a member of the genus *Mastadenovirus* in the *Adenoviridae* family. Adenoviruses (AdVs) are classified as Risk Group 2 microorganisms (Standards Australia/New Zealand, 2010). The characteristics of the parent organism provided a baseline for comparing the potential for harm from dealings with the GM vaccine. As such, the relevant biological properties of ChAd Y25 are discussed here.

27. Human adenoviruses (HAdVs) are categorised into seven species A to G based on their serology, sequence homology, serum neutralisation, hemagglutination properties and genome sequence (Ismail et al., 2018; Lange et al., 2019; Bots and Hoeben, 2020). Simian adenoviruses (SAdVs) are isolated from great apes (chimpanzees, bonobos and gorillas) and are found to be generally similar to HAdVs. Therefore, SAdVs have been grouped within the HAdV species B, C, E and G (Dicks et al., 2012; Lange et al., 2019).

28. HAdV species E has only one member isolated from humans i.e., HAdV-4 (Dicks et al., 2012; Gray and Erdman, 2018; Lion, 2019) but includes several ChAds which are being evaluated for use as vaccines (Dicks et al., 2012). As there is limited information available on ChAds, much of the parent organism information has been based on HAdVs as they are closely related.

3.1 Pathology

29. ChAd Y25 is classified into HAdV species E and is a principal cause of mild respiratory tract infections in the great apes (Lange et al., 2019). ChAd Y25 is also known to cause gastrointestinal tract and eye infections in great apes.

30. ChAds are not isolated from humans but neutralising antibodies to ChAds have been detected in people (Xiang et al., 2006). The detection of antibodies against ChAd and SAdVs in the general population indicates prior exposure to chimpanzees or may be due to the presence of cross-reactive HAdV antibodies (Xiang et al., 2006; Hoppe et al., 2015). However, people exposed to ChAd have not developed symptoms (Xiang et al., 2006), therefore, ChAds are not considered to be the cause of disease in humans.

31. In contrast, HAdVs are common pathogens of humans and cause a wide range of illnesses such as the 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) (Public Health Agency of Canada, 2014; CDC - Adenoviruses, 2019).

32. HAdV infection is generally mild and self-limiting. Overall, HAdV infections are responsible for about 2-5% of all respiratory infections in humans (Allard and Vantarakis, 2017). HAdV species E are the most common cause of human respiratory diseases and eye diseases (Ghebremedhin, 2014; Ismail et al., 2018).

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

3.2 Structure and genomic organisation

34. AdVs are non-enveloped, double-stranded DNA viruses with an icosahedral surface shell (capsid) and a core that contains DNA. The genome of AdVs has approximately 30-35 kilobases (kb) which includes 30-40 genes (Lasaro and Ertl, 2009; Charman et al., 2019). The genome is flanked by inverted terminal repeats (ITRs).

35. HAdVs and ChAds have a similar genome organisation and sequence similarity (Roy et al., 2004) with the exception of some variations in the coding sequences located in the E3 gene.

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

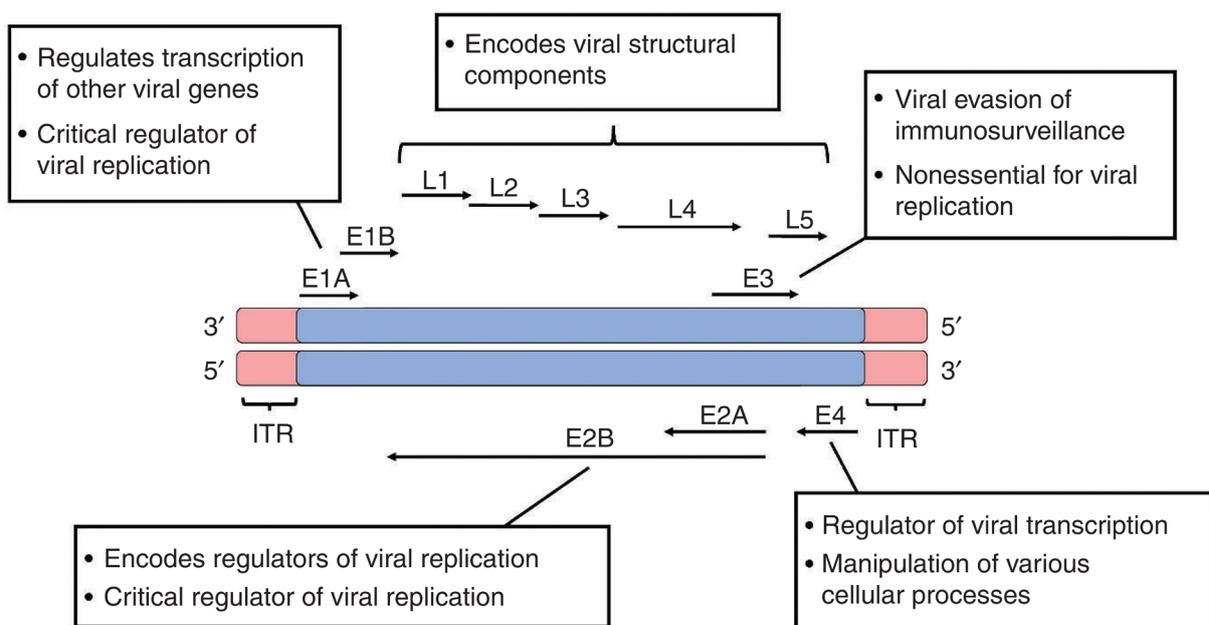


Figure 2: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).

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

38. The E2 gene is sub-divided into E2A and E2B that encode E2 proteins which are mainly involved in viral DNA replication and transcription of late genes (Roy et al., 2004; Saha and Parks, 2017). The E3 gene encodes viral proteins that destabilize host immune responses. The E4 gene modulates cellular function and assists with viral DNA replication and RNA processing.

3.3 Viral infection and replication

39. AdVs can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. AdVs most frequently infect epithelia of the upper or lower respiratory tract, eyes, gastrointestinal and urinary tract tissues.

40. HAdV species C and E use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins as the main receptor to gain entry to a variety of different cell types (Zhang and Bergelson, 2005; Lasaro and Ertl, 2009; Morris et al., 2016; Bots and Hoeben, 2020). Similarly, ChAds also use the CAR protein for entry into the host cells (Morris et al., 2016; Bots and Hoeben, 2020).

41. The replication of AdVs takes place in the nucleus of the host cell and uses the host cell nuclear machinery to make copies of itself (Figure 3). Briefly, the AdV attaches to the receptors present on the cell membrane leading to internalisation of the virus by endosomal uptake. The virus is then uncoated resulting in the release of viral particles into the cytoplasm. The viral genome is transported into the nucleus where the transcription occurs (described above in para 37 and 38; (Charman et al., 2019)). The viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made. The new virus particles are then assembled. Finally, the host cell breaks apart releasing the viruses (Waye and Sing, 2010b). Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes.

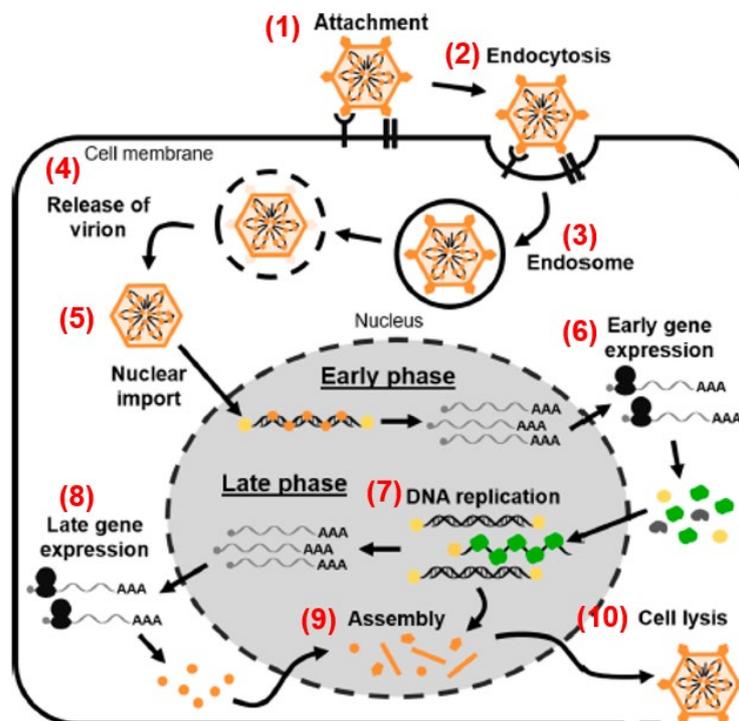


Figure 3: Overview of the adenovirus replication cycle (Charman et al., 2019).

3.4 Mutation and recombination of adenovirus

42. AdVs do not have the machinery for efficient integration into the host genome and therefore AdVs exhibit extremely low levels of integration i.e., integration is a rare event (Harui et al., 1999; Desfarges and Ciuffi, 2012; Hoppe et al., 2015; Dehghan et al., 2019). However, random integration of virus DNA into the host genome has been observed in rare cases (Harui et al., 1999; Stephen et al., 2008). Instead, AdV DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999).

43. Where a cell is infected by multiple HdAVs at the same time, exchange of genetic material can occur which promotes the molecular evolution of HAdVs through a process called homologous

recombination. Homologous recombination appears to be restricted to members of the same species and occurs in the regions of high sequence similarity (Lukashev et al., 2008). For instance, a comparison of DNA sequences from eight HAdV-C strains revealed 17 positions with nucleotide variations. However, only one of them altered the amino acid composition. Thus, it appears that HAdV-C accumulate predominantly neutral point mutations in their genomes that do not cause substantial modifications. This indicates a high-stability and conservation of protein sequence and may explain the relatively small number of HAdV-C serotypes.

44. Homologous recombination has been described in six HAdV species resulting in an increased number of members within those species (e.g., HAdV-B and HAdV-D). For example, bio-informatics analysis suggested that HAdV-4, a species E adenovirus like ChAd Y25, was a result of a recombination event between species B and C (Gruber et al., 1993).

45. Similarly, novel SAdVs have also been shown to arise by recombination (Ismail et al., 2018). There is 99.5% sequence homology between HAdV-76 and SdV-35.1 (categorised into species B) found in chimpanzee hosts and HAdV-4 also has 97% sequence homology to SAdV-26 genome (Dehghan et al., 2013; Dehghan et al., 2019). Further, there is evidence for possible cross-species transmission and genomic recombination between humans and chimpanzee hosts (Lasaro and Ertl, 2009; Roy et al., 2009; Wevers et al., 2011; Hoppe et al., 2015; Borkenhagen et al., 2019; Dehghan et al., 2019).

3.5 Epidemiology

3.5.1 Host range and transmissibility

46. ChAds have a restricted host range and chimpanzees are the natural host (Bots and Hoeben, 2020). ChAds are not known to cause disease in any other animal species or in plant cells (Wold and Toth, 2013). Experimentally, ChAds have been shown to infect mice, cotton rats, calves and humans when used at high concentrations.

47. ChAds are capable of infecting people as antibodies against ChAd have been detected in people exposed to chimpanzees, and where hunting and preparing nonhuman primates for food is widespread and eating bush meat is common. However, there is no evidence to indicate that people can pass on the virus to other people or animals (Xiang et al., 2006). Furthermore, in the US, 23 zoo keepers who have routine contact with chimpanzees did not have detectable antibodies to chimpanzee adenoviruses in their sera despite the high prevalence of antibodies to chimpanzee adenoviruses in captive chimpanzees in the zoo (Xiang et al., 2006). This data suggests that chimpanzee adenoviruses do not appear to spread easily to humans through occupational contact with chimpanzees.

48. Transmission of AdVs from an infected individual is primarily via direct contact with conjunctival secretions, via inhalation of aerosols or via faecal-oral route (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Khanal et al., 2018). The virus can also be spread indirectly via contact with infected articles e.g. handkerchiefs, linens or utensils contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017).

3.5.2 Shedding

49. The predominant natural tropism of ChAd Y25 is respiratory and ocular (eye). ChAds were detected in the faeces of healthy populations of chimpanzees and other great apes present in the wild and in captivity (Roy et al., 2009; Tong et al., 2010; Wevers et al., 2011).

50. Following natural HAdV infection in humans, virus particles are shed via respiratory or ocular 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 AdV is thought to be facilitated by very high levels of viral particles shed into sputum or oral secretions of the infected person (Allard and Vantarakis, 2017).

51. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing two HAdV serotypes (HAdV-4 and HAdV-7). Over 50% of the vaccine recipients tested

positive for AdV faecal shedding at various time points between 7-28 days following vaccination. No faecal shedding was detected 28 days following vaccination or at any time point in throat swabs (Allard and Vantarakis, 2017).

3.5.3 Occurrence in the environment

52. ChAds and chimpanzees are not native to Australia. ChAd Y25 is not found in the natural ecosystem outside its natural host. Therefore, their occurrence is limited in Australia. However, HAdVs are ubiquitous in populated environments.

53. HAdVs have been detected in various waters worldwide including wastewater, river water, drinking water, oceans and swimming pools (Allard and Vantarakis, 2017). HAdVs are frequently detected in high concentrations in domestic sewage and sludge in some countries and in certain situations are used in surveillance for faecal contamination (Allard and Vantarakis, 2017).

3.5.4 Control, environmental stability and decontamination methods

54. In otherwise healthy adults, infection with HAdV is generally asymptomatic or associated with mild disease and is generally managed through a combination of supportive care of the infected person and enhanced personal hygiene measures to limit transmission. Antiviral drugs may be used in immunocompromised patients or those with severe disease.

55. Despite the high prevalence of HAdV infection, there are currently no adenovirus-specific drugs that demonstrate efficacy as antiviral agents (Waye and Sing, 2010a; CDC - Adenoviruses, 2019). The antiviral agents commonly used in the first line adenoviral therapy are cidofovir and ribavirin (Waye and Sing, 2010a; CDC - Adenoviruses, 2019; Lion, 2019).

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

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

58. AdVs are found 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 e.g. heating to 56°C for 30 minutes or 60°C for 2 minutes or autoclaving (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017; Gray and Erdman, 2018).

Section 4 The GM vaccine - nature and effect of the genetic modification

59. The GM vaccine consists of a recombinant, replication defective virus, which was modified to produce the SARS-CoV-2 spike glycoprotein. The GM vaccine is designed to prevent COVID-19 caused by infection with SARS-CoV-2.

4.1 The genetic modifications

60. The GM vaccine was produced by deleting E1 and E3 genes from the ChAd Y25 genome and by replacing the E4 region open reading frame (Orf)4, Orf6 and Orf6/7 genes with equivalent genes from HAdV-5 (Dicks et al., 2012). This results in a replication defective GMO which produces more virus during manufacture. In addition, a construct containing a human cytomegalovirus (CMV) promoter driving a

codon-optimised full length SARS-CoV-2 spike gene that has been fused to a human tissue plasminogen activator (tPA) leader sequence was then inserted into the E1 locus (van Doremalen et al., 2020b) to boost induction of an immune response.

61. The SARS-CoV-2 spike (S) protein consists of the receptor binding (S1) and membrane fusion (S2) domains. The S1 receptor binding domain has been shown to be responsible for host range and tissue tropism (Huang et al., 2016; Li, 2016; Letko et al., 2020; Mousavizadeh and Ghasemi, 2020; Samrat et al., 2020). The receptor binding domain of the spike protein facilitates the virus attachment via angiotensin-converting enzyme 2 (ACE2) receptors present on human cells and initiates fusion of virus and cell membranes, mediating the entry of SARS-CoV-2 into the target host cells. The role of the spike protein in receptor binding and entry into the host cells make the spike protein an attractive vaccine candidate and many COVID-19 vaccines being developed use this protein (Folegatti et al., 2020b; Logunov et al., 2020; Sadoff et al., 2020; Samrat et al., 2020; Zhu et al., 2020).

62. The GM vaccine was generated by inserting a gene encoding the SARS-CoV-2 S glycoprotein into the ChAdOx1 vaccine vector sequence. The process can be largely divided into three parts, deletion of E1 and E3 genes, modification of E4 gene and insertion of SARS-CoV-2 S gene, which will be discussed in detail below.

4.1.1 Deletion of E1 and E3 genes

63. The E1 and E3 genes were deleted from the ChAd Y25 genome using the BAC vector (Dicks et al., 2012).

4.1.2 Modification of E4 gene

64. The E4 gene was modified by replacing ChAd Y25 native E4 Orf4, Orf6 and Orf6/7 genes with the equivalent genes from HAdV-5 (Dicks et al., 2012). Therefore, the resultant vector contains E4 Orf4, Orf6, Orf6/7 coding regions from HAdV-5 and the E4 Orf1, Orf2 and Orf3 coding regions from ChAd Y25 (Dicks et al., 2012). This vector was initially called ChAdY25-E and was later renamed to ChAdOx1.

4.1.3 Insertion of gene encoding SARS-CoV-2 spike protein

65. The full length sequence of the SARS-Cov-2 spike protein (GenBank accession number MN908947) was codon optimised to improve expression in human cells and the tPA leader sequence was fused upstream of the spike protein sequence. The sequence encoding both the spike protein and tPA was then cloned into an expression cassette containing a modified human CMV promoter with tetracycline operator sites and a poly-adenylation signal from bovine growth hormone. The expression cassette was then inserted into the E1 locus of the ChAdOx1 vector to generate the GM vaccine.

4.2 Effect of the genetic modification

66. Due to deletion of E1 and E3 genes, the resultant GMO is unable to replicate in cells and is unable to evade the host immune response.

67. Due to modification of the E4 gene, the GMO demonstrates increased virus yield i.e., allows efficient expression and growth of the virus during manufacturing of the GM vaccine.

68. Insertion of the gene encoding the full length SARS-CoV-2 spike protein in the ChAdOx1 vector was designed to induce antibodies against the SARS-CoV-2 virus in vaccinated people. The SARS-CoV-2 S glycoprotein is not toxic and does not confer any advantages to the adenoviral vector. Further, the antigen expression cassette does not alter the transmission route or host range of the ChAdOx1 vaccine vector.

69. As a result of these genetic modifications, the GMO cannot replicate in the host cells and will induce an immune response in humans but will not cause ill-health.

4.3 Characterisation of the GMO

70. Data obtained from experiments and clinical trials using the proposed GMO and from other clinical trials using the same backbone/platform (ChAdOx1 vector) with different genes for a range of diseases has been used to describe the characteristics of the GMO.

4.3.1 Genetic stability and molecular characterisation

71. The ChAdOx1 vector has been used in several clinical trials for testing against other human diseases, including the Middle Eastern Respiratory Syndrome (MERS) virus, a beta coronavirus that is related to SARS-CoV-2 (Antrobus et al., 2014; Coughlan et al., 2018; Folegatti et al., 2020a; Wilkie et al., 2020). The ChAdOx1 vector has been found to be genetically stable, safe and well tolerated in humans.

72. Further, studies have shown that the formation of replication competent ChAdOx1 during manufacture is very low due to differences in the E1 flanking sequence between HAdV-5 and ChAds (Tatsis and Ertl, 2004; Tatsis et al., 2006; Colloca et al., 2012; Ghebremedhin, 2014; Morris et al., 2016).

73. The sequence of the expression cassette for the SARS-CoV-2 S protein gene including the promoter and poly A regions were confirmed by DNA sequencing. DNA sequences for ChAdOx1 (NCBI reference sequence: txid1123958) and spike protein are available in GenBank (NCBI reference sequence: YP_009724390.1; GenBank accession number MN908947.3).

74. The GM vaccine does not contain a selectable marker, however the GMO can be distinguished from the ChAd Y25 virus (parent strain) or SARS-CoV-2 using a specific PCR test. These genetic markers include the tPA leader sequence inserted into the SARS-CoV-2 S protein sequence, the absence of E1 and E3 genes, and the modified E4 gene.

75. The applicant has stated that the GMO will be routinely monitored during manufacturing to ensure the virus has not gained replication competency. Thus, each vaccine batch will be subjected to a number of tests to ensure consistency and quality of the manufactured product. Vaccine quality will be assessed by TGA. Further, the genetic stability of the GMO will be also examined to confirm the presence of the full genomic sequence.

76. The use of the BAC vector in the generation of the GMO allows stable incorporation of gene sequences and improves genetic stability to the virus (Dicks et al., 2012).

77. Adenoviral vectors (including ChAdOx1 vector) are considered non-integrating vectors which do not have a propensity to integrate or reactivate in a host (Danthinne and Imperiale, 2000; EMEA, 2007; FDA, 2020). The viral DNA is maintained as multiple episomal copies in the infected nuclei. However, some experimental studies in cell lines and mice have described possible integration of AdV vectors into host genomes at very low frequencies (Hillgenberg et al., 2001; Stephen et al., 2010). A study on cell lines from human, hamster, monkey and mice calculated the integration frequency of approximately one in every 10^3 to 10^5 transduced cells (Harui et al., 1999). In a separate study on immunodeficient mice, intravenous administration of replication incompetent AdV vector showed possible low integration of the AdV vector into the host genome (Stephen et al., 2010). However, the authors did acknowledge that the most common route of vector delivery for AdV vectors (i.e. intramuscular route of injection) would result in much lower incidence of integration (Stephen et al., 2010). Modified AdVs have been used in clinical trials and as human therapies since 1993 and to date none have shown integration of AdV vectors into the host genome.

4.3.2 Biodistribution and shedding of the GMO

78. Biodistribution studies with this GMO have not been conducted. However, biodistribution data from similar, replication incompetent ChAd-based vaccines (AdCh63-ME-TRAP and AdCh63-MSP-1 for malaria, AdCh3NSmut for hepatitis C and ChAd155-RG for rabies) showed limited spread to the draining lymph node and no other spread beyond the immediate site of injection following intramuscular injection in mice and rats (BE/20/BVW2, 2020; Napolitano et al., 2020).

79. Similarly, local administration (intranasal, intrabroncheal, intramyocardial, intramuscular or intratumoural injection) of replication defective HAdV-5 and HAdV-35 (E1 and E3 genes deleted) in rabbits and humans showed negligible virus shedding in pharyngeal, rectal, nasal swabs, urine and blood samples (Crystal et al., 2002; Sheets et al., 2008; Wold and Toth, 2013). In addition, no recombinant competent virus was detected in the analysed samples, suggesting that no homologous recombination was occurring with other AdVs.

80. A small number of studies with other replication deficient adenoviral vectors have reported shedding of vector DNA or infectious particles, while many others have not detected any shedding (Schenk-Braat et al., 2007). In general, shedding of replication defective adenoviral vectors is considered to be a rare event (Wold and Toth, 2013). Shedding is dependent on the route of administration, site of administration, type of samples analysed and length of time after administration. For instance, shedding of chimpanzee adenoviral based vaccine PanAd3-RSV (E1 and E4 deleted) was studied in a Phase I clinical study following intramuscular or intra-nasal administration (Green et al., 2015). Urine and throat swabs from 40 subjects were collected 3 days following intramuscular vaccination, and viral shedding was evaluated using a specific PCR test. The results were negative for all samples, demonstrating that there was no detectable shedding of the vaccine following intramuscular administration by 72 hours post administration. Similarly, nasal samples collected 3 days after intranasal administration of PanAd3-RSV did not detect any viral shedding (Green et al., 2015).

81. The GMOs inability to replicate prevents its dissemination in the vaccinated person. Taking into consideration the above mentioned biodistribution and shedding data from replication incompetent adenoviral based vaccines, the GMO is expected to be confined to the intra-muscular injection site and the draining lymph nodes of the human host and no viral DNA excretion is expected. Thus, there is no evidence to suggest that the GMO would be present in the environment from shedding following vaccination of people.

4.3.3 Stability in the environment and decontamination

82. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Other recombinant AdVs (AdV expressing GFP) have been shown to have reduced capacity to survive in fresh surface water, cold water and dark sediments compared to wild-type AdVs (Rigotto et al., 2011; Elmahdy et al., 2018). It is likely that, with regard to environmental stability, this GMO will be similar to or have reduced survival than wild-type AdVs (see Chapter 1, Section 3.5.4). Further since the GMO is replication incompetent, it is not possible for the GMO to multiply and spread in the environment and any initial GM vaccine would be degraded over time.

83. Methods of decontamination effective against the parent organism, ChAd Y25, are expected to be equally effective against the GMO (see Chapter 1, Section 3.5.4).

4.3.4 Non-clinical studies

84. Pre-clinical studies with the GM vaccine in mice, pigs and rhesus macaques have shown a good safety profile and the ability of the vaccine to elicit both neutralising antibody and T-cell responses following a single or homologous prime-boost regime (Graham et al., 2020; van Doremalen et al., 2020b). Further, the vaccine protected SAR-CoV-2 infected rhesus macaques from viral pneumonia and immune-enhanced inflammatory disease. In addition, no infectious virus particles were detected in the lungs and intestinal tissues of these infected animals (van Doremalen et al., 2020b). Whilst a single dose of GMO induced antigen-specific antibody and T cell responses in mice and pigs, a booster immunisation enhanced antibody responses, particularly in pigs and significantly increased SARS-CoV-2 neutralising antibody titres (Graham et al., 2020).

4.3.5 Safety and immunogenicity in clinical studies

85. A phase 1/2 clinical trial with the GMO has been completed. The GM vaccine was found to be safe, well tolerated and elicited immune response in 543 vaccinated individuals aged 18-55 years (Folegatti et al., 2020b). However, protection against SARS-CoV-2 in humans was not examined in this study. The

most common side effects following vaccination were pain, redness, swelling, itching at the site of injection and fever, malaise, fatigue, headache, vomiting, joint pain and muscle ache. No serious adverse events were observed in this study (Folegatti et al., 2020b).

86. Similarly, an ongoing phase 2/3 clinical trial demonstrated that the GM vaccine is safe and well tolerated in both older adults (56-69 years and 70 years and older) and younger adults (18-55 years) after prime-only and prime-boost vaccination (Ramasamy et al., 2020). Further, immune responses were induced in all age groups and were boosted and maintained at 28 days after booster vaccination. The adverse events reported reflected those observed in the phase 1/2 clinical trial with reactions overall less common in older adults compared to younger adults. In this study, 13 serious adverse events were reported out of around 400 vaccinated individuals as of 26th October 2020 but none of them were considered to be related to the GM vaccine.

87. The interim analysis of four clinical trials in Brazil, South Africa and the UK showed that the GM vaccine is safe and efficacious against symptomatic COVID-19 with prime-boost vaccination (Voysey et al., 2020). The efficacy of the GM vaccine in individuals who received two standard doses was 62.1% whereas efficacy was 90% in individuals who received first low dose and a second standard dose. Overall, the GM vaccine showed efficacy of 70.4% in vaccinated individuals across both groups. In this study, 175 serious adverse events occurred in 168 vaccinated individuals, where 84 events were reported in the GM vaccine group and 91 events in the control group.

Note: Clinical trials with the GMO are currently ongoing and the data taken from the published studies in this section represent an interim analysis, therefore, the safety and immunogenicity data from clinical studies might change once the studies are completed. The TGA would formally assess the patient safety and the quality and efficacy of the COVID-19 vaccine prior to its registration in the ARTG.

Section 5 The receiving environment

88. The receiving environment forms part of the context for assessing risks associated with import, transport, storage and disposal of the GM vaccine (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 vaccination

89. The intended primary receiving environment would be the muscles (at the site of injection) of the vaccine recipient as the GM vaccine will be delivered via intramuscular injection by a trained healthcare professional in vaccination centres.

90. The secondary receiving environment would be the vaccination centres where the vaccine is prepared and administered. Most vaccination centres would be equipped to deal with scheduled drugs and infectious agents.

91. The principal route by which the GMO may enter the wider environment following vaccination is via shedding. However, as the injection of non-replicating GMO is via intramuscular injection, wide spread shedding is not expected due to localisation of viral particles at the injection site and draining lymph nodes. Further, GMO may also enter the environment via accidental spilling of unused vaccine.

5.2 Presence of related viral species in the receiving environment

92. 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.

93. AdVs belong to five genera: *Aviadenoviruses* (infecting birds), *Mastadenovirus* (infecting mammals), *Atadenovirus* (infecting a broad range of hosts including reptiles, lizards and some mammals), *Siadenovirus* (infecting one species of frog and tortoise and multiple species of domestic, wild and captive birds) and *Ichtadenovirus* (infecting fish) (Tong et al., 2010; Lange et al., 2019; Vaz et al., 2020).

As such, they are a common cause of infection in animals and humans of all ages 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 3.5.3.

94. As chimpanzees are not native to Australia, the presence of ChAds is expected to be very limited in the Australian environment.

5.3 Presence of similar genetic material in the environment

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

96. The genes introduced in the GMO would be functionally similar to ones present in the naturally occurring SARS-CoV-2 virus and human adenovirus 5. The genes introduced into the GMO were derived from the naturally occurring SARS-CoV-2 virus and human adenovirus 5, so similar genetic material would already be present in the environment, as evidenced through detection in wastewater.

Section 6 Previous authorisations

97. The GM vaccine has been approved for commercial use in the European Union. In addition, the GM vaccine has been authorised for emergency use in several countries including the UK, Argentina, Brazil, El Salvador, India, Dominican Republic, Mexico, Morocco and Pakistan.

98. There are currently 7 clinical trials (NCT04324606, NCT04400838, NCT04536051, NCT04444674, NCT04516746, NCT04540393 and NCT04568031) ongoing to test the safety, immunogenicity, and efficacy of GM vaccine in different countries (the UK, the United States (US), Brazil, South Africa, Argentina, Chile, Colombia, Japan, Peru and the Russian Federation) for the prevention of COVID-19.

99. The initial importation, transport, supply, storage and disposal of the GM Master vaccine seed into Australia and dealings involving quality control sampling and batch release testing is covered under a Notifiable low risk dealing approval (NLRD) held by AstraZeneca.

100. The Regulator has approved DNIR licences (DNIR-630 and DNIR-632) to manufacture, supply frozen bulk drug substance, formulate and fill/finish the GM vaccine as part of the overall program for the supply of recombinant antigen for the prevention of COVID-19 in Australia.

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 4). 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.

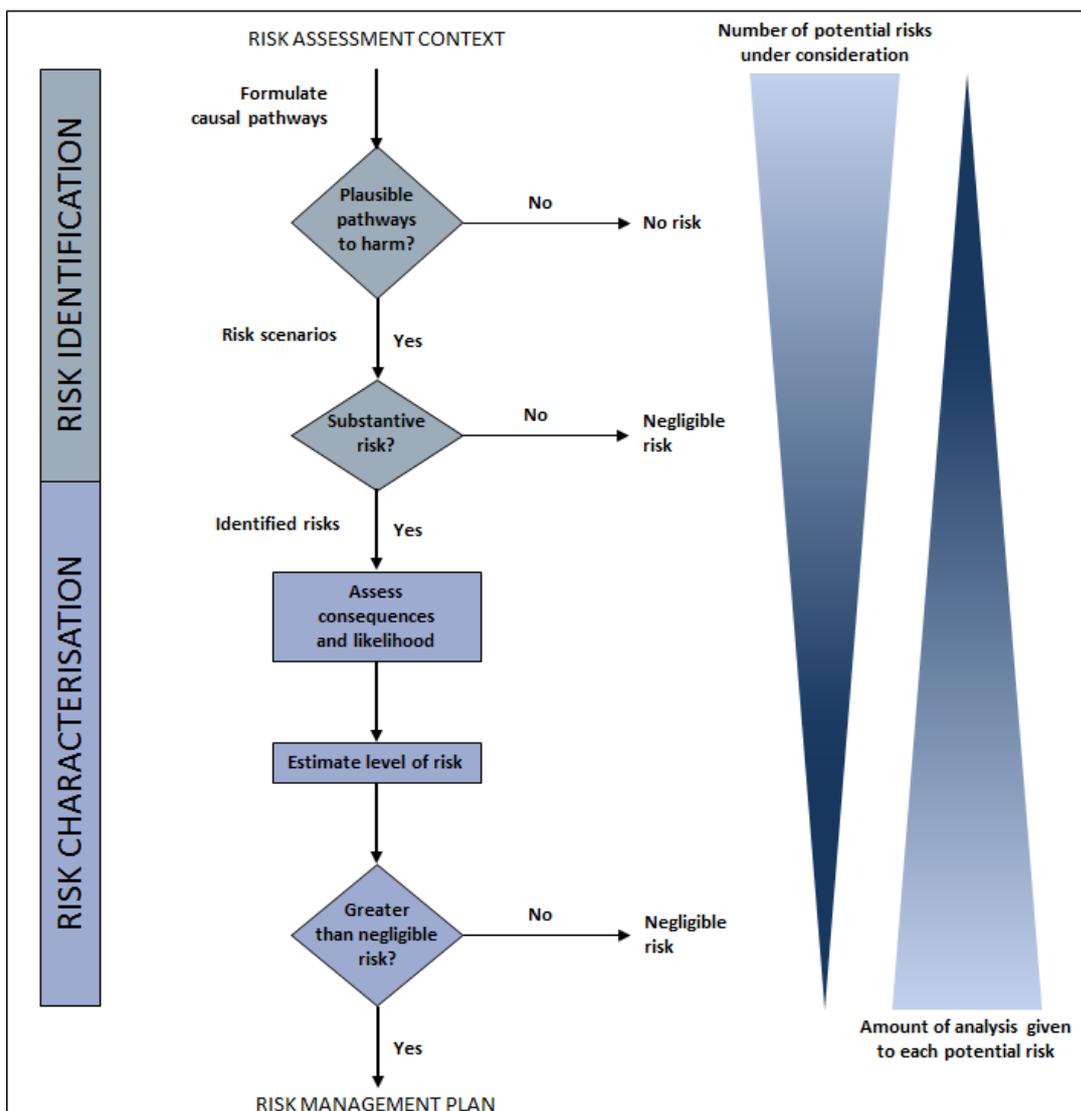


Figure 4: The risk assessment process.

102. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013).

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 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 are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the short and long term, do not advance in the risk assessment process (Figure 4), 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 hypothetical risk scenarios are comprised of three components (Figure 5):

- i. The source of potential harm (risk source)
- ii. A plausible causal linkage to potential harm (causal pathway), and
- iii. Potential harm to people or the environment.

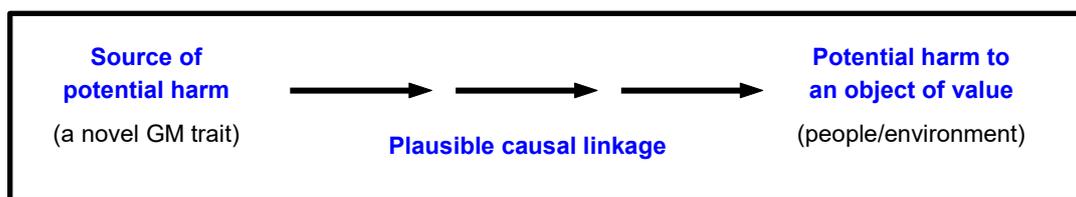


Figure 5: Components of a risk scenario.

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 of the GMO is the chimpanzee adenovirus isolate Y25 (ChAd Y25). Details of the pathogenicity and transmissibility of ChAd is discussed in Chapter 1. Infection is generally the result of inhalation of aerosol droplets excreted from respiratory or ocular secretions containing the virus or mucosal exposure to the virus or via faecal-oral transmission. ChAd infects chimpanzees and causes common cold-like symptoms, bladder infections or diarrhoea.

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

110. Potential sources of harm can be due to the intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology. Unintended effects can arise through a horizontal gene transfer (HGT) which is the stable transfer of genetic material from one organism to another without sexual reproduction. All genes within an organism, including those introduced by gene technology, can be transferred to another organism by HGT. A gene transferred through HGT could confer a novel trait to the recipient organism. The novel trait may result in negative, neutral or positive effects on the fitness of the recipient organism. HGT commonly occurs from cells to viruses but rarely occurs from viruses to their

host cells, with the exception of retroviruses and some DNA viruses. However, this pathway is further considered as a potential source of risk.

111. As discussed in Chapter 1, Section 4.1, the GMO has been modified by the deletion of E1 and E3 genes, by modifying the E4 gene and by insertion of gene encoding a codon-optimised full length SARS-CoV-2 spike protein. These introduced genes and their encoded proteins are considered further as a potential source of risk.

2.2 Causal pathway

112. The following factors were taken into account when postulating possible causal pathways to potential harm:

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

113. The TGA regulates quality, safety and efficacy of the GM vaccine (i.e., GMO) under the *Therapeutic Goods Act 1989*, as mentioned in Chapter 1, Section 1.1. This includes:

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

114. The current assessment focuses on risks posed to people other than the intended vaccine recipient, and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO.

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

116. As discussed in Chapter 1, Section 4.3.2, the ChAd-based viral vectors were found to be localised to the site of injection and draining lymph nodes after intramuscular injection. Further, no virus shedding was detected with ChAd-based and HAdV-based viral vectors. Therefore, the GMO is

expected to be confined to the intramuscular injection site and the draining lymph nodes of the vaccine recipients and no virus shedding is expected from the vaccine recipients resulting in release of the GMO into the environment. Thus, there is no potential risk of the GMO to be shed from the vaccine recipients and therefore, this risk scenario will not be considered further.

117. As mentioned in Chapter 1, Section 3.4, adenoviruses remain episomal throughout the infection and do not integrate into the host DNA. Similarly, the vectors derived from these adenoviruses are considered as non-integrating vectors which do not have a propensity to integrate or reactivate following latency in a host (EMEA, 2007; FDA, 2020). Further, adenoviral vectors (including ChAdOx1 vector) have been used extensively in clinical studies as a vaccine and 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.

2.3 Potential harms

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

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

2.4 Postulated risk scenarios

119. Three risk scenarios were postulated and screened to identify substantive risk. These hypothetical scenarios are summarised in Table 1 and discussed in depth in Sections 2.4.1-2.4.3 (this chapter).

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

Table 1 Summary of hypothetical risk scenarios from dealings with GM vaccine

Risk scenario	Risk source	Potential causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes during (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO ↓ Transduction of cells by GMO ↓ Expression of the spike protein	Adverse immune reactions (e.g., cytokine storm)	No	<ul style="list-style-type: none"> • The GMO is replication incompetent. GMO will not produce further viral particles to sustain an infection. • Any reactions to the spike protein would be transient and rapidly cleared by the immune system. • GMO has shown a good safety profile. • The dose received through accidental exposure would be far smaller than that administered during vaccination and would not be sufficient for immunisation of exposed persons.

Risk scenario	Risk source	Potential causal pathway	Potential harm	Substantive risk	Reason
					<ul style="list-style-type: none"> • Import, transport, storage and disposal will follow well established procedures.
2	GMO	<p>Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1</p> <p style="text-align: center;">↓</p> <p>Transduction of cells by GMO</p> <p style="text-align: center;">↓</p> <p>Transduced cells co-infected with AdV</p> <p style="text-align: center;">↓</p> <p>(a) Complementation of E1 and E3 by AdV (b) Homologous recombination with AdV</p> <p style="text-align: center;">↓</p> <p>(a) Production of more replication incompetent ChAdOx1 with spike protein with immune evasion properties (b) Formation of replication defective AdV expressing spike protein;</p> <p style="text-align: center;">OR</p> <p>Replication competent GMO without spike protein</p>	<p>Adverse immune reactions (e.g., cytokine storm)</p> <p>Disease in people or animals</p>	No	<ul style="list-style-type: none"> • Co-infection of the same cell with both GMO and AdV at the same time is a rare event. • A large proportion of the population have a pre-existing immunity to HAdV reducing the likelihood of HAdV infection. • There is a low probability of continuous complementation of GMO by AdV because AdV infection is self-limiting. • Recombination among adenoviruses is restricted to the same species. • There is low homology between E1 flanking regions of GMO and HAdVs. Site-directed recombination was used to insert the transgene into E1 gene of GMO further decreasing the likelihood of recombination with HAdV. • Natural occurring homologues (wild-type ChAdV) are only known to circulate in chimpanzees. ChAd is not known to cause disease in humans and other animals.
3	GMO	<p>GMO release into the environment (e.g. sewerage, spills)</p> <p style="text-align: center;">↓</p> <p>Exposure to people or animals</p> <p style="text-align: center;">↓</p> <p>As per scenario 1-2</p>	<p>Adverse immune reactions (e.g. cytokine storm);</p> <p>Disease in people or animals</p>	No	<ul style="list-style-type: none"> • As discussed in Risk Scenario 1 and 2. • Chimpanzees are the only natural hosts to ChAds. Chimpanzees are not native to Australia and would only be found in zoos. No other animals are expected to be infected with ChAds. • GMO does not infect aquatic species. GMO cannot persist and replicate inside or outside the host, hence GMO is unable to maintain a stable presence in the

Risk scenario	Risk source	Potential causal pathway	Potential harm	Substantive risk	Reason
					environment for long periods.

2.4.1 Risk scenario 1

Risk source	GMO
Potential causal pathway	<p>Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes during</p> <p>(a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO</p> <p style="text-align: center;">↓ Transduction of cells by GMO ↓ Expression of the spike protein</p>
Potential harm	Adverse immune reactions (e.g., cytokine storm)

Risk source

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

Potential causal pathway

122. People (including the person handling the GMO) and animals could be directly or indirectly exposed to the GMO in a number of ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO and preparation of the GMO. It could also be transmitted when contaminated surfaces, such as hands or tissues, make contact with mucous membrane and via needle stick injury. This exposure could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

123. As discussed in Chapter 1, Section 2.1, the GMO would be distributed via vaccination centres. There is the potential for exposure of people involved in the administration of the GM vaccine by needle stick/sharps injury, aerosols formation during preparation and/or due to breakage/spillage of GM vaccine onto surfaces during preparation and administration.

124. The GMO would be prepared and administered by authorised, experienced and trained medical staff. All personnel working in settings where healthcare is provided, including vaccination services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019)* and the *Australian Immunisation Handbook*. Compliance with these behavioural practices at vaccination centres will limit and control unintended exposure of people to the GMO.

125. Caregivers and healthcare personnel who come into close contact with vaccinated people during administration may be inadvertently exposed to the GMO. Caregivers and others exposed to the GM vaccine in this way would only be expected to be exposed to low levels of the GMO and this is not expected to result in any negative effects or ill-health. Furthermore, formation of replication-competent adenovirus or presence of the vector in healthcare personnel who came in close contact with the patients have not been observed in studies which looked into these parameters (Schenk-Braat et al., 2007).

126. The above mentioned controls would minimise the potential exposure of people to the GMOs during administration of the vaccine.

Exposure during import, transport and storage of the GMO

127. If the GM vaccine was unintentionally/accidentally spilled or lost during import, transport or storage, this could result in exposure to people or animals in the area, as aerosol droplets could be formed, leading to aerosol or liquid contact with eyes or mucous membranes/skin. Further, people or animals could be inadvertently exposed to the GMO via contact with materials or surfaces contaminated with the GMO through subsequent hand to mouth transmission. This could result in infection with the GMO.

128. The applicant proposes to import the GMO from overseas as a multi-dose vial. These vials would be packaged in secondary cartons and the cartons packed in shipping cartons for distribution (Chapter 1, Section 2.1). Transport of GMO between the port of entry and the warehouse would continue in this packaging. This would lower the likelihood of unintended dispersal of the GMOs.

129. Similarly, the GMO manufactured within Australia will also be supplied as a multi-dose vial and these vials would also be packaged into secondary cartons followed by shipping boxes. This would lower the likelihood of unintended dispersal of the GMOs.

130. Vaccines are classified as Schedule 4 medicines. Therefore, storage, handling and transport would be in accordance with *the Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8 (NCCTG 2011) and the WHO's Good Distribution Practices for pharmaceutical products (WHO 2010)*. These practices would minimise the chances of damaged and leaking stock going unnoticed and increase the chances of GM vaccine being handled by individuals who would know how to decontaminate a spill, thus minimising the probability of unintended dispersal of the GMOs.

131. Additionally, the GM vaccine will be transported and stored according to the *National Vaccine Storage Guidelines: Strive for 5* (Department of Health, 2019) and the *Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2020)*. The cold chain, which is intended to preserve the potency of the vaccine, requires cold packaging/refrigeration and this adds a level of containment during import, storage and transport.

132. The GMO may cause mild disease in chimpanzees and other great apes but is not expected to cause any disease in humans and other animals. Therefore, the risk of exposure to the GMO resulting in disease in other people and animals is very low. Further, the exposure to animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

133. The applicant proposes that the people involved in the import, transport and storage of the GM vaccine will have access to the material safety data sheet (MSDS). The MSDS would provide procedures to implement in response to a spill where any spilled/residual GMO would be quickly inactivated with a suitable disinfectant effective against the GMO. Therefore, the consequence of an accidental spill during import, transport and storage would be minimised by implementing spill clean-up procedures that would kill the GMO.

134. The import, transport and storage procedures proposed by the applicant 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 disposal of the GMO

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

- distribution warehouses where stocks of the GM vaccine are held

- locations where the GM vaccine is administered.

136. 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 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, and
- medicines for destruction be enclosed in sealed packaging or in a container.

137. The unused and expired vials of the GMO as well as the vials with residual GMO, syringes and waste contaminated with the GMO would be treated as clinical/medical waste and disposed of in accordance with the waste disposal methods approved by the Environmental Protection Agency or Health Department in the relevant State or Territory (TAS, 2007; NT, 2014; WA, 2016; ACT, 2017; NSW, 2018; QLD, 2019; SA, 2020; VIC, 2020). Adherence with these procedures would also reduce the likelihood of accidental exposure of people or animals to the GMO.

138. For productive infection to occur, individuals must be exposed to an infectious dose. Residual liquid in used vials and used syringes would not contain a sufficient titre to cause productive infection. The same would apply to secondary waste such as gloves that may be contaminated with the GMO. The GMO is unable to replicate inside or outside the host, so viruses in the used vials could not multiply to reach an infective dose. Thus, the dose received through accidental exposure would be far smaller than that administered during vaccination. Therefore, even if an individual or animal is inadvertently exposed to the GMOs, they are unlikely to develop disease.

139. Taken together, these proposed disposal and decontamination procedures would minimise and control risks associated with conducting these dealings with the GMOs.

Potential harm

140. If people or animals are exposed to the GMOs, they could develop flu-like symptoms or local inflammation for a short period of time before the virus is cleared by the immune system. It is highly unlikely that exposed people or animals would experience adverse immune responses and severe illness following exposure, as the GMO does not cause disease in humans or animals. In chimpanzees and great apes, exposure to high concentrations of the GMO could result in mild disease symptoms in these animals but is unlikely to sustain the infection due to the replication defective nature of the GMO.

141. As the GMO is replication incompetent, it is unable to produce further viral particles which are required to sustain an infection. In addition, any reactions to the spike protein would be transient and the GMO would be rapidly cleared by the immune system. 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, exposure to the GMO is not expected to result in an infection and would not result in an increased disease burden in humans or animals.

142. As mentioned in Chapter 1, Section 4.1, the SARS-CoV-2 virus enters a host's cells via the ACE2 receptor, which is involved in the renin-angiotensin-aldosterone system. When exposed to ChAdOx1 nCov-19, there is a possibility that the spike proteins produced will bind to ACE2, which can then prevent the conversion of angiotensin II into angiotensin. These could result in more angiotensin II binding to the AT1 receptor, which can lead to detrimental effects such as vasoconstriction and enhanced inflammation and/or increased angiotensin II expression in the lungs. However, there has not been any reported cases of such effects. Further, it is very unlikely that the amount of spike protein present in the replicative defective viral vectored vaccine can have a sustained effect on people. To date, vaccines that have used the spike proteins from SARS-CoV-2 have shown a good

clinical safety profile (Folegatti et al., 2020b; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al., 2020; Zhu et al., 2020).

143. Vaccines against SARS-CoV-2 using the full length spike protein in replicative defective viral vectors including ChAdOx1 based vaccine have shown the ability to generate neutralising antibodies against SARS-CoV-2 (Folegatti et al., 2020b; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al., 2020; Zhu et al., 2020). There is potential for these vaccines to cause antibody-dependant enhancement²-mediated viral entry or immunopathology via the generation of sub- or non-neutralising antibodies towards the spike protein (Arvin et al., 2020; Su et al., 2020). However, there has not been any reports of antibody-dependant enhancement (ADE) associated with these COVID-19 vaccine candidates to date. The administration of convalescent plasma from patients who had recovered from SARS-CoV-2 infection into 20,000 patients who had a high risk of severe COVID-19 disease showed low incidence of serious adverse events (Joyner et al., 2020). Further, no ADE was observed with inactivated-whole SARS-CoV-1 (Luo et al., 2018), DNA vaccine expressing SARS-CoV-2 S protein (Arvin et al., 2020), ChAdOx1 MERS (van Doremalen et al., 2020a) and ChAdOx1 nCov-19 (van Doremalen et al., 2020b) in rhesus macaques upon re-infection. To date, there is no evidence demonstrating a risk of ADE in humans in relation to SARS-CoV-2 infection.

Conclusion

144. The potential for an unintentional exposure of people and animals to the GMO resulting in increased disease burden in humans and animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

² Antibody-dependant enhancement can occur when pre-existing sub- or non-neutralising antibodies towards a virus can enhance the viral entry into host's cells during secondary viral infections. This antibody-dependant enhancement mediated viral entry has been mostly documented in flaviviruses (e.g. dengue virus) but also observed in various viral infections such as HIV, Ebola and coronaviruses (e.g. MERS and SARS-CoV-1).

2.4.2 Risk Scenario 2

Risk source	GMO
Potential causal pathway	<p style="text-align: center;">Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Transduction of cells by GMO</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">Transduced cells co-infected with AdV</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>↙</p> <p>Complementation of E1 and E3 by AdV</p> <p>↓</p> <p>Production of more replication incompetent GMOs with immune-evasion properties</p> </div> <div style="text-align: center;"> <p>↘</p> <p>Homologous recombination with AdV</p> <p>↓</p> <p>Formation of replication defective AdV expressing spike protein OR Replication competent GMO without spike protein</p> </div> </div>
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk source

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

Potential causal pathway

146. The transmission of GMO could occur by the pathways mentioned in Risk Scenario 1 which could potentially result in transduction of host cells at the exposed area. If the person or animal exposed to the GMO has an existing infection with AdVs at the same time as exposure or acquired an AdV infection while the GMO is present, this co-infection could potentially result in complementation or recombination of the GMO causing adverse immune reactions.

Complementation of E1 and E3 by AdV

147. The GMO could regain the ability to replicate and some immune-evasion properties in the host cells via transient complementation of E1 and E3 genes by AdVs, respectively. For complementation to occur, the person or animal exposed to the GMO would also need to be infected with an AdV (either ChAd or HAdV) at the same time and in the same cell. This could result in the production of more replication incompetent GMOs with immune-evasion properties.

148. ChAds naturally circulate in chimpanzees and chimpanzees are not native to Australia but a limited number of chimpanzees are present in Australian zoos. The exposure of captive chimpanzees to the GMO is highly unlikely as the dealings covered by the licence (i.e., import, transport, storage and disposal) would not occur in the vicinity of the captive chimpanzees. In addition, people exposed to the GMO visiting a zoo is unlikely to spread the GMO to chimpanzees due to the replication deficient nature of the GMO. Further, a study demonstrated that ChAd neutralising antibodies were not detected in zoo keepers who work closely with chimpanzees, suggesting that the ChAds do not appear to spread easily to humans through occupational contact with chimpanzees (see Chapter 1, Sections 3.1 and 3.5.1). Therefore, co-infection of the GMO and the wild-type ChAds occurring at the same time and in the same cell in humans or animals is highly unlikely.

149. HAdV infects over 80% of the human population, therefore, there is a possibility for a GMO exposed person to acquire HAdV infection and which could provide E1 and E3 genes *in trans* for complementation to occur. This could result in the multiplication of GMOs in the host.

150. Some ChAds (including ChAd Y25 (GMO parent organism)) and HAdV-4 are categorised into the same HAdV Species E and share a close homology in their genome (Tatsis and Ertl, 2004). This could allow the E1 and E3 genes in an HAdV-4 infected person to complement the missing E1 and E3 genes in the GMO. Therefore, it is possible that co-infection of HAdV-4 and the GMO in the same cells could result in the production of more GMOs with immune-evasion properties in the host. However, there is a low probability of continuous complementation of the GMO by HAdV-4 as HAdV infection is self-limiting (Lichtenstein and Wold, 2004). Thus, the likelihood of a person having an HAdV-4 infection which could continuously complement the missing E1 and E3 genes in the GMO is very low.

151. Similarly, ChAds and HAdV-5 also share a close homology (94% similarity) in their genome (Morris et al., 2016; Bots and Hoeben, 2020) that could allow the E1 and E3 genes from a HAdV-5 infected person to complement the missing E1 and E3 genes in the GMO. Therefore, it is possible that co-infection of HAdV-5 and GMO in the same cells could result in the production of more GMOs with immune-evasion properties in the host. However, a large proportion of the population already have a pre-existing immunity to HAdV-5 which reduces the likelihood of HAdV-5 re-infection. In addition, HAdV infections are also self-limiting, decreasing the probability of continuous complementation of GMO by HAdV (Lichtenstein and Wold, 2004). Thus, this reduces the chances of co-infection in the host and eventual production of more GMOs with immune evasion properties in the host.

152. Studies have demonstrated that other HAdVs especially from subgroup B are incapable of replicating in cell lines that express E1 gene from HAdV-5 (Kovesdi and Hedley, 2010). This data suggests that HAdVs could only replicate in permissive cells which provide the essential viral replication E1 gene *in trans* i.e., requires serotype/species specific provision of E1 gene for complementation. Therefore, even if co-infection with other HAdVs and the GMO were to occur in the same cell, the GMO would still be unable to multiply in the host and would not increase the number of GMOs in the host.

Homologous recombination with AdV

153. Similar to complementation, homologous recombination also requires the person or animal exposed to the GMO to be infected with a wild-type AdV (either ChAd or HAdV) at the same time in the same cell. This co-infection and recombination process could result in the generation of two different GM recombinants. These GM recombinants could contain either the gene encoding S protein or E1 gene due to co-localisation of these genes in the GMO genome and the packaging constraints on the virus genome size. Firstly, the wild-type AdV could receive the spike protein gene from the GMO and gain immuno-stimulatory function. Secondly, the GMO could regain its E1 gene but lose the gene encoding spike protein and become replication competent. Further, there is also a possibility for recombination to occur between the GMO and the E3 gene from the wild-type AdV. These new recombinant viruses could then be shed from the host and transmitted to other hosts in the environment.

154. A recombinant virus generated through homologous recombination has the potential to alter the characteristics (e.g., pathogenicity, host range, tissue tropism, latency, and infectivity) of the GMO. As mentioned in Chapter 1, Section 3.5.1, ChAds are host specific and thus only infect chimpanzees. However, ChAds have been shown to experimentally infect mice, cotton rats, calves and humans when given at high concentrations. In the unlikely event of a GMO exposed person shedding a high amount of recombinant viruses in the environment where these animals are found, there is a potential for infection of animals due to the presence of high levels of recombinant viruses. However, the amount of shedding in people due to exposure to the GMO in the context of import, transport, storage and disposal is negligible. Further, exposure of these animals would be expected

to be minimal and the exposure of these animals to the amount of recombinant virus needed to cause an infection would be very unlikely. Nevertheless, homologous recombination is unlikely to expand the host range beyond humans or chimpanzees (Rogers et al., 2020).

155. As discussed in Chapter 1, Section 3.4, recombination between adenoviruses is restricted to the same species (Lukashev et al., 2008). For homologous recombination to occur, a GMO exposed person or chimpanzee is required to be infected with a wild-type ChAd at the same time in the same cell. As discussed above, it is unlikely that co-infection with wild-type ChAds and the GMO would occur at the same time and in the same cell in humans or animals. However, in the unlikely event that a GMO exposed person or chimpanzee does get infected with a ChAd, a recombinant ChAd could be formed through homologous recombination. This recombinant virus would not be able to contain both E1 gene and the gene encoding spike protein due to co-localisation and the packaging constraints on the virus. This could therefore only result in the formation of replication competent ChAd (without spike protein and E3 gene) or replication incompetent AdV with spike protein.

156. There is evidence of recombination occurring between human and non-human adenoviruses (Lasaro and Ertl, 2009; Roy et al., 2009; Wevers et al., 2011; Hoppe et al., 2015; Borkenhagen et al., 2019; Dehghan et al., 2019). ChAds (e.g., ChAd68 and ChAd Y25) share about 90% sequence homology with the known sequence of HAdV-4 (Tatsis and Ertl, 2004). HAdV-4 is the only human member categorised into species E (same as the ChAd Y25) and is frequently implicated in outbreaks of acute respiratory disease in military recruits (Wang et al., 2018; Mennechet et al., 2019; Tian et al., 2020). The neutralising antibodies to HAdV-4 were found to be present in about 70%, 50% and 8.5-17% of the study participants in Africa, China and the US respectively, suggesting that HAdV-4 infection rates are higher than reported AdV cases (Wang et al., 2018; Mennechet et al., 2019; Tian et al., 2020). In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health (1991-2000) showed an average of 1400 reported cases of adenovirus infection per year including 201 reported cases of HAdV-4 infection (Spencer, 2002). It is important to note that majority of reported adenovirus infections have not been serotyped and that testing for adenovirus infections may not be common in Australia. However, these numbers may indicate a low prevalence of adenovirus infections in Australia. Further, an increase in the frequency of HAdV-4 infections has been observed in people over the past 10 years and a new variant of HAdV-4 has been recently found to be circulating in the Hong Kong population (Zhang et al., 2019). Therefore, there is the potential for homologous recombination to occur if a person exposed to the GMO is also infected with HAdV-4 at the same time and in the same cells. This could potentially result in the replication of GMO (without E3 gene) in the host causing over-production of spike proteins and subsequently an adverse immune reaction. Similarly, production of recombinant replication incompetent adenovirus with spike protein could also result in an adverse immune reaction.

157. HAdV-5 infections are common in humans and therefore, there is a possibility for a person exposed to the GMO to be co-infected with a HAdV-5. As mentioned in Chapter 1, Section 3.4, homologous recombination is restricted to members of the same AdV species, although 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 the GMO and HAdV-5 belongs to different species i.e., species E and C, respectively. Therefore, the homologous recombination between different species is less likely to occur due to differences in their sequence homology. The E1 flanking sequences of HAdV-5 and the SAdVs are different which further reduces the chance of site specific recombination (Tatsis and Ertl, 2004; Tatsis et al., 2006; Colloca et al., 2012; Ghebremedhin, 2014; Morris et al., 2016). In addition, the method used to insert the transgene into E1 gene of the GMO further decreases the likelihood of recombination with HAdV-5. This severely restricts homologous recombination and formation of replication defective HAdV-5 expressing spike protein or replication competent GMO without spike protein.

158. As the GMO is prepared by deletion of E1 and E3 genes, there is also the potential for recombination to occur at the E3 gene between the GMO and the wild-type AdV (ChAd or HAdV). This recombination could only occur if the person exposed to GMO is also infected with the wild-type AdV in the same cell at the same time. In the context of import, transport, storage and disposal of the vaccine assessed in this application, the potential for a person to be exposed to the GMO is highly unlikely (see risk scenario 1). In a rare event, this co-infection of GMO and wild-type AdV could result in an insertion of E3 gene into the GMO genome resulting in a replication deficient GMO with immune-evasion properties. However due to the packaging constraint on the virus genome size, this would result in an unstable recombinant virus which would be cleared by the immune system.

159. In an unlikely event, co-infection of the GMO and the wild-type AdV (ChAd or HAdV) in the same cell at the same time and recombination event between these viruses could result in the acquisition of both E3 and E1 genes in the GMO. This would result in a recombinant virus which would have properties similar to the parent virus (GMO with E1 and E3 genes) or similar to the GMO (a recombinant adenovirus with a spike protein and lack of E3 gene).

160. As recombination requires high sequence homology, there is limited possibility of recombination occurring between the GMO and the other viruses present in the exposed person. Similarly, if a person exposed to the GMO gets co-infected with SARS-CoV-2, the recombination between them is not plausible as the GMO is a DNA virus whereas SARS-CoV-2 is a RNA virus. Different molecular mechanisms are involved in recombination processes between DNA and RNA viruses which reduces the likelihood of recombination between DNA and RNA viruses (Bujarski, 2008; Taucher et al., 2010).

161. The presence of pre-existing neutralising antibodies to HAdV (Lasaro and Ertl, 2009; Alonso-Padilla et al., 2016) in the GMO-exposed person would limit distribution and shedding of AdVs if homologous recombination occurs in the person exposed to the GMO.

162. Increased expression of spike protein in the host is unlikely to result in the production of novel toxic or allergenic compounds. The genome of the GMO including the introduced genes has been fully sequenced. These proteins are not known to be toxic to humans.

Potential harm

163. If complementation were to occur, the number of replication incompetent GMOs produced in the host cells would increase resulting in increased expression of spike proteins in the host. Similarly, homologous recombination in people and chimpanzees would increase the expression of the introduced genes i.e., spike proteins. The exposed individuals may generate a stronger antibody response for the S glycoprotein of SARS-CoV-2 and also develop T-cell responses. These are not expected to cause harm to affected individuals. If the person exhibits any symptoms of adenoviral infection, effective antiviral treatments can be used to treat the infection.

164. As ChAds do not cause any disease in humans and other animals, the formation of a replication competent GMO without spike protein would not result in any harm. Similar to a previous study (Xiang et al., 2006), antibodies in humans could be formed in response to GM recombinant virus (GMO without spike protein) but no clinical symptoms would be expected.

Conclusion

165. The exposure of people to a GMO which has acquired the E1 gene or E3 gene or transferred spike proteins to other AdVs 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
Potential causal pathway	Release of GMO into the environment via accidental spill/unused residues (e.g. sewerage, spills) ↓ Exposure to people or animals ↓ As per scenario 1-2
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk Source

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

Potential causal pathway

167. The GMO could be released into 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. This could result in exposure of people and animals to the GMO and could potentially result in adverse immune reactions and/or disease in people and animals.

168. As discussed in Risk Scenario 1, accidental spills associated with import, transport, storage and disposal have been considered and the proposed measures would reduce the chances of GMO being released into the environment.

169. In the event of a spill without correct decontamination with suitable disinfectants, the GMO could possibly persist/survive on surfaces for more than 12 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 and Section 4.3.3). This could result in the persistence of the GMO in the environment.

170. As mentioned in Chapter 1, Section 3 and 5.2, the ChAd is a member of the genus *Mastadenovirus* the members of which infect a wide range of mammals including non-human primates, bats, felines, swine, canine, ovine and caprine (Roy et al., 2004; Borkenhagen et al., 2019). Therefore, it is possible that the GMO could infect other mammals including non-human primates. Given that the GMO is replication incompetent, this could result in infection but no replication of the GMO in the other mammals.

171. As mentioned above, ChAd is not known to infect insects, birds and non-mammalian aquatic organisms including fresh and salt water species. Therefore, the likelihood of ChAd infecting other species in the Australian environment is very low.

172. Chimpanzees are the only natural hosts of ChAds and are not native to Australia and would only be found in zoos. The prevalence of wild-type ChAds in Australia would be very low and the impact of the GMO infecting the chimpanzee is also very low.

173. Similar to the parent organism, the GMO can 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 presence of the GMO in the sewerage and subsequently GMO dispersal in the aquatic environment. The impact of survival of the GMO in an aquatic environment is likely to be very low as the GMO is replication incompetent and would eventually degrade.

174. In the unlikely event that 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. Therefore the

likelihood of infection of humans or animals following exposure to an environmental source is remote.

175. 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

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

Conclusion

177. 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

178. Uncertainty is an intrinsic part of risk analysis³. There can be uncertainty in identifying the risk source, the causal linkage to harm, the type and degree of harm, the likelihood of harm or the level of risk. In relation to risk management, there can be uncertainty about the effectiveness, efficiency and practicality of controls.

179. There are several types of uncertainty in risk analysis (Clark and Brinkley, 2001; Hayes, 2004; Bammer and Smithson, 2008). These include:

- uncertainty about facts:
 - knowledge – data gaps, errors, small sample size, use of surrogate data
 - variability – inherent fluctuations or differences over time, space or group, associated with diversity and heterogeneity
- uncertainty about ideas:
 - description – expression of ideas with symbols, language or models can be subject to vagueness, ambiguity, context dependence, indeterminacy or under-specificity
 - perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

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

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

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

³ A more detailed discussion is contained in the Regulator's *Risk Analysis Framework* available from the OGTR [website](#) or via Free call 1800 181 030.

Section 4 Risk evaluation

183. Risk was 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.

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

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

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

186. 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.

187. In the context of the control measures proposed by the applicant and the operating guidelines of the pertinent regulatory agencies, and considering both the short and long term, none of these scenarios was identified as representing a substantive risk requiring further assessment. The principal reasons for this include:

- The GMO is replication incompetent which will prevent it from multiplying in other cells;
- The GMO would be restricted to the site of injection and/or draining lymph nodes and would not be shed from the vaccine recipients;
- The likelihood of complementation and recombination of GMO with other adenoviruses is very low;
- The GMO does not cause disease in humans and other organisms other than great apes; and
- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccinees) would be minimised due to implementation of well-established import, transport, storage and disposal procedures.

Therefore, any risks to the health and safety of people, or the environment, from the proposed commercial supply of the GM vaccine 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 environment⁴.

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

Chapter 3 Risk management plan

Section 1 Background

188. Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator’s decision-making process and is given effect through proposed licence conditions.

189. 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.

190. 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.

191. 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

192. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed supply of the GMO. These risk scenarios were considered in the context of the proposed receiving environment and the Australia-wide release, and considering both the short and long term. The risk evaluation concluded that no specific risk treatment measures are required to treat these negligible risks.

Section 3 General risk management

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

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

3.1 Applicant suitability

194. 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.

195. The licence conditions include conditions that require the licence holder to inform the Regulator of any circumstances that would affect their suitability.

196. In addition, any applicant organisation must have access to a properly constituted Institutional Biosafety Committee and continue to be an accredited organisation under the Act.

3.2 Testing methodology

197. The licence conditions include conditions that require AstraZeneca 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 methodology is required prior to conducting any dealings with the GMO.

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

198. When this licence is issued, any person, including the licence holder, could conduct any permitted dealing with the GMO.

3.4 Reporting requirements

199. The licence conditions include conditions that require the licence holder to immediately report any of the following to the Regulator:

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

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

201. 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

202. 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.

203. 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

204. 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.

205. For the current application for a DIR licence, the Regulator has included 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. The licence conditions include conditions that require the licence holder to maintain ongoing oversight which are achieved through 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).

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 system

206. 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

207. 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.

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

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

210. 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 180. However, specific indicators of harm may also be identified during later stages, e.g., through either of the other components of PRR.

211. 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

212. The third component of PRR is the review of RARMPs after a commercial/general release licence is issued. Such a review would take into account 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

213. The risk assessment concludes that the proposed commercial release of this GM COVID-19 vaccine poses negligible risks to the health and safety of people or the environment as a result of gene technology.

214. The risk management plan concludes that these negligible risks do not require specific risk treatment measures. However, general conditions have been 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 authorities⁵ 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	<p>Broadly supportive of application DIR 180.</p> <p>While it is unlikely that there would be a risk to the food chain, this risk needs to be considered and the question addressed. Likewise, any risk to the environment and the ecosystem will also need to be addressed.</p> <p>Further reviews by the TGA and RARMP are required to ensure that the risk to public health and safety is minimal.</p> <p>The vaccine has double-stranded DNA of the 'spike' protein, which is stable, rather than the single stranded RNA of the COVID-19 virus itself which is highly unstable. It is also stated that the clinical results were largely absent, but notes this will be the main focus of the TGA, which will be able to get more up-to-date results later after the UK data become available.</p>	<p>Submission has been noted.</p> <p>The risk to the environment and the ecosystem have been considered in Chapter 2 of the RARMP.</p> <p>Submission has been noted.</p> <p>The safety, immunogenicity and efficacy of the GM vaccine from published clinical trials are discussed in Chapter 1, Section 4.3.</p>
2	<p>We have reviewed the material provided in the summary application. As the critical evaluations about the use or otherwise of this vaccine will be undertaken by the TGA, we are supportive of this application based on the current information provided while awaiting the RARMP at a later date.</p>	<p>Submission has been noted.</p>
3	<p>At this stage of the process, we highlight the importance of having strong systems in place for monitoring and follow-up any adverse impacts from the supply of the vaccine. I request that this be considered in the development of the consultation RARMP.</p>	<p>Draft licence conditions in Chapter 4 of the RARMP cover monitoring and follow-up of any adverse impacts from the supply of the vaccine. Impact in the vaccinated individuals will be assessed as part of the TGA assessment and requirements.</p>

⁵ Prescribed experts, agencies and authorities include GTTAC, State and Territory Governments, Australian government agencies and the Minister for the Environment.

Submission	Summary of issues raised	Comment
4	<p>The supply appears to be of low risk to human health and the environment.</p> <p>We had concerns about the potential for shedding of adenovirus vaccine vector from immunised humans into the sewage system, and the potential for the vector to recombine with human infective adenovirus, possibly resulting in an associated risk of harm to human health once in the receiving environment. We recommend that the Risk Assessment and Risk Management Plan very clearly address the perceived or actual risk of such recombination occurring. This will give the community confidence that there is no risk of adenovirus vaccine vector shedding into the environment.</p>	<p>Submission has been noted.</p> <p>The potential of the GMO to recombine with other adenoviruses has been considered in Risk scenario 2 (see Chapter 2, Section 2.4.2).</p> <p>The potential for the GMO to shed from the vaccinated person and into the environment is addressed in Chapter 1 Section 4.3.2 and Chapter 2, Section 2.4.3 (Risk scenario 3).</p>
5	<p>While it is likely that the environmental risks will be negligible for this vaccine, this is likely to be the first of several COVID-19 viral vaccine assessments and vaccination of the public is likely to be on a significant scale. Therefore, recommends full consideration and assessment of the following factors in the preparation of the RARMP.</p> <ul style="list-style-type: none"> • Viral replication and shedding • Persistence • Host range • Recombination <p>Any recent information or data on risks such as zoonosis, recombination, host range changes associated with the use of GM adenoviruses should also be included in the RARMP.</p>	<p>The potential for viral replication, shedding, persistence, host range and recombination have been discussed throughout Chapter 1 (Section 3.4, 3.5.1, 3.5.2, 3.5.4, 4.3.2 and 4.3.3) and Chapter 2 (Risk scenario 2 and 3).</p> <p>Risks associated with GM adenoviruses has been included in Chapter 2.</p>
6	<p>Overall, supported the licence application of the AstraZeneca Pty Ltd and look forward to the release of the Risk Assessment and Risk Management Plan (RARMP) for the proposed commercial supply of COVID-19 vaccine.</p> <p>Essentially, no detail on the batch to batch consistency methods to be used, to test are provided in the document and believe that this section has not been completed adequately. Details on testing methods need to be provided, for both Australian and overseas manufacturing.</p>	<p>Noted</p> <p>The GM vaccine may be manufactured overseas and/or in Australia. The Regulator has recently approved DNIR-630 and DNIR-632 for manufacturing and formulation of the GM vaccine.</p> <p>Batch to batch testing will be regulated by the TGA under cGMP licensing to the Australian and overseas manufacturing sites.</p> <p>The draft licence requires the applicant to provide a testing</p>

Submission	Summary of issues raised	Comment
		method to reliably detect the GMO, and the presence of the introduced genetic materials in a recipient organism.
	What mechanisms will be implemented to ensure all administering sites comply with any TGA-mandated post release review requirements, including any adverse effect reporting as part of ongoing monitoring and oversight as well as ability to rapidly share information if required?	Noted. Adverse event reporting is included in the draft licence. This would also be considered by TGA under their assessment.
	Risk to the integrity of the vaccine if there are accidents during storage or transportation? E.g. power failure and temperature change. Will guidelines be developed to assist in decision-making in the event of uncertain integrity?	Submission has been noted. Effects of Improper storage and the impact on vaccine efficacy would be considered by TGA under their assessment. The Vaccine Storage Guidelines 'Strive for 5' provides information and advice for vaccine storage management for Australian immunisation service providers, from medical practices to large hospitals, clinics and outreach providers. These guidelines describe the best approach to ensure that clients receive effective and potent vaccines and provide advice on what should be done in the event of a cold chain breach.
	The survivability data presented in the application is inconsistent. This inconsistency must be clarified prior to use.	Chapter 1, Section 3.5.4 and Section 4.3.3 details the published data on survival of adenoviruses on various surfaces, water types and sediments.
	Risk to patients if vaccine administration is not intramuscular but is accidentally administered Intravenously or it is eaten? This may be highly unlikely but human error can occur.	The potential for contact with the GMO via other routes is discussed in the risk scenarios in Chapter 2. Risks to people receiving the vaccine would be considered by TGA under their assessment. The COVID-19 vaccination policy states that the States and Territories will be responsible for ensuring an appropriately qualified and trained workforce can support delivery of the vaccine. More details about the COVID-19

Submission	Summary of issues raised	Comment
		vaccination policy can be found at https://www.health.gov.au/resources/publications/australian-covid-19-vaccination-policy
	Raised concerns about aerosolization/ vaporisation of the vaccine if spilled/vial broken or other risks to the healthcare professional delivering the vaccine, which might be increased by use of a multi-dose vial?	The potential for aerosol formation, spilled/broken vial and risk to the healthcare professionals have been addressed as part of Risk scenario 1 (Chapter 2, Section 2.4.1).
	Are there any additional concerns regarding adenovirus-naïve patients (children) or immunocompromised persons?	Risks associated with direct use of the vaccine and patient suitability would be considered by the TGA in their assessment.
	Is there a risk to animals/wildlife if wastewater or general waste/clinical waste in the disposal of unused product?	The potential risk to animals/wildlife is discussed in Risk scenario 3 (Chapter 2, Section 2.4.3).
	Risk at manufacturing locations to workers, environment and wildlife. Consider by-products in process.	The potential risk of exposure of people during preparation and administration and handling of the GM vaccine is discussed in Risk scenario 1 (Chapter 2, Section 2.4.1). The risk to manufacturing individuals for Australian manufactured GM vaccine is considered as part of DNIR-630 and DNIR-632 assessment.
	Are there any short or long-term effects on the utility of tetracyclines in the vaccinated population if leakage in wastewater/flora/fauna etc?	The vaccine does not contain tetracycline. It contains a CMV promoter with a tetracycline operator site. This tetracycline operator site does not confer resistance to tetracyclines.
	Consider how outback/nursing posts/no air-conditioning situations will be managed to meet the expected conditions for site of Australian release.	See above re COVID-19 vaccination policy.
		Issues relating to sustainability are outside the scope of the Regulator's

Submission	Summary of issues raised	Comment
	This application doesn't seem to have a sustainability/climate change lens. Are there any opportunities to have a lower waste footprint that could be explored? Should this be done at a state/territory level?	assessment required by the Act. Disposal of waste is the responsibility of the States and Territories.
7	<p>Draft recommendations</p> <p>The committee agrees that the following should be included in the RARMP: potential accidental exposure of humans and other organism to the GMO resulting in harm, potential for complementation and recombination of the GMO and other adenoviruses and potential for GMO to be harmful to the environment.</p> <p>The committee also suggested to consider risks associated with:</p> <ul style="list-style-type: none"> • possible integration of the adenoviral DNA into human genomes; and • appropriate methods for decontaminating any spills. 	<p>Submission has been noted.</p> <p>The potential for random integration of vector DNA is discussed in Chapter 1 (Section 3.4 and 4.3.1) and Chapter 2 (Section 2.2.).</p> <p>Appropriate decontamination methods are discussed in Chapter 1, Section 3.5.4.</p>

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	The committee 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. The committee agrees with the overall conclusion of the RARMP.	Submission has been noted.
2	<p>It is likely that the environmental risks will be negligible due to replication deficiency and thus negligible shedding into the environment; the narrow host range (only infects chimpanzees and humans) and recombination is unlikely to alter host range.</p> <p><i>We recommend that the RARMP discuss further the potential presence of wild type adenoviruses in vaccines and the risk of recombination with the GM virus in risk scenario 2 and section 3.4.</i></p> <p>While it is recognised that recombinants are unlikely to be more harmful than the GM virus or wild type chimpanzee adenovirus (ChAdV) or human adenovirus 4 (HAdV4), as mentioned in the RARMP, recombinants may have unexpected altered properties such as replication ability, shedding, virulence, latency and host range. While unlikely to alter host range substantially beyond humans and chimpanzees, this should be discussed considering experiments on the GM chimpanzee adenovirus have shown that it can infect mice, cotton rats, calves and humans (par 46).</p>	<p>Submission has been noted.</p> <p>Additional consideration and discussion has been included in the RARMP about potential for presence of wild-type adenoviruses in exposed individuals and the risk of recombination with the GMO (Chapter 2, Section 2.4.2 (Risk scenario 2)).</p> <p>Additional text has been added to the RARMP to discuss the potential for recombinant viruses to infect mice, cotton rats, calves and humans (Chapter 2, Section 2.4.2 (Risk scenario 2)).</p> <p>Morris et al 2016 discusses a range of simian adenoviruses as vaccine vectors including ChAdOx1, however the paper</p>

Submission	Summary of issues raised	Comment
	<p><i>Recombination with wild type chimpanzee adenovirus</i></p> <p>Recent reports on this vaccine have highlighted the possibility of the vaccine not being as effective in people from sub Saharan Africa, China and Brazil due to the presence of neutralising antibodies to the chimpanzee adenovirus vector (Morris <i>et al</i> 2016). The presence of antibodies indicates the presence of chimpanzee adenoviruses in humans from certain countries where chimpanzees are native. This information on the risk of recombination occurring between GM chimpanzee adenovirus and a wild type ChAdV possibly and presence and persistence in certain nationalities in Australia should be included in risk scenario 2.</p> <p><i>Recombination with wild type human adenovirus</i></p> <p>We recommend the RARMP include more discussion of the likelihood of recombination occurring with HAdV4. Par 157 states that ‘As recombination requires high sequence homology, there is limited possibility of recombination occurring between the GMO and the other viruses present in the exposed person’. However, HAdV4 has very high sequence homology to the GM virus and is most similar phylogenetically to the GM chimpanzee adenovirus 25 (Roy <i>et al</i> 2009) and therefore the likelihood of recombination occurring should be discussed in risk scenario 2.</p>	<p>does not precisely discuss the COVID-19 vaccine. The neutralising antibodies to some adenoviral vectors such as HAdV-5, HAdV-26, ChAd-63, ChAd1, ChAd6 and ChAd68 were observed in certain populations and this raises the possibility of these vectors not being as effective in these pre-exposed populations from certain countries. The neutralising antibodies to ChAdOx1 has been found to be low in the UK (0%) and in Gambia (9%) suggesting that ChAdOx1 vector could be efficacious in most people (Dicks <i>et al</i> 2012). The clinical trials with the COVID-19 vaccine have shown safety and efficacy in the UK, Brazil and South Africa, suggesting that the vaccine is effective in a wide range of populations.</p> <p>Additional text has been added to the RARMP discussing the likelihood of recombination of GMO with wild-type chimpanzee adenovirus (Chapter 2, Section 2.4.2 (Risk Scenario 2)).</p> <p>Additional text has been added to the RARMP discussing the likelihood of recombination of the GMO with wild-type adenovirus (HAdV-4) (Chapter 2, Section 2.4.2 (Risk Scenario 2)).</p>
3	<p>The release appears to be of low risk to human health and the environment. Advise that we have no objection to the issue of a licence for DIR 180.</p> <p>The potential for shedding could be considered an ‘indicator of harm’ and be addressed by OGTR within the licence for DIR 180. We recommend licence conditions are included that require AstraZeneca to provide analytical data from stool samples obtained from vaccine recipients during the current clinical trials. Samples should be analysed for the marker gene specific to the adenovirus vaccine vector to demonstrate</p>	<p>Submission has been noted.</p> <p>The principal route by which the GMO may enter the wider environment following vaccination is via shedding (Chapter 1, Section 5.1). However, as the injection of non-replicating GMO is via intramuscular injection, wide-spread shedding is not expected due to localisation of viral particles at the injection site and draining lymph nodes (Chapter 1, Section 4.3.2). Therefore, a</p>

Submission	Summary of issues raised	Comment
	conclusively the absence of viable virus that could be shed to sewer.	licence condition to provide additional analytical data is not necessary.
4	Overall, AstraZeneca Pty Ltd’s application has negligible risks to the health and safety of people and the environment. Specifically, we are satisfied that the measures taken to manage the short and long term risks from the proposal are adequate.	Submission has been noted.
5	We have reviewed this application and are broadly supportive of DIR 180. However, suggest consideration be given to strengthening the licence conditions. In particular we note that Section 2.2 pages 33 onward implies that the regulator has to initiate a request for new information relating to the vaccine use if problems occur which then allows the owner of the license to assess the 'reasonability ' of the request before complying. The ACT suggests that stronger language requiring the recording and disclosure of issues be considered.	Submission has been noted. Licence condition 14 requires the licence holder to disclose any new information that would affect the risk assessment to the Regulator. Licence condition 16 enables the Regulator to request more information from the licence holder, in addition to that provided under condition 14, or to conduct additional research.
6	Overall, we support the Gene Technology Regulator’s conclusion of the RARMP that the proposed supply of the commercial supply of a genetically modified COVID-19 vaccine poses negligible risks to human health and safety and the environment.	Submission has been noted.
7	Agree the risk posed by this vaccine to the environment are negligible. As the vaccination task force is still working on the plan for how vaccines will be disseminated, we do not agree that the all centres that will be involved in the vaccination will know about the standard procedures for GMO. Therefore, recommends that OGTR give more specific advice about the following: <ul style="list-style-type: none"> • If people administering the vaccine need to wear gloves • How the vaccine vials, needles and syringes are disposed of • How bandaides or swabs of the site are disposed of How to manage vaccine spills	Submission has been noted. The RARMP concludes that no special conditions are proposed to manage the risk from the GMO as standard healthcare practices for vaccination are sufficient. As described in Risk scenario 1, all personnel working in vaccination services are required to follow the <i>Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019)</i> and the <i>Australian Immunisation Handbook</i> . This includes wearing gloves for each invasive procedure, disposing of single use sharps in an approved sharps container at point of use, cleaning surfaces immediately after a spill.

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

The Regulator received 44 submission from the public on the consultation RARMP. The issue raised in the submission is 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	Quote from submission: “Please do not approve this vaccine. I believe in you being trustworthy and people with a conscious and so you will look into this deeply and not approve any vaccine as you know it is not in our best interests.”	The Regulator makes licence decisions on the basis of consideration of risks to people and the environment. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.
2	<p>Submitter “Concur with this statement in the risk assessment: “The risk assessment concludes that the proposed commercial release of this GM COVID-19 vaccine poses negligible risks to the health and safety of people or the environment as a result of gene technology.”</p> <p>“It is clear that considerable care has been taken in the design of the vaccine and in carrying out the risk assessment. One concern is that a 4-week period of public consultation, even in view of Christmas, is too long. It may be in the national interest to make this vaccine available as early as possible, for example to ring-vaccinate outbreaks, and I urge your office to consider issuing an earlier interim approval for its use in this restricted setting.”</p>	<p>Submission has been noted.</p> <p>The consultation for this application is open for 30 days, the minimum required by the <i>Gene Technology Act 2000</i>.</p>
3	<p>“I am offering some suggestions that I would like to support the entry of the import as follows;</p> <p>1) To be aware that Australia has a Airport Transport Location with prepared facilities to assist entry and exit of medical needs.</p> <ul style="list-style-type: none"> • The Airport has recently suffered cyclone conditions and is now resuming to the crowd and regional marketplace. • The Airport is connected to the original hospital in the area Tennant Creek and surrounding hospitals functioning poison controls attracted some Australian Awarded Medical Professionals and don't forget Charles Darwin. • The Airport is surrounded by sand that is sinking and wasting back, incl. wastelands. 	<p>The Regulator makes licence decisions on the basis of consideration of risks to people and the environment.</p> <p>The vaccine will be imported into Australia by air and packaged according to rules set by the International Air Transport Association. According to the packaging rules, the vaccine will be enclosed within at least two layers of impact resistant and leak-proof packaging. This packaging is expected to provide a high level of protection against damage, spill or loss of the vaccine during transport.</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> • Situations effecting the environment can be controlled by wasting back as with substances like U92r % C4H10 where it is noted the infectior is not trapesing. It could be not wanting lava or fire, gas or a new chemical C4H10, C02, C12, F2, C2, H2, N2,. The hillsides are deriving a G maybe chemically unknown and these wastebaks cancel out dangerous things and substances. Like the black seeping coastlines. U92 as a waste is merely salt and can be seen as a resource energy and fuel for the future. Salt Split. <p>2) To be concerned about follow up</p> <ul style="list-style-type: none"> • An oxidised substance for clearing any wounds or infections from the movement of the inoculation devices, including the entry of old leprosy and Spanish flu locks. • Then the concerns of side effects and waste products including faeces. • Effluent and Waste Bins so forth could be addressed if you want to.” 	<p>Before this vaccine can be used, both the TGA and the OGTR must approve it. Details around administration of the vaccine and potential adverse reactions will be considered in the TGA assessment.</p> <p>Waste generated during administration of the vaccine will be disposed of as clinical waste according to the regulations in place in each State and Territory.</p>
<p>4</p>	<p>Submitter is “strongly opposed to the approval of the AstraZeneca vaccine.”</p> <p>This submission contained a 34 page document describing the issues discussed below and the following attachments.</p> <ul style="list-style-type: none"> • Attachment 1-4 were related to mRNA based vaccines • Attachment 5 is FDA information about COVID-19 adverse events • Attachment 6: information about Nuremberg Code and Australian constitution. <p>“If the Australian Government approves the use of this vaccine throughout Australia, that it will be committing a Crime Against Humanity as clearly stated in the Nuremberg Code. It will also be breaking S 51 s.XXIII (A) of the Australian Constitution.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • The vaccine created by the Institut Pasteur called Chadox1-nCov-19 was manufactured in 2019. It included nanoparticles or chips patented by Bill Gates and had to work with 5G. This vaccine has been sold to several countries for billions of dollars. • The ingredients used by AstraZeneca in their COVID-19 vaccine are considered to be dangerous to human health. In addition, concerns regarding “the vaccine contains genetic material from three sources from an aborted 14 week old Caucasian male, virus from Chimpanzees and more cells from 	<p>Submission has been noted.</p> <p>The attachments were reviewed. Attachments 1-4 were relating to different COVID-19 vaccines which is outside the scope of this assessment conducted by the Regulator.</p> <p>The issues regarding consent are outside the scope of this assessment conducted by the Regulator.</p> <p>Noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment. The vaccine contains a ChAdOx1 vector containing the spike protein. This ChAdOx1 vector acts as carrier to deliver the spike protein in the host rather than a gene editing platform. After injection, the adenoviral vector enters human cells</p>

Submission	Summary of issues raised	Comment
	<p>human embryonic kidneys cells from a different human cell line.”</p> <ul style="list-style-type: none"> • “The Chadox1 ingredient uses genetically modified Adenoviruses that create a gene editing platform in the host’s body. This means that after vaccination, the individual’s immune system becomes confused and compromised, that a much higher probability of death will occur from a Coronavirus infection for the rest of their life.” • “It is impossible to eliminate the changes to host’s genetic makeup from the vaccine because the source of the viral protein means the individual becomes like a Genetically Modified Organism (GMO) because the host’s body is continually producing the virus protein.” 	<p>and prompts the immune system to start producing antibodies to protect against any coronavirus infection.</p> <p>This comment was made in relation to an mRNA vaccine that is not the subject of this application.</p>
	<ul style="list-style-type: none"> • Wild-type coronavirus infection after COVID-19 vaccination in people would trigger the immune system and will cause harm/death. • AstraZeneca has been penalised over \$1.1 billion for 21 violations of civil and criminal matters since 2003 and company’s unfair and deceptive practices in its marketing of the antipsychotic drug Seroquel. 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The RARMP prepared in relation to the proposed dealings considers the risks to human health and safety and to the environment posed by dealings being assessed in the application. The Regulator’s decision regarding the suitability of the applicant to hold the licence involves a separate and additional consideration in accordance with section 57 and 58 of the <i>Gene Technology Act 2000</i>.</p>
	<ul style="list-style-type: none"> • AstraZeneca to seek exemption from coronavirus vaccine liability claims in most countries and who pays for the compensation if a COVID-19 vaccine has rare side effects? • Issues were raised for other COVID-19 vaccines particularly Moderna and Pfizer and were labelled as experimental vaccines. In addition, these vaccines have resulted in deaths after vaccination in healthy medical professionals. Further, 87,000 nurses and 33 medical professionals and scientists have publicly criticized and opposed to these mRNA based vaccines. 	<p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator for this vaccine.</p>
	<p>The submission included an excerpt from an article was stated in the emails where Australian HPV vaccine researcher Professor Ian Frazer discusses coronavirus and difficulties developing a coronavirus vaccine.</p>	<p>The article was dated 17 April 2020, the general coronavirus content was in relation to the SARS-CoV-1 which is different from SARS-CoV-2. Articles published after April 2020 has discussed the development of COVID-19 vaccines.</p>

Submission	Summary of issues raised	Comment
	<p>Submitter was concerned about “possible adverse event outcomes” as described in the FDA working list.</p> <p>Quote from submission: “Given that the COVID-19 experimental vaccines fail every one of the 10-point Nuremberg Code, no government in the world should be ‘mandating’ these ‘vaccines’ upon their people. To do so makes anyone involved in the process guilty of committing a crime against humanity.”</p>	<p>Possible risks for the vaccine recipients will be considered by the TGA. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible.</p> <p>The Regulator must consider risks to human health and safety and to the environment posed by the genetic modification being described in the application.</p>
5	<p>Submitter is “vehemently opposed to this vaccine being approved for Australia.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • Vaccine uses “a gene for the generic Coronavirus spike protein in a modified version of a chimpanzee adenovirus (a virus that typically causes cold and flu-like symptoms).” “The true Covid-19 strain have never been actually identified.” • COVID-19 vaccines “do not stop people getting the virus and do not stop the virus from spreading.” • “Adverse risks associated with these vaccines have been in the range of around 2.8-3+% in other countries so far. In Australia, that’s likely to be close to 750,000 adverse reactions in the short term - no long term data is yet available.” 	<p>Submission has been noted.</p> <p>The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000 (the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p> <p>Noted. The COVID-19 vaccine is aimed to reduce the severity of the disease in people.</p> <p>Possible risks for the vaccine recipients will be considered by the TGA. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible.</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> “Testing has been rushed and highly selective. The decision to accept this or any other DNA/RDNA vaccines should be deferred for a period of 2 years until complete data can be provided.” “Successful alternative treatments in place such as Ivermectin, hydroxychloriquine, Zinc, Vit D etc. - there is no rush and Australia has no major outbreaks that cannot be managed.” 	The issues raised in relation to different COVID-19 treatments are outside the scope of this assessment conducted by the Regulator.
6	<p>Submitter is “100% opposed to any form of this vaccine being approved for Australia.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “It is nothing short of willful misconduct to ignore the safety concerns of this vaccine. Vaccines take decades to develop and test and the fact that there has never been a successful coronavirus vaccine in decades of attempts is proof enough that this is impossible to achieve.” “The ignorance and rejection of proven treatments such as Ivermectin is an absolute disgrace, and further proof that there are other agendas at play and none that include preserving human life. This is the biggest crime against humanity in all of history.” <p>This submission also contained an attachment titled ‘America’s Frontline Doctors White Paper On Experimental Vaccines For COVID-19’ which raises concerns about just how dangerous these vaccines are.</p>	<p>Submission has been noted.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p> <p>The issues raised in relation to different COVID-19 vaccines and treatments are outside the scope of this assessment conducted by the Regulator.</p> <p>The attachment contains information on the AstraZeneca and other COVID-19 vaccines. The quality, safety and efficacy of the vaccine will be assessed by the TGA.</p>
7	<p>Submitter is “strongly opposed to the release and use of this vaccine without much more extensive testing, trials and observation.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “Do not need experimental, possibly dangerous treatments for a virus that affects, at worst, 0.04% of the population and kills less than 1% of infected people. The vaccine is likely to be more deadly than the disease.” 	<p>Submission has been noted.</p> <p>The Regulator cannot issue the licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in such a way as to protect the health and safety of people and the environment. The Regulator makes licence decisions on the basis of consideration of risks to people and the environment. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport,</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> Concerns were raised regarding adverse effects from numerous medications in the past have not become apparent for many months or years and lack of knowledge about the long term effects of AstraZeneca modified virus and other vaccine ingredients. “Urge caution before releasing this drug for public administration. Please hit the pause button for at least 2 years while further investigation and testing takes place.” 	<p>storage and disposal of the vaccine are negligible.</p> <p>Possible risks for the vaccine recipients will be considered by the TGA. Further, the quality, safety and efficacy of the vaccine will be assessed by the TGA.</p> <p>Conditions of the licence for the vaccine cover the monitoring and follow-up of any adverse impacts from the supply of the vaccine. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible.</p>
8	<p>Quote from submission: “This experimental medical intervention is diabolical.”</p> <p>Raised issues about the mRNA based COVID-19 vaccines from a physician Frank Shallenberger MD, HMD.</p>	<p>Submission has been noted.</p> <p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator on this vaccine.</p>
9	<p>Submitter has strong objection to the roll out of any mRNA vaccines in Australia.</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “Should the roll out go ahead, people should get adequately informed about the risks and that they have a choice in the matter. In this regard and in order to enable them to make an informed decision it is also absolutely essential to inform the public that there are other treatment options instead of being suppressed as they currently seem to be.” “The hasty roll out of a "vaccine" that has never been used before and has not undergone testing for long term side effects.” Safety of the AstraZeneca vaccine after admitting the dosing mistake. “The large number of adverse events in the general population when the vaccines were only tested on healthy fit individuals with anyone who had any health issues being excluded from the trials”, uncertainty about how body would react to autoimmunity issues, fertility, carcinogenic effects and chronic illnesses and previous trials for coronavirus vaccine were unsuccessful most likely due to pathogenic priming. The links to the two articles were provided in the 	<p>Submission has been noted.</p> <p>The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible. The licence conditions cover the monitoring and follow-up of any adverse impacts from the supply of the vaccine. The risks to human health and environment in the context of import, transport, storage and disposal are considered in the RARMP. Risks associated with direct use of the vaccine will be considered by the TGA. Further, the quality, safety and efficacy of the vaccine will be assessed by the TGA.</p> <p>The potential for adverse immune reactions to occur as a result of gene technology was considered in three postulated risk scenarios in Chapter 2, Sections 2.4.1–2.4.3 of the RARMP.</p>

Submission	Summary of issues raised	Comment
	<p>submission: Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity and Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus.</p> <ul style="list-style-type: none"> • Other treatments such as Ivermectin, Doxycycline and zinc have been very successful in treating COVID-19 patients. • Raised issues about the mRNA based COVID-19 vaccines such as short term adverse reactions, people dying after vaccination, and the vaccine doesn't actually seem to stop people from getting the virus or from transmitting it, but only reduces the symptoms. As such it seems rather ludicrous to then unleash such technology on the population. 	<p>The issues raised in relation to different COVID-19 treatments are outside the scope of this assessment conducted by the Regulator.</p> <p>These issues do not directly relate to the AstraZeneca COVID-19 vaccine as the technologies are different.</p>
10	<p>Quote from submission: "If the Astra Zeneca Covid 19 vaccine is an mRNA vaccine it will cause untold harm." Further, concerns were raised regarding infiltration of every cells, collapsing of organs.</p>	<p>The AstraZeneca vaccine (ChAdOx1-S[recombinant]) is a viral vector based vaccine and is not an mRNA vaccine. Thus, the issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator.</p>
11 43	<p>Two identical submissions were received.</p> <p>"We object to the Astra Zeneca vaccine you are reviewing, and any vaccine for use in Australia including any such related to so called 'Covid 19', and including any vaccine containing any genetically modified ingredients, or vaccines or medicines that alter genes of any recipient intentionally or unintentionally."</p>	<p>Submission has been noted. The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000 (the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result</p>

Submission	Summary of issues raised	Comment
	<p>Issues raised in the submission were:</p> <ol style="list-style-type: none"> 1. How is expression of covid spike expression turned off? 2. “Demonstrate beyond reasonable doubt that no public official in this country is personally profiting from vaccine” 3. Public demonstration of administration of the vaccine to politicians and other public officials 4. Demonstrate the existence of the virus 5. Demonstrate the existence of the virus variants 6. “Refute the contents and the studies of the book 1200 studies The Truth Will Prevail as attached to this email” 7. “Demonstrate the so called 'Covd 19' virus infects human tissue” 8. “Demonstrate clinical trials into every possible other treatment, pharmaceutical or otherwise, have under gone full double blind peer reviewed long term trials and been unsuccessful” 9. “You are directed to keep this avenue for submissions open until every single man and woman in Australia has been personally notified of the capacity to make a submission...” 10. Refute the statement that “there is no such thing as informed consent when the risks of taking a vaccine are unknown.’ <p>The following attachments were attached to the email:</p> <p>“mistake dose.pdf”</p> <p>“AstraZeneca Corporate Rap Sheet.pdf”</p> <p>“TGA complaint-TGA.pdf”</p> <p>“EUA CDC Panel ifu.pdf”</p> <p>“Global COVID Report – Compressed”</p> <p>“CDC_Scientist_Make_2_COVID_Admissions_that_Destroy_Official_Narrative.pdf”</p> <p>“1200-studies-The truth Will Prevail-v2.6_05-05-20.pdf”</p>	<p>of the import, transport, storage and disposal of the vaccine are negligible.</p> <p>1: The vaccine has been modified so that after it enters the first cell it cannot go on to make further copies of itself.</p> <p>When the first cell dies, no more spike protein is made.</p> <p>Requests 2 to 10: The Regulator imposes licence decisions on the basis of consideration of risks to people and the environment posed by the gene technology. The subjects raised in these points are not related to the application of gene technology.</p> <p>9. The consultation for this application was open for 30 days which is the minimum specified by the <i>Gene Technology Act 2000</i>. Invitations to comment were issued through a national newspaper, online notice and direct mail to those who have subscribed to <i>OGTR News</i>.</p>
12	<p>Submitter does “not consent to any gene/DNA altering pharmaceutical product to be released or injected into myself or my children/family, or the Australian people.” Does “not consent to deceptive, false pretense in labelling this DNA altering abomination, a 'vaccine'...in the traditional sense and as most people would be familiar with this term.”</p>	<p>Submission has been noted.</p>

Submission	Summary of issues raised	Comment
13	<p>Submitter “Express non consent to this dangerous experiment.” Does “not consent to AstraZeneca and their experimental vaccine.”</p> <p>A link for YouTube video titled “Sucharit Bhakdi Full Interview Planet Lockdown”</p>	Submission has been noted.
14	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • “The corona virus patent is a functional forgery.” • “Please provide evidence the legality of this biological weapon?” <p>A YouTube link titled “London real Transform yourself dr” by Dr David E Martin, PHD (National Intelligence Analyst) was provided.</p>	The issues raised in the submission are outside the scope of this assessment conducted by the Regulator.
15	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • The consequences of this injection are not known at all, as it is a first in humans. • What if the cells of some "vaccinees" made too many viral compounds, causing uncontrollable reactions in our bodies? • The possibility of integration into our chromosomes. There is therefore a real risk of transforming our genes permanently. There is also the possibility, by modifying the nucleic acids of our eggs or sperm, to transmit these genetic modifications to our children. The people who promote these gene therapies, falsely called “vaccines” are sorcerer's apprentices and take the citizens of the world, for guinea pigs 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The vaccine has been modified to limit the amount of time that the virus protein is made.</p> <p>The possibility of integration has been discussed in Chapter 2, Section 2.2 of the RARMP.</p>
16 18	<p>Two identical submissions were received. Submission is “to notify my objection to the approval of the COVID 19 solution in Australia.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • “The Astra Zeneca ChAdOx1 nCoV-19 uses Adenovirus Vector based treatment that have never been licensed for human use in more than 25 worldwide experimentation. The constant trade off immunogenicity and toxicity explains why adenovirus vector vaccines never demonstrated efficient results on large scale clinical trials.” • “The solution developed by Astra Zeneca does not guarantee absence of dangerous side effects on the short, mid or long term as it has been created within a time range 2 to 5 time shorter than a normal research process would normally take.” 	<p>Submission has been noted.</p> <p>The quality, safety and efficacy of the vaccine will be assessed by the TGA</p> <p>Possible risks for the vaccine recipients will be considered by the TGA. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible. The licence</p>

Submission	Summary of issues raised	Comment
		conditions in Chapter 4 of the RARMP covers the monitoring and follow-up any adverse impacts from the supply of the vaccine.
17	<p>Quote from submission: “Do not consent to this nor do thousands of Australians.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • “You as an organisation are threatening the Australian people with planned genocide. This is in breach of Nuremberg Code.” • Government should provide education on healthy eating and natural supplements such as Vitamin D, A and C along with zinc; herbal remedies formulated to give strength to the immune system and also homoeopathy • Flu vaccine resulted in illness in a range of people. • Scientists/professors and doctors warning against any of the COVID-19 vaccine (mainly related to mRNA based vaccines) • “No Vax can be made mandatory. The people have freedom of choice – and freedom of movement at all times!” Government lies it’s not mandatory but there are restrictions on where you can go. 	<p>Submission has been noted.</p> <p>The issues raised in relation to different COVID-19 vaccines and treatments are outside the scope of this assessment conducted by the Regulator.</p>
	<ul style="list-style-type: none"> • The ingredients of AstraZeneca COVID-19 vaccine is total revulsion and criminal. 	<p>Submission has been noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment.</p>
19	<p>Quote from submission: “Do not consent and will decline this service/product due to the continual deceptions risking the population with no immunity against this company.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • “The Moderna and Pfizer “alleged vaccine” trials have explicitly acknowledged that their gene therapy has no impact on viral infection or transmission whatsoever and merely conveys to the recipient the capacity to produce an S1 spike protein endogenously by the introduction of a synthetic mRNA sequence.” • Definition of vaccine and marketing of the alleged vaccine through the mainstream media to the Australian population is deemed 	<p>Submission has been noted.</p> <p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator for this vaccine.</p>

Submission	Summary of issues raised	Comment
	<p>“unfair or deceptive acts or practices in or affecting commerce”.</p> <ul style="list-style-type: none"> The ingredients present in the AstraZeneca COVID-19 vaccine. 	<p>Submission has been noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment.</p>
20	<p>Submitter is “totally opposed to any controls on people who chose not to vaccinate.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “How does anyone know for sure what vaccinations will do to some folks now or in the future. Who will bear the possible harms & costs? “ It should “not even be approved until there is overwhelming proof of efficacy & 100% total safety.” Vaccine should not be “Compulsory” or to “force or coerce”. 	<p>Submission has been noted.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p> <p>Noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment.</p>
21	<p>Quote from submission: “Do not consent to the AstraZeneca Covid19 Vaccine.” Not against vaccinations but “totally against unsafe vaccinations, which clearly this one is.”</p> <p>The submission also contained 82 Youtube video links and website links and documentaries where doctors express an opinion on vaccines safety and efficacy.</p> <p>Issues raised in the submission were:</p>	<p>Submission has been noted.</p> <p>These submissions were general in nature and did not mention matters directly relevant to the AstraZeneca COVID-19 vaccine. Thus, they are outside the scope of the Regulator’s assessment required by the Act.</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> The safety of the AstraZeneca COVID-19 vaccine. 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000 (the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p>
	<ul style="list-style-type: none"> Provided information on mRNA based vaccines - many ethical Doctors and Scientists are speaking out against and providing reasons why vaccines should not be enforced. 	<p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator for this vaccine.</p>
	<ul style="list-style-type: none"> The “government are not educating people on what to eat to boost their immune system, which is designed to stop any virus from taking hold.” 	
	<ul style="list-style-type: none"> Provided information on mRNA based vaccines by Robert Kennedy’s Children’s Health Defense states that in December 2020, 3,916 COVID vaccine-related adverse events, including 13 deaths, were reported to VAERS. Plus Johns Hopkins Scientist: ‘A Medical Certainty’ Pfizer Vaccine Caused Death of Florida Doctor. Dr. Jerry L. Spivak, an expert on blood disorders at Johns Hopkins University, told the New York Times Tuesday that he believes “it is a medical certainty” that Pfizer’s COVID vaccine caused the death of Dr. Gregory Michael. This is not an isolated incidence. 	

Submission	Summary of issues raised	Comment
22	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • General concerns about health effects and effectiveness of other vaccines, including cholera, MMR, flu and HPV vaccines. • Concerns about politicians and pharmaceutical companies ignoring or suppressing information about the safety of vaccines in general. • This is an untested fake vaccine loaded with nanoparticles and other nasties. • Is concerned that the public consultation was advertised in a manner that will reach very few and during holiday time. Requested that the Australian community be given more time for input. 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia. These submissions were general in nature and did not mention matters directly relevant to the AstraZeneca COVID-19 vaccine. Thus, these issues are outside the scope of this assessment conducted by the Regulator.</p> <p>These issues are outside the scope of this assessment conducted by the Regulator.</p> <p>The vaccine contains a ChAdOx1 vector containing the spike protein. This ChAdOx1 vector act as carrier to deliver the spike protein in the host. The AstraZeneca vaccine does not contain nanoparticles.</p> <p>Public consultation was conducted in accordance with section 52 of the <i>Gene Technology Act 2000</i>. Invitations to comment were issued through national newspaper, online notices and direct email.</p>
23	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • Concerned that “mandatory roll out of vaccines for COVID-19 is disproportionate to the disease” and that high mortality rates are due to inappropriate medical treatment of patients. • Banning the use of hydroxychloroquine as a prophylactic is a crime against humanity. • Refers to research by James Lyons-Weiler on pathogenic priming: “He has done many animal studies and has found that 21% of subjects die due to pathogenic priming from these unsafe proteins, creating pathogenic priming causing the subject to have serious adverse immune disfunction making them more susceptible to covid19 infection and transmission in the future. So what you and the other unknowledgeable public health officials are doing is priming our elderly and first responders to be infection promoters thus 	<p>Submission has been noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment.</p> <p>The issues raised in relation to different COVID-19 treatments are outside the scope of this assessment conducted by the Regulator.</p> <p>Possible risks for the vaccine recipients will be considered by the TGA. The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible. The potential for adverse immune reactions to occur as a result of gene technology was considered in three</p>

Submission	Summary of issues raised	Comment
	<p>prolonging huge numbers of infection and suffering.”</p> <ul style="list-style-type: none"> “AstraZeneca is well known for fraud and huge blunders at the expense of the unsuspecting public.” “Dr. Lyons Whyler states emphatically public health officials need to be scientists first and qualified at that, to conduct public health. This is not the case in Australia, and we are paying the penalty for this government’s failure to respond intelligently for the sake of a diverse and informed public.” 	<p>postulated risk scenarios in Chapter 2, Sections 2.4.1–2.4.3 of the RARMP.</p> <p>The RARMP prepared in relation to the proposed dealings considers the risks to human health and safety and to the environment posed by dealings being assessed in the application. The Regulator’s decision regarding the suitability of the applicant to hold the licence involves a separate and additional consideration in accordance with section 57 and 58 of the Act.</p> <p>Submission has been noted.</p>
24	<p>Submitter expresses “objection to the approval of the AstraZeneca Covid-19 vaccine.” “Strongly objects to this experimental gene therapy/biological agent being approved for use in Australia.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> It is in fact not a vaccine but an experimental biological agent. Has “objection on the grounds that it includes adenovirus vector derived from a chimpanzee, Human Embryonic kidney cells (HEKS) from aborted foetal tissue and Genetically Modified Organisms.” “No previous mRNA vaccine has ever been successfully created as during the drug trials the Ferrets became ill and many died. The humans are in fact the guinea pigs in this rushed to market gene therapy.” “The survival rate of Covid-19 is greater than 99%, and experienced by healthy people as a mild cold or flu.” “The so called vaccine will not stop community transmission, will not stop the need to socially distance or wear a mask, you can only begin to wonder what the purpose of this alleged vaccine is?” Concerns about the safety and effectiveness of the vaccine. “The safety profile on VAERS is horrific with over 7000 reported adverse 	<p>Submission has been noted.</p> <p>Submission has been noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment.</p> <p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator.</p> <p>Submission has been noted. The COVID-19 vaccine is aimed to reduce severity of the disease in people.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia. Possible risks for the vaccine</p>

Submission	Summary of issues raised	Comment
	<p>events in the US alone, and this is only short term.”</p> <ul style="list-style-type: none"> “There are hundreds of Dr’s not affiliated with vaccine companies, and without an agenda educating people of the potential dangers of this agent, perhaps the OGTR should do some independent research.” 	<p>recipients will be considered by the TGA. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible. The potential for adverse immune reactions to occur as a result of gene technology was considered in three postulated risk scenarios in Chapter 2, Sections 2.4.1–2.4.3 of the RARMP.</p> <p>Submission has been noted. The Regulator has prepared a risk assessment and risk management plan (RARMP) by thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature.</p>

25	Near-identical submissions were received from five	
30	members of the public.	
33	This is “to inform you of my objection to the new gene	Submission has been noted. The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000 (the Act)</i> . The Regulator must consider each application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.
37	therapy vaccine being presented for consideration via	
39	AstraZeneca as a Covid-19 vaccine.” Does “not support	
	any foreign GMO substances in my food nor in my body by any other means and do not agree to being a part of any medical experiment and believe we hold the right to exercise this choice as per the Nuremberg Code, pursuant to the trials.”	

Issues raised in the submission were:

- “The injection is not a vaccine as it does not provide any immunity from COVID-19 or SARS-CoV-2. As per the meaning of “immunity”: A situation in which you are

Submission	Summary of issues raised	Comment
	<p>protected against disease.” “And “Vaccine”: A substance containing a virus or bacteria in a form that is not harmful, given to a person or animal to prevent them from getting the disease that the virus or bacteria can cause - the vaccine protects against some kinds of the bacteria.”</p> <ul style="list-style-type: none"> Concerned that there is insufficient research on mutating power; long-term repercussions; “no animal trials to see short or long term effects on this kind of therapy”; “no research whatsoever on children 0 to 16 years old, as to what this gene therapy can do when injected into the body”; and, “insufficient studies or research as to the efficacy of this form of gene therapy.” <p>The submission contained links to two journal articles related to mRNA vaccines:</p> <ul style="list-style-type: none"> Shankar et al., 2018 (DOI: 10.2174/2211738506666180611100416) Shirasuna et al., 2019 (DOI: 10.1002/jcp.27475) <p>“As explained by Johns Hopkins, “Side effects were more frequent after the second dose in the vaccine trials.” Another article, titled Exogenous nanoparticles and endogenous crystalline molecules as danger signals for the NLRP3 inflammasomes, supports that the increasingly inflammatory side effects observed in those who received the vaccine in Pfizer’s and Moderna’s clinical trials are attributable to the LNPs and that these side effects get worse with repeated injections. We have seen this increased “reactogenicity” clearly in the data from both Pfizer’s and Moderna’s COVID-19 clinical trials. Both causing concerns as to this new form of therapy and lack of research in humans and long term effects.”</p>	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator.</p>
26	<p>Submitter is “strongly opposed to the proposed approval of the Astra Zeneca vaccine by the regulator on several grounds.”</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “The trials of the vaccine were rushed, and several months is an inadequate timeframe to find out the possible long-term adverse events the vaccine may cause.” 	<p>Submission has been noted.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The RARMP concluded that risks to human health and safety as a result of the import, transport, storage and disposal of the AstraZeneca vaccine are negligible. The licence conditions cover the monitoring and follow-up of any adverse impacts from the supply of the vaccine.</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> “A number of doctors and scientists have warned the Astra Zeneca vaccine could potentially cause serious adverse events that may not become apparent at first, or for several months or even longer, especially due to the well known phenomenon of Antibody Dependent Enhancement (ADE) found in previous coronavirus vaccines. They have also raised a number of other concerns about the safety of this kind of vaccine.” 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p>
	<p>The submission contained several links including links to the following peer-reviewed journal articles:</p> <ul style="list-style-type: none"> - Wang and Zand, 2020 (DOI: 10.1017/cts.2020.39) - Buchbinder et al., 2020 (DOI: 10.1016/S0140-6736(20)32156-5) 	<p>With regard to Wang and Zand, 2020, this article focusses on pathogenic priming, please see above. With regard to Buchbinder et al. (2020), this article cautions against the use of human adenovirus type-5 vectors. The GM vaccine evaluated for DIR-180 is based on a chimpanzee adenovirus.</p>
	<ul style="list-style-type: none"> “Astra Zeneca asked for and has been granted by the Morrison government indemnity from prosecution for its covid19 vaccine – how confident can the company be of the alleged safety of its own product if it demands protection from lawsuits over possible adverse reactions?” 	<p>This issue is outside the scope of the Regulator’s assessments.</p>
	<ul style="list-style-type: none"> “The company Astra Zeneca has a long history of criminal activity, including being found to have previously committed medical fraud. Thus there are good reasons to mistrust them.” 	<p>The RARMP prepared in relation to the proposed dealings considers the risks to human health and safety and to the environment posed by dealings being assessed in the application. The Regulator’s decision regarding the suitability of the applicant to hold the licence involves a separate and additional consideration in accordance with section 57 and 58 of the Act.</p>
	<ul style="list-style-type: none"> “The argument that a covid19 vaccine is necessary because people are dying in a pandemic and that this would justify any serious injury or deaths the vaccine might cause, is based on the assumption that there is no alternative way to save lives other than a vaccine. However there are safer alternative treatments for covid19 that governments in the West have ignored, one of them being ivermectin...” 	<p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator</p>
	<ul style="list-style-type: none"> “Given the recent reports from Norway of deaths of elderly people that are likely linked to the Pfizer vaccines there, and the sudden death of previously healthy Miami doctor Michael Gregory from an autoimmune disease that began shortly after receiving the 	<p>Submission has been noted. The Regulator is required to assess GMO applications in accordance with the <i>Gene Technology Act 2000</i> and prepare a risk assessment and risk management plan (RARMP). The RARMP includes a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and</p>

Submission	Summary of issues raised	Comment
	Pfizer vaccine, you have a grave responsibility to ensure that adequate safety testing has been done on the Astra Zeneca vaccine, and not bow to any political pressure to authorise another experimental vaccine which has not been proven safe, or that could in a worst case scenario lead to more deaths.” “And I sincerely hope you will resist any pressure from politicians or health bureaucrats to rush this review of the drug. Also bear in mind that there are lawyers who will watch your decision with great interest.”	international scientific literature. It is finalised following an extensive consultation process involving prescribed experts, Australian Government authorities and agencies, experts, State and Territory Governments, the Minister for the Environment and the public. The Regulator cannot issue the licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in such a way as to protect the health and safety of people and the environment. The Regulator makes licence decisions on the basis of consideration of risks to people and the environment.

27	Issues raised in the submission were:	
	<ul style="list-style-type: none"> The usage of the term vaccine for medical procedures with gene experiments and associated safety of the vaccine. 	
	<ul style="list-style-type: none"> “This SARS-CoV-2 spike protein - What guarantee and safety is given that it will not interfere with infertility?” 	Risks associated with direct use of the vaccine including safety and usage are considered by the TGA in their assessment.
	<ul style="list-style-type: none"> “Why do we rely on the Consultation Version? Once has to ask, what is the Original Version hiding?” 	The RARMP is marked as a consultation version as it has been released for consultation and is the original version of the RARMP. The published RARMP will take into account submissions received during the consultation period.
	<ul style="list-style-type: none"> “The fact that the clinical trials were conducted only on 18-55 year olds - Will the Office of Gene Technology Regulator alert by Medial Release the Over 55 years not receive the genetically modified alleged Covid-19 gene procedure and/or alleged "vaccine?"” 	The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.
	<ul style="list-style-type: none"> “What consideration and compensation will be given to people who suffer injury as a consequence of this Genetically Modified Covid-19? What recommendation will OGTR to the Federal and State Health Minister?” 	The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator.
	<ul style="list-style-type: none"> “Injecting a Modified Organism in the draining lymph nodes is pure negligence, and then claim no shedding from vaccine recipients. (Proof that this is not a "like" and/or "weakened virus.)” 	The AstraZeneca vaccine is proposed to be administered in the muscle and not injected into the lymph nodes. The adenoviral vector is limited to the site of injection and/or could drain into lymph nodes and will be cleared by the immune system. The viral vector is a virus that carries a gene into the host and this virus does not have the ability to multiply and spread from the site of

Submission	Summary of issues raised	Comment
		injection due to modifications made in the virus. Therefore, shedding is not expected from vaccine recipients.
	<ul style="list-style-type: none"> The GMO does not cause disease in humans and other organisms other than great apes; “Where is the evidence? Also: What is the answer as to why the great apes get a disease?” 	This is discussed in the RARMP. Please refer to Chapter 1, Section 3.1.
	<ul style="list-style-type: none"> “Who are the people who sit on the Committee for OGTR to make the Application Determination?” 	<p>The Gene Technology Regulator is an independent statutory office holder who is supported by staff in the OGTR. The Regulator is required to assess GMO licence applications in accordance with the <i>Gene Technology Act 2000</i>. The Regulator consults prescribed experts, Australian Government authorities and agencies, experts, State and Territory Governments, the Minister for the Environment and the public. The Regulator cannot issue the licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in such a way as to protect the health and safety of people and the environment. The Regulator makes licence decisions on the basis of consideration of risks to people and the environment.</p>
	<ul style="list-style-type: none"> Old people dying due to illness, not fed healthy food and do not receive good amount of vitamins rather than COVID-19. 	These issues are outside the scope of this assessment conducted by the Regulator.
	<ul style="list-style-type: none"> PCR testing for COVID-19 is not accurate and provide false positives. 	
	<ul style="list-style-type: none"> Dealings with GMOs need more time to guarantee its safety. 	The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.
	<ul style="list-style-type: none"> “By what long term evidence exists that the “level of risk was assessed as negligible”. If there is this negligible risk, the consideration for compensation of injury should be included in this Application.” 	The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000(the Act)</i> . The Regulator must consider each
	<ul style="list-style-type: none"> The “genetically modified gene organisms” is Not Negotiable. How many people need to die and be damaged before this draconian form of medical procedure be stopped?” 	<p>application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are</p>

Submission	Summary of issues raised	Comment
	Discussion of ADE by Norman Swan - ABC information from 8 Sep2020 was cited in the submission.	<p>consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed.</p> <p>Impact of ADE has been discussed in the RARMP (Chapter 2, Section 2.4.1). The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p>
28	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • Concern regarding the long-term safety of the vaccine and that the manufacturer and government will have no liability should the vaccine cause harm in people. • Concern that vaccine approval is driven by profit rather than safety. • Concern that the vaccine is resulting in an increase in deaths, with the claim that Nurse Tiffany Dover died after receiving a vaccine. 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000 (the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p> <p>This submission relates to different COVID-19 vaccines which are outside the scope of this assessment conducted by the Regulator.</p>
29	The submission contained 12 website links about safety measures against AstraZeneca. These links refer to a range of articles concerning safety of the AstraZeneca vaccine, halt of clinical trials, violation tracker parent company summary and people dying after participating in the clinical trials.	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The RARMP prepared in relation to the proposed dealings considers the risks to</p>

Submission	Summary of issues raised	Comment
	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> Proposes that “Ivermectin is more effective than the vaccine” Raised various concerns arising from a 2 hour video titled “Focus on Fauci”: corruption, profiteering and conflicts of interest between government and ‘Big Pharma’ and Risks associated with mRNA vaccines. Link to US petition to stop forced experimental vaccines 	<p>human health and safety and to the environment posed by dealings being assessed in the application. The Regulator’s decision regarding the suitability of the applicant to hold the licence involves a separate and additional consideration in accordance with section 57 and 58 of the Act.</p> <p>The issues raised in relation to different COVID-19 vaccines and COVID-19 treatments are outside the scope of this assessment conducted by the Regulator</p>
31	<p>Requests that the OGTR rejects the AstraZeneca vaccine.</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> Concerns over GM viral particles in sewerage discharges, their persistence and impacts they may have on other organisms. Concerns regarding the unknown risks of GM material due to unpredictable effects on human health and the environment. Concerns over the safety of the vaccine. “Norway recently recorded 30 deaths from a vaccine by Pfizer given to elderly patients in aged care. The death of a healthy doctor in the USA is attributed to a COVID vaccination. COVID vaccine development is still in its infancy.” 	<p>Submission has been noted.</p> <p>The AstraZeneca vaccine does not have the ability to multiply and spread from the site of injection due to modifications made in the virus (Chapter 1, Section 4.3.2). Therefore, shedding is not expected from vaccine recipients. The RARMP considers persistence in sewerage, waterways and the environment (Chapter 1) and the impacts on other organisms (Chapter 2, Section 2.4) and concludes that the proposed import, transport, storage and disposal of the vaccine poses negligible risks to human health and safety and the environment.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>. The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator</p>
32	<p>Quote from Submission: “Would not, under any circumstances, take this experimental genetically altering medical device.”</p> <p>Issues raised in the submission were:</p>	<p>Submission has been noted.</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> That vaccine approval is driven by profit and that there is no accountability in the “pharmaceutical industry, university medical schools, research departments and indeed the private ownership of the TGA.” 	These issues are outside the scope of this assessment conducted by the Regulator.
34	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> Safety provisions and “lack of animal-testing” The forced vaccination of healthcare workers and other vulnerable people. 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The Regulator must consider risks to human health and safety and to the environment posed by genetic modification being assessed in the application.</p>
35	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “In previous attempts to manufacture and produce a vaccine for Sars-Cov 1, the results have been negative when it comes to animal trials. After the animals were injected with this vaccine then came in contact with the natural corona virus, all the animals died, hence why it was never released. ... Yet, the Australian Government is ready to release this vaccine without full and proper trials, firstly on animals and then on humans.” “There are already treatments available for this “new disease” labelled COVID-19 and that there is no need for a vaccine. ... Ivermectin and Hydroxychloroquine along with zinc are two very effective treatments.” The COVID-19 vaccines are not necessary at all, and “this whole charade is just big pharma making billions of dollars out of human fear and suffering.” ... “It seems to me that this Government has clearly got their priorities wrong and are putting the lives of Australians at risk.” “Firstly this so-called global pandemic is not a real Pandemic at all, and never was. The media and Government hype and hysteria can only be contributed to the much larger agenda in my opinion. This is what you should be assessing, not whether the AstraZeneca vaccine is safe. Keep the people in a state of panic and fear and sell them a cure they have no idea about. Problem, reaction, solution.” 	<p>The quality, safety and efficacy of the vaccine would be assessed by the TGA in their assessment.</p> <p>The issues raised in relation to different COVID-19 treatments are outside the scope of this assessment conducted by the Regulator.</p> <p>The issues raised are outside the scope of this assessment conducted by the Regulator.</p>
36	<p>Submitter is “highly concerned with this going ahead” and does not think “that this should be commercially supplied.”</p> <p>Issues raised in the submission were:</p>	<p>Submission has been noted.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> • Concerns over not enough long term studies on the safety of the vaccine. No knowledge on what vaccine can do to fertility or immune systems that are already compromised (i.e. Auto immune illnesses). • “Previous corona virus vaccines during their phase 2 trials, had a high death rate in animals.” “The phase 2 trials that AstraZeneca has conducted are not sufficient to rule this out.” 	<p>vaccine intended for use in people in Australia.</p> <p>The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000 (the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed. The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p>
38	The submission contained a 28 page document.	
	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • A mandatory vaccine against a bio-engineered virus on a global scale is wrong, abhorrently wrong. ...”ANY policy of mandatory vaccination which uses coercive measures of “no jab, no pay” or “no jab, no play” or “no jab no fly” ... is abhorrent, morally repugnant and corrupt.” • These vaccines is a breach of the Nuremberg Code regarding human experimentation. It is a breach of inalienable human rights including self-determination. • “Failure of prior coronavirus vaccine trials (SARS-CoV-1, MERS-COV) to be safe and effective, causing immune hyper-reactions and death in test animals upon subsequent viral challenge.” 	<p>The Regulator must consider risks to human health and safety and to the environment posed by genetic modification being assessed in the application.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p>

Submission	Summary of issues raised	Comment
	<ul style="list-style-type: none"> • “There are numerous effective existing medications which can be used as an off-label prescription, which kill the virus and prevent spread.” • The use of aborted foetal cells is against the core values many Australians hold dear as Christians. “Vaccines have been made with aborted human foetal cells, murder, which is against many religious beliefs and should NEVER be forced upon any person, religious or not.” 	<p>The issues raised in relation to different COVID-19 treatments are outside the scope of this assessment conducted by the Regulator</p> <p>Submission has been noted. The Gene Technology Regulator is responsible for regulating dealings with GMOs under the <i>Gene Technology Act 2000</i>. The Regulator’s considerations are limited to risks to the health and safety of people and the environment.</p>
40	<p>The submission contained a 7 page document. Issues raised in the submission were:</p>	
	<ul style="list-style-type: none"> • “How can a vaccine be approved as safe, when it has been developed in less than a year, where more common vaccines need minimum 4 years but up to 20 years to be proven safe for humans?” 	<p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p>
	<ul style="list-style-type: none"> • “Who knows the side effects, what happens in 4 years for example? An approval means for the general population is now participating in an experiment.” 	<p>Possible risks for the vaccine recipients will be considered by the TGA. Further, the quality, safety and efficacy of the vaccine will be assessed by the TGA.</p>
		<p>Conditions of the licence for the vaccine cover the monitoring and follow-up of any adverse impacts from the supply of the vaccine. The Regulator’s assessment concluded that risks to human health and safety as a result of import, transport, storage and disposal of the AstraZeneca COVID-19 vaccine are negligible.</p>
	<ul style="list-style-type: none"> • “It is known and in studies established, that the improvement of the immune system is key to safe lives especially of the risk age group over 70, administering Vitamin D etc. would it not be priority to use any medication known other than an experimental vaccine to safe lives?” 	<p>The issues raised in relation to different COVID-19 treatments are outside the scope of this assessment conducted by the Regulator</p>
	<ul style="list-style-type: none"> • “Is this rollout in the interest of the health of the population or in the interests of lobbyists and big pharma?” 	
	<ul style="list-style-type: none"> • “I have loved one, who work in the health sector and are already scared to be pushed to take the “ jab”. Of course, it will be not mandatory, you might loose your job...” 	<p>The Regulator must consider risks to human health and safety and to the environment posed by genetic modification being assessed in the application.</p>
	<ul style="list-style-type: none"> • It took short time to develop these vaccines and how long these proteins will be produced? “Do you know, where those proteins dock on or maybe just go into the 	<p>The vaccine has been modified to limit the amount of time that the virus protein is made. The potential for contact with the GMO via other</p>

Submission	Summary of issues raised	Comment
	<p>bloodstream during administration and go into the brain?"</p> <p>The submission included excerpts and references to the following articles:</p> <p>"Did the oxford covid vaccine work in monkeys? not really"</p> <p>"A leading coronavirus vaccine trial is on hold: scientists react"</p> <p>"The risks of rushing a covid 19 vaccine"</p> <p>"Governments need to resist pharma pressure and be transparent"</p> <p>"AstraZeneca has paused enrolment in trials for the coronavirus vaccine developed by the University of Oxford"</p> <p>"AstraZeneca Covid-19 vaccine study put on hold due to suspected adverse reaction in participant in the U.K."</p> <p>"Don't rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees"</p>	<p>routes is discussed in the risk scenarios in Chapter 2. Risks to people receiving the vaccine would be considered by TGA under their assessment.</p> <p>Submission has been noted.</p>
<p>41</p>	<p>The submission linked the AstraZeneca vaccine to depopulation agendas and included comments describing lockdown measures in America as domestic terrorism.</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • "These products violate the Nuremberg Code." • There is no correlation between vaccine and protection from SARS-CoV-2. • No existing vaccines have been shown to be effective against infection with any betacoronavirus, the family that includes SARS-CoV-2, which causes Covid-19." <p>The submission also included references to 2 YouTube links, 1 Facebook, 1 Instagram link and references to articles related to mRNA based COVID-19 vaccines.</p>	<p>The quality, safety and efficacy of the vaccine would be assessed by the TGA in their assessment</p> <p>Submission has been noted. The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator</p>
<p>42</p>	<p>Submitter is "opposed to Oxford AstraZeneca vaccine approval to rollout because there's gene technology GMO organism in this vaccine."</p> <p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> • The vaccine is a GMO and it will change the DNA in the body. • "All vaccines approved are still in a clinical trial, so everyone vaccinate takes part in those trials. Never a similar vaccine has been approved for humans due to the danger for 	<p>Submission has been noted.</p> <p>The vaccine contains a ChAdOx1 vector containing the spike protein. This ChAdOx1 vector act as carrier to deliver the spike protein in the host. After injection, the adenoviral vector enters human cells and prompts the immune system to start producing antibodies to</p>

Submission	Summary of issues raised	Comment
	<p>human. Animal trials have been skipped” for these vaccines.</p> <ul style="list-style-type: none"> The short term and long term impact of the vaccine on our body. <p>The submission included references to the following articles and resources:</p> <p>“Informed consent disclosure to vaccine trial subjects of risk of COVID-19 vaccines worsening clinical Informed consent disclosure to vaccine trial subjects of risk of COVID-19 vaccines worsening clinical disease”</p> <p>“Oxford–AstraZeneca COVID-19 vaccine efficacy”</p> <p>“America's Frontline Doctors White Paper On Experimental Vaccines For COVID-19”</p> <p>“Australian Government Department of Health Resources for COVID-19”</p>	<p>protect against any coronavirus infection. The vaccine does not change the DNA in the body.</p> <p>The TGA has responsibility for assessing the quality, safety and efficacy of any vaccine intended for use in people in Australia.</p> <p>The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000(the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed.</p> <p>The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p>
44	<p>Issues raised in the submission were:</p> <ul style="list-style-type: none"> “The Astra-Zeneca vaccine has been made using chimpanzee DNA? We already saw what happened in the late 1950’s with the Salk and Sabin polio vaccines that were contaminated with at least 3 monkey viruses. So is this going 	<p>The functions of the Gene Technology Regulator are defined by the <i>Gene Technology Act 2000(the Act)</i>. The Regulator must consider each application for a licence for work with GMOs based on criteria listed in the Act and prepare a risk assessment and risk</p>

Submission	Summary of issues raised	Comment
	<p>to happen all over again, just for greed and profits?”</p> <ul style="list-style-type: none"> • “The regulators that are supposed to protect the people, appear to be compromised to vested interests, and this is just appalling!” 	<p>management plan (RARMP). The RARMP is a thorough and critical assessment of data supplied by the applicant, together with a review of other relevant national and international scientific literature. Australian Government departments and agencies, technical experts, State and Territory Governments, the Minister for the Environment and the public are consulted during development of the RARMP to ensure that topics of concern related to risks to health and safety of people and the environment are identified and addressed.</p> <p>The RARMP prepared for the COVID-19 vaccine from AstraZeneca concluded that risks to people and the environment as a result of the import, transport, storage and disposal of the vaccine are negligible.</p>
	<ul style="list-style-type: none"> • Vaccines resulted in death of elderly people in Norway, the UK, Israel and the USA. “How can such dangerous products just be approved and ‘rubber-stamped’?” • A text written by Dr David Martin (dated 5 January 2021) regarding mRNA based vaccine and the use of the term “vaccine” to sneak this thing under public health exemptions. This is not a vaccine (referring to mRNA vaccine). 	<p>The issues raised in relation to different COVID-19 vaccines are outside the scope of this assessment conducted by the Regulator.</p>