Australian Government
Department of Health and Aged Care
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan (Consultation version) for

DIR 202

Commercial supply of a live attenuated vaccine containing canine distemper virus and a genetically modified canine parvovirus (Nobivac Puppy DP Plus) for dogs

Applicant: Intervet Australia Pty Ltd

24 April 2024

This RARMP is open for consultation until 19 June 2024.

Written comments on the risks to human health and safety and the environment posed by this proposed supply of the GM canine parvovirus vaccine are invited. You may make your submission.

via mail to: The Office of the Gene Technology Regulator, MDP 54 GPO Box 9848, Canberra ACT 2601

or

via email to: ogtr@health.gov.au.

Please note that issues regarding food safety and labelling, the use of agricultural chemicals, and marketing and trade implications **do not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

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Summary of the Risk Assessment and Risk Management Plan (Consultation Version) for Licence Application DIR 202

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application (DIR 202) for import, transport, storage and disposal for the commercial supply of a live attenuated vaccine containing canine distemper virus (CDV) and a genetically modified (GM) canine parvovirus (CPV) (Nobivac Puppy DP Plus) for dogs. These activities are classified as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under the *Gene Technology Act 2000*.

Before the vaccine containing a GM component can be used, Intervet Australia Pty Ltd must also obtain regulatory approval from the Australian Pesticide and Veterinary Medicines Authority (APVMA). The APVMA administers the *Agricultural and Veterinary Chemicals Code Act 1994* (the Agvet Code) to regulate agricultural and veterinary chemical products, including veterinary vaccines. For commercial products, the standard form of approval is through registration. The APVMA can impose conditions on the use of veterinary products via registrations and permits.

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 negligible risks to the environment. Licence conditions have been drafted for the proposed supply. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether or not to issue a licence.

The application

Application number	DIR-202
Applicant	Intervet Australia Pty Ltd
Project title	Commercial supply of a live attenuated vaccine containing canine distemper virus and a genetically modified canine parvovirus (Nobivac Puppy DP Plus) for dogs[1]
Parent organism	Canine parvovirus type 2 (CPV-2)
Introduced gene and modified trait	Introduction of a wild type CPV-2c capsid into the attenuated CPV 154 strain, resulting in an attenuated live vaccine that does not cause severe disease in dogs.
Previous releases	The GM vaccine has not been previously approved for release in Australia
Current approvals	The GM vaccine is currently approved for use in 36 countries by the European Medicines Agency and the Philippines Federal Drug Administration.
Proposed locations	Australia-wide
Primary purpose	Commercial supply of the GM vaccine against CDV and CPV-2 in dogs.

[1] The title for the licence application submitted by Intervet Australia Pty Ltd is “Nobivac Puppy DP Plus Live Vaccine”.

Risk assessment

The risk assessment process considers 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 are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application, relevant previous approvals, current scientific knowledge and advice received from a wide range of experts, agencies and authorities consulted on the preparation of the RARMP. Both the short- and long-term risks were considered.

Credible pathways to potential harm that were considered include; the potential exposure of people to the GMO; the potential exposure of animals to the GMO; and the potential for the GMO to recombine with other similar viruses. The potential for the GMO to be released into the environment and its effects were also considered.

The risk assessment concludes that risks to the health and safety of people are negligible and the risks to the environment from the proposed supply of this vaccine are negligible. Specific risk treatment measures are included in the licence to maintain the risk context.

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

- The GMO has a limited host range, is attenuated and unlikely to cause disease in dogs or other susceptible mammalian species;
- Canine parvovirus does not cause disease in humans or animals other than dogs, except for some susceptible mammalian carnivore species including big cats;
- The likelihood of accidental exposure to the GMO by people and the environment would be minimised due to well-established transport, storage and disposal procedures that are regulated by each State and Territory; and local councils;
- The GMO would be imported under a DAFF import permit, that requires specific import conditions to manage biosecurity risks;
- The GMO would need to be registered with the APVMA, who would impose conditions on the use, transport, storage and disposal of the vaccine; and
- Recombination of the GMO with another parvoviruses is possible but since the vaccine contains genetic material from CPV-2 similar to that circulating in Australia, similar genetic material would already be present in the environment.

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 the negligible risks can be managed to protect the health and safety of people and the environment. The risk of recombination leading to novel CPV-2 strains was assessed as negligible given the risk context in which the dealings would be conducted which includes APVMA registration. As the product is not currently registered by the APVMA and to maintain critical aspects of the risk context, specific risk treatment measures, such as vaccination of only healthy dogs, a time window between live vaccine administrations and restriction to not vaccinate a dog with two compatible live vaccines concurrently were included in the draft licence (see Chapter 4).

General conditions were also included in the draft licence to ensure that there is ongoing oversight of the GM vaccine. Conditions were included requiring the applicant to report any new information obtained after release of the GMO to allow the collection of information to verify the findings of the RARMP. Post-market surveillance of veterinary vaccines is carried out in an ongoing capacity by State and Territories. The draft

licence also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and other reporting requirements, which include an obligation to report any unintended effects.

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Abbreviations

ACT	Australian Capital Territory
AgVet Code	*Agricultural and Veterinary Chemicals Code Act 1994*
AHA	Animal Health Australia
APVMA	Australian Pesticides and Veterinary Medicines Authority
CPV-2	Canine Parvovirus Type 2
DAFF	Department of Agriculture, Fisheries and Forestry
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EPA	Environment Protection Authority
GLP	Good Laboratory Practice
GM	Genetically modified
GMP	Good Manufacturing Practice
GMO	Genetically modified organism
GTTAC	Gene Technology Technical Advisory Committee
HGT	Horizontal gene transfer
IR	internal repeat
kb	Kilobase pair of DNA
LGA	Local government area
ml	Milli litre
NSW	New South Wales
NT	Northern Territory
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
SA	South Australia
TAS	Tasmania
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
USA	United States of America
VIC	Victoria
WA	Western Australia

Chapter 1 Risk assessment context

Section 1 Background

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

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

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

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

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

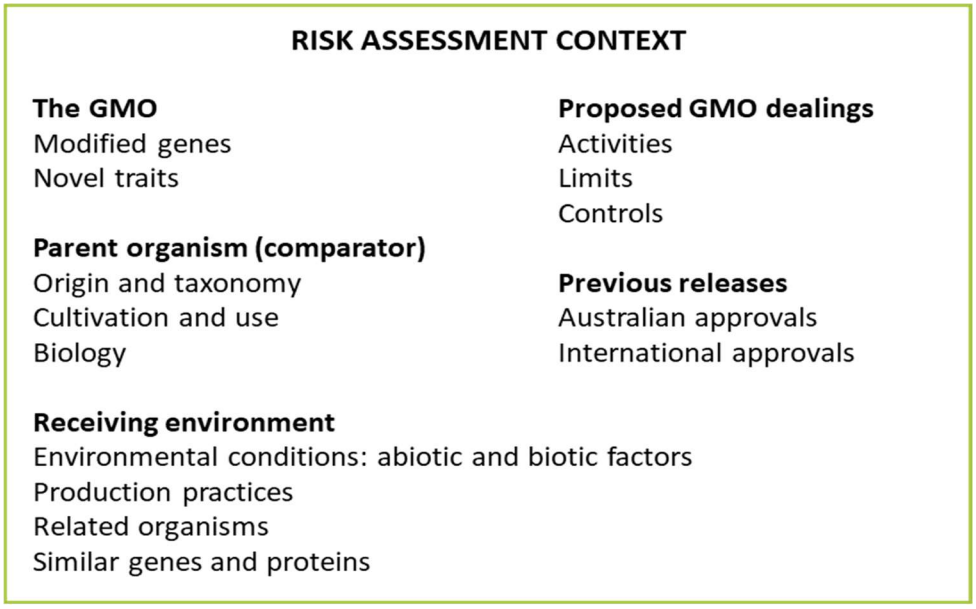

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. Since this application is for commercial purposes, it does not meet the criteria for a limited and controlled release application under section 50A of the Act. Therefore, under section 50(3) of the Act, the Regulator was required to seek advice from prescribed experts, agencies and authorities on matters relevant to the preparation of the RARMP. This first round of consultation included the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government

authorities and agencies prescribed in the Regulations and the Minister for the Environment. A summary of issues contained in submissions received is provided in Appendix A.

7. Section 52 of the Act requires the Regulator to seek comment on the RARMP from the experts, agencies and authorities outlined above, as well as the public through a second round of consultation.

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 the Australian Pesticides and Veterinary Medicines Authority (APVMA) and the Department of Agriculture, Fisheries and Forestry (DAFF). Proposed dealings may also be subject to the operation of State legislation declaring areas to be GM, GM free, or both, for marketing purposes.

9. The APVMA provides a national registration and permit scheme for agricultural and veterinary chemical products. It administers the provisions of the *Agricultural and Veterinary Chemicals Code Act 1994* (AgVet Code). For registration, the APVMA assesses whether a new veterinary vaccine meets the criteria set out in the AgVet Code before it is registered in the Register of Agricultural and Veterinary Chemical Products. A new veterinary vaccine that is not registered may be legally used for animal trials by obtaining a permit from the APVMA.

10. As part of the registration process, the APVMA must first approve the new active constituent; and then assess the quality, safety and efficacy of the vaccine. Quality aspects could include batch-to-batch consistency in vaccine composition, purity and potency. The product must also be manufactured in premises that comply with Good Manufacturing Practice (GMP), which is also audited by the APVMA. Safety aspects include the toxicological profile of the vaccine and its residues, including metabolites and degradation products. The APVMA approves the label, which includes instructions for the handling, storing and directions for supply of veterinary vaccines to ensure safe use. The APVMA would also carry out an environmental risk assessment to minimise environmental risks. The APVMA may also impose conditions on a permit for the supply of veterinary vaccines for research purposes. The States and Territories are responsible for the enforcement of the conditions associated with an APVMA registration and carry out post-market surveillance.

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

12. For the commercial supply of a GM veterinary 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 GMO in the environment.

Section 2 The proposed dealings

13. Canine parvovirus type 2 (CPV, or CPV-2) or *Carnivore protoparvovirus 1* is a viral gastrointestinal infection, which is highly infectious and causes severe infection in dogs between 6 weeks and 6 months of age (Miranda and Thompson, 2016). There are three described antigenic variants of CPV-2, (CPV-2a, CPV-2b and CPV-2c), with varied prevalence around the globe (Miranda and Thompson, 2016). The most prevalent antigenic variants detected in Australia are CPV-2a and CPV-2b, however CPV-2c has been detected in Australia since 2017 (Woolford et al., 2017). CPV-2 is transmitted by faecal to oral contact and is shed primarily in the faeces of infected dogs (Ogbu et al., 2017). Clinical symptoms occur 3 to 7 days after infection and present in two major clinical manifestations: gastroenteritis or myocarditis (Ogbu et al., 2017; Rabbani et al., 2021). Both clinical forms can be fatal. There are currently 17 non-GM live attenuated CPV-2 vaccines that are registered for use in Australia (APVMA PubCRIS database). These vaccines consist of attenuated strains of CPV-2.

14. Intervet Australia Pty Ltd (Intervet) is seeking authorisation for the commercial supply of a vaccine containing attenuated canine distemper virus (CDV) and genetically modified (GM) CPV-2 (known as Nobivac DP Puppy Plus) to prevent canine distemper disease and CPV disease in dogs Australia-wide.

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

(a) import the GMO;

(b) transport the GMO;

(c) dispose of the GMO;

and 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

16. The vaccine, including the GM CPV-2 component, would be manufactured overseas in Good Manufacturing Practises (GMP) licensed sites and imported into Australia under an import permit from the Department of Agriculture, Forestry and Fisheries (DAFF). The product would need to be registered through the APVMA before commercial use. As mentioned in Section 1.1, the APVMA would also approve the labels for the GM vaccine, which would contain instructions for the handling, storing and directions for supply to ensure safe use.

17. The vaccine would be transported to Schedule 4 licensed warehouses (prescription only medicines and prescription animal remedies, Therapeutic Goods (Poisons Standard – October 2023) Instrument 2023). The vaccine is freeze-dried in rubber stoppered vials with aluminium caps. The vial is contained within a product carton containing one vial and enough solvent to make up one dose. Cartons will be labelled with an approved APVMA label indicating the contents of the vial and an accompanying leaflet with instructions for use, storage and disposal. The label does not indicate that this vaccine contains a GM component but as part as the constituent statements, the label indicates that each dose contains a live attenuated canine distemper virus and a live recombinant canine parvovirus strain 630a.

18. The vaccine would be administered to dogs in the normal course of vaccination schedules, between 4 and 6 weeks of age. At this age, most young dogs are still with a breeder and are kept isolated to limit exposure to diseases. During vaccination periods, veterinarians also advise that dogs are kept indoors until the vaccines have been effective and to limit exposure between animals and the environment. The vaccine may also be used in outbreak areas to break the chain of transmission of wild-type CPV-2.

19. The applicant has stated that the vaccine would be used as per an approved APVMA registration.

20. Administration of the vaccine will occur via subcutaneous injection into the scruff of the neck by trained veterinarians. The applicant proposes to register this method of administration with the APVMA.

21. All residual vaccine and associated waste which has come in to contact with the vaccine (such as syringes and vials) would be discarded in veterinary clinics in accordance with State/Territory, local council and Environmental Protection Agency (EPA) requirements, and conditions imposed by the APVMA registration of the GMO. These requirements and guidelines all aim to limit the exposure of other people or animals to the waste.

Section 3 Parent organism

22. The vaccine contains attenuated CDV and GM CPV-2. This assessment only focuses on the GM component of this vaccine. The GM CPV-2 (CPV-630a) is derived from an attenuated CPV-2 strain, currently used as a vaccine (CPV-154), which was originally isolated in the United Kingdom in 1980 (Churchill, 1987). CPV-2 is a member of the *Parvoviridae* family, *Protoparvovirus* genus and is also known as *Carnivore protoparvovirus 1* (Decaro et al., 2020; Singh et al., 2021). The characteristics of the parent

organism provide a baseline for comparing the potential for harm from dealings with the GM vaccine. As such, the relevant biological properties of CPV-2 will be discussed here.

3.1 Pathology

23. CPV-2 is a highly contagious viral enteric pathogen that causes haemorrhagic enteritis and myocarditis in dogs. It presents in two major clinical forms, depending on the age of the affected dog; i) dogs of any age develop gastroenteritis with vomiting and diarrhea and ii) puppies less than 3 months old develop myocarditis with potential heart failure (Decaro and Buonavoglia, 2012; Ogbu et al., 2017; Rabbani et al., 2021). Clinical signs generally appear between 3-7 days following exposure (Rabbani et al., 2021). The clinical course of the disease is highly variable, depending on age, infectious dose, immune-status and the presence of maternally derived antibodies, with more severe disease observed in dogs less than 6 months old or immune-compromised dogs (Ogbu et al., 2017; Rabbani et al., 2021). CPV disease is often fatal in dogs less than 6 months old and has killed puppies in as little as two days following clinical manifestation (Ogbu et al., 2017; Rabbani et al., 2021).

24. Typical clinical signs of the gastroenteritis form of the disease include loss of appetite, depression, vomiting, bloody diarrhea, anaemia, dehydration and fever (Ogbu et al., 2017; Rabbani et al., 2021; Tuteja et al., 2022). Estimated mortality rate ranges from 25-35% in dogs less than 12 months old but can reach 91% without treatment, while in adult dogs the rate is typically less than 1% (Ling et al., 2012). Clinical signs of the myocarditis form include cold extremities, gasping respiration, abdominal swelling or sudden death in puppies between 2 and 16 weeks of age, with a mortality rate between 20-100% (Meunier et al., 1984; Decaro and Buonavoglia, 2012; Rabbani et al., 2021).

25. CPV-2 infection may also present with marked haematological changes that can result in transient immunosuppression and reduction in white blood cells, and can be a predictor of disease prognosis (Ogbu et al., 2017). Death resulting from CPV-2 induced immune suppression is largely due to co-infection with other pathogens (Alves et al., 2020).

3.2 Structure and genomic organisation

26. CPV-2 has a single-stranded DNA genome approximately 5,200 base pairs (bp) in length. The genome contains two open reading frames (ORFs), the first encoding two non-structural proteins (NS1 and NS2) and the second encodes three structural proteins (VP1, VP2, and VP3) (Decaro and Buonavoglia, 2012; Rabbani et al., 2021). The VP1 and VP2 proteins make up the viral capsid in a 1:11 ratio to form a 60-subunit spherical capsid (Figure 2) approximately 25 nm in size (Decaro and Buonavoglia, 2012; Tuteja et al., 2022). VP3 is derived from VP2 via proteolytic cleavage and is only present in complete virions (Rabbani et al., 2021).

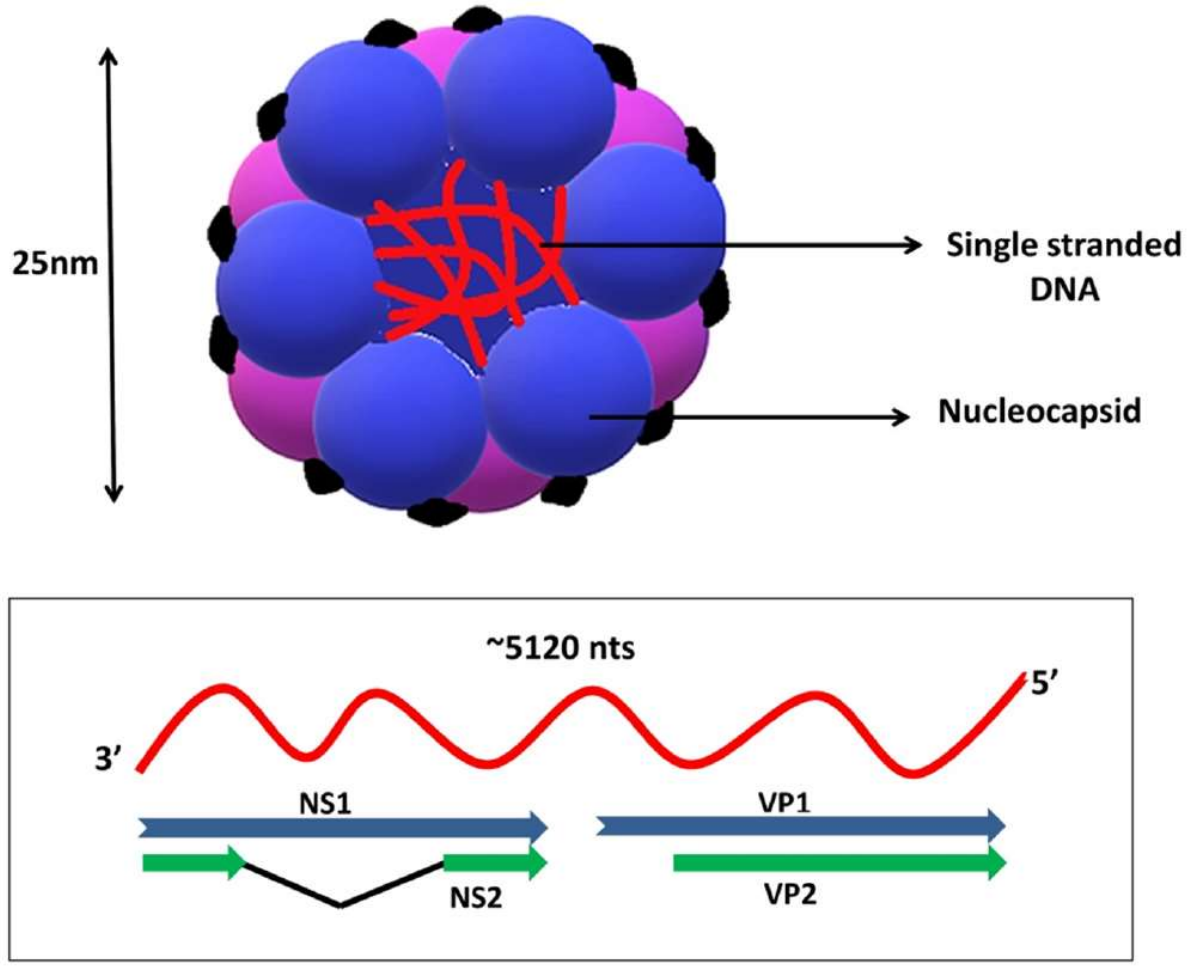

Figure 2. Structure and genome of CPV-2. Single stranded DNA is contained within a nucleocapsid made up of VP1 and VP2 subunits, VP3 not depicted as it is produced post-translationally. The CPV-2 genome encodes non-structural (NS) proteins and structural proteins (VP) that comprise the capsid (Tuteja et al., 2022).

27. The CPV-2 capsid is made up of 60 structural protein subunits, VP1 (5-6 subunits) and VP2 (54-55 subunits). VP1 and VP2 are encoded within the same ORF and produced by alternative splicing of the viral mRNAs (Miranda and Thompson, 2016), with VP3 produced by proteolytic cleavage of VP2 within host cells. VP2 encodes the capsid proteins that make up the so-called three spike region on the capsid surface (Miranda and Thompson, 2016; Vannamahaxay and Chuammitri, 2017). Small sequence changes in VP2 produce the antigenic variation that defines the CPV-2 variants that have emerged since 1970; CPV-2a, CPV-2b and CPV-2c (Vannamahaxay and Chuammitri, 2017).

3.3 Viral infection and replication

28. CPV-2 targets rapidly dividing cells, such as intestinal crypts, lymphoid organs, or myocardial cells in neonatal or very young puppies. Early replication occurs mostly in the lymphatic system and spread by infected leukocytes to crypt epithelia in the small intestine (Decaro and Buonavoglia, 2012). Infection of intestinal cells typically coincides with symptomatic onset and viral shedding in the faeces. Infected intestinal crypt cells impairs cells turnover, leading to necrosis and villi collapse and causing haemorrhagic diarrhea (Ogbu et al., 2017).

29. Cells are infected by VP2 binding to the canine transferrin receptor type-1 which facilitates cell entry. Inside the cell, the capsid breaks down and the virus is released into the cytosol then transported to the cell nucleus by a nuclear localisation signal encoded within VP1 (Mattola et al., 2021; Tuteja et al., 2022). In the cell nucleus, the virus replicates using host cell machinery and is encapsidated within newly

assembled capsid proteins (Mattola et al., 2021). Replicated virions leave the cell by lysis, leading to necrosis of infected cells (Ogbu et al., 2017; Mattola et al., 2021; Tuteja et al., 2022).

3.4 Variants and potential for recombination of CPV-2

30. CPV-2 is thought to have evolved from the highly similar Feline Panleukopenia Virus (FPV), which readily infects felines and causes similar symptoms (Ogbu et al., 2017; Rabbani et al., 2021). The first circulating CPV-2 identified shares a high level of sequence similarity to FPV but has an altered host range to canines. The first antigenic variant of CPV-2, CPV-2a, emerged almost a decade after CPV-2 was initially identified and regained the ability to infect felines (Ogbu et al., 2017). CPV-2a contains 5-6 amino acid changes within the VP2 protein compared with CPV-2, three of which allow replication in cats (Miranda and Thompson, 2016). CPV-2b and CPV-2c, detected in 1984 and 2000 respectively, are most similar to CPV-2a but contain different amino acids at residue 426 (Miranda and Thompson, 2016; Vannamahaxay and Chuammitri, 2017). CPV-2a contains asparagine, CPV-2b contains aspartic acid and CPV-2c contains glutamic acid at residue 426 which is a major antigenic site (Figure 3) (Miranda and Thompson, 2016; Vannamahaxay and Chuammitri, 2017). Different isolates of CPV-2 are named based on the amino acid differences within the antigenic site of VP2, however there is documented additional sequence variation within each strain (Kwan et al., 2021).

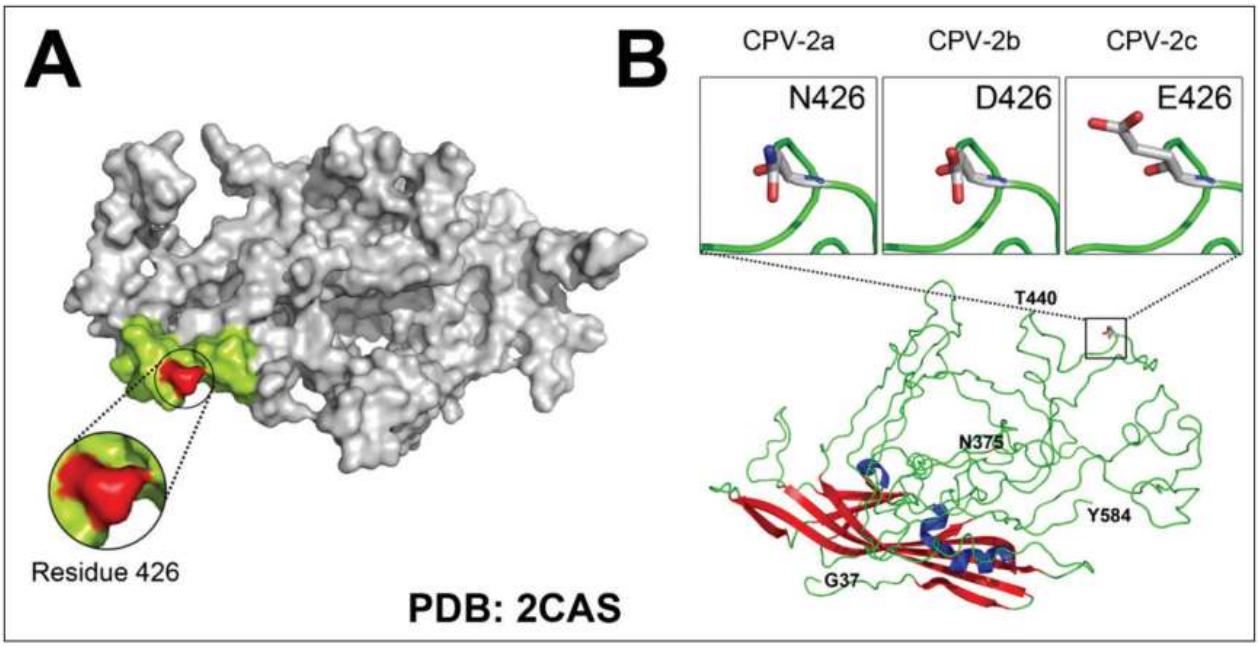

Figure 3. Amino acid variations in CPV-2 capsid protein VP2. (A) VP2 structure, residue 426 is shown in red with surrounding amino acids shown in green. Enlarged inset shows residue 426. (B) VP2 capsid protein is made up of eight-stranded antiparallel β barrels (red), α helices (blue) and loops (green). G37 is the N-terminal and Y584 is the C-terminal. Enlarged insets show the structural differences from amino acid variations between CPV-2a, CPV-2b and CPV-2c of residue 426 (N=asparagine, D=aspartic acid, E=glutamic acid). Sequence information obtained from PDB accession number 2CAS (Vannamahaxay and Chuammitri, 2017).

31. Recombination requires a cell to be simultaneously co-infected by two viruses, which is not commonly reported but has been shown to occur for CPV-2 and other parvoviruses (Decaro et al., 2007; Mochizuki et al., 2008). Instances of recombination between wild-type variants CPV-2a and CPV-2c has been observed (Pérez et al., 2014), as has recombination between wild type strains and vaccine strains (Mochizuki et al., 2008). However, under field conditions there is a limited temporal window for a dog to be exposed to multiple CPV-2 strains, reducing the likelihood of recombination events.

32. Reversion to virulence of modified live virus CPV-2 vaccine strains has been theorised, however numerous studies have failed to demonstrate that this occurs (Churchill, 1987; Decaro et al., 2007; Sehata et al., 2017; Pearce et al., 2023).

3.5 Epidemiology

3.5.1 Host range and transmissibility

33. Canines are the primary host for CPV-2. Puppies less than 6 months of age are most susceptible to CPV-2 (Ogbu et al., 2017; Tuteja et al., 2022). Natural infection with CPV-2 has also been observed in coyotes, raccoons, foxes, wolves, honey badgers, cheetahs, African wild cats and Siberian tigers (Ogbu et al., 2017).

34. CPV-2 is not known to infect humans, other non-canid or non-felid vertebrates or other organisms including invertebrates, plants, microorganisms and aquatic organisms.

35. CPV-2 is mainly transmitted from infected to susceptible hosts through oral routes by direct contact between dogs, or indirect contact with surfaces contaminated with infected faeces (Ogbu et al., 2017; Rabbani et al., 2021). The infectious dose of CPV-2 for a naïve dog is, on average, 1000 viral particles (Nandi and Kumar, 2010). CPV-2 infection can be detected using numerous molecular and biochemistry methods, including polymerase chain reaction (PCR) in stool samples and enzyme-linked immunosorbent assay (ELISA) or hemagglutination assay (HA) in blood and plasma (Ogbu et al., 2017; Tuteja et al., 2022).

36. CPV-2 can be indirectly transmitted between dogs through contaminated indoor or outdoor surfaces, shoes, clothing and food bowls (Ogbu et al., 2017; Rabbani et al., 2021). CPV-2 is highly stable in the environment at ambient temperatures, resistant to desiccation, and can persist in the environment for up to 7 months (Gordon and Angrick, 1986; McGaving, 1987).

3.5.2 Bio-distribution and shedding

37. CPV-2 primarily targets mitotically active cells for replication. Cells in the pharynx, gastroenteric associated lymphoid tissues and lymphocytes are among the first cells targeted by the virus, which facilitate dissemination into the blood stream (Ogbu et al., 2017; Tuteja et al., 2022). Once in the blood stream, the virus preferentially invades rapidly dividing cells in the bone marrow, intestines and, in very young puppies, myocardial cells (Ogbu et al., 2017; Rabbani et al., 2021), however, CPV-2 has been detected in all tissues, including the brain (Decaro and Buonavoglia, 2012).

38. CPV-2 shedding begins 3-7 days after infection, coinciding with the onset of symptoms (Ogbu et al., 2017; Rabbani et al., 2021). CPV-2 can be shed in faeces for up to 54 days post infection (Decaro et al., 2005b), usually peaking at up to 35 million viral particles being shed during the two weeks following exposure (Nandi and Kumar, 2010).

39. CPV-2 can persist in the environment for up to 7 months, if protected from light (Gordon and Angrick, 1986).

3.5.3 Prevalence

40. CPV-2 is considered endemic in Australia with an estimated 20,000 cases per year (Kelman et al., 2020). Historically, only CPV-2a and CPV-2b circulated in Australia, however CPV-2c has been detected in Australia since 2017 (Woolford et al., 2017). There is evidence that the predominant circulating strain is CPV-2b (Kwan et al., 2021).

3.5.4 Controls and other vaccine currently available

41. Vaccination and isolation are the main methods used to control CPV-2 (Miranda and Thompson, 2016; Decaro et al., 2020; Tuteja et al., 2022). There are three main types of CPV-2 vaccines used worldwide; inactivated CPV-2, live attenuated CPV-2 and recombinant CPV-2. Inactivated vaccines are the least used type due to a higher rate of immunisation failure than live attenuated or recombinant

vaccines, and are primarily recommended for immunocompromised dogs (Decaro et al., 2020). There are currently two inactivated and 21 attenuated live CPV-2 vaccines, including CPV-154, approved for use in Australia (APVMA PubCRIS database). Live virus CPV-2 vaccines are typically recommended from 6 to 8 weeks of age.

42. Live attenuated CPV-2 vaccines have been shown to result in a drop of white blood cells counts, but to a much lesser extent than wild type CPV-2 (Day et al., 2016; Pearce et al., 2023). Immunocompromised dogs vaccinated with live attenuated CPV-2 vaccines show a comparable vaccine response to healthy dogs, with an elevated incidence of mild vaccine associated adverse events (Bergmann et al., 2020, 2021).

43. Like many vaccine strains of CPV-2, CPV-154 was derived from a virulent field isolate in Britain in 1987, attenuated by serial passages in cell culture (Churchill, 1987). Attenuated live CPV vaccines are the most commonly used worldwide, usually containing attenuated CPV-2 and CPV-2b.

44. Attenuated live vaccines have demonstrated a high level of immunisation and a long duration of immunity (Decaro et al., 2020; Dall'Ara et al., 2023a; Dall'Ara et al., 2023b). Natural CPV-2 infection or successful immunisation produces a robust sterilising immunity, with subsequent exposure to CPV-2 or CPV-2 vaccines, in the form of boosters, resulting in no viremia or viral shedding (Decaro et al., 2020; Rabbani et al., 2021).

45. The sterilising immunity produced by natural infection or vaccines generally shows protective cross-reactivity against different strains of CPV-2. CPV-154, based on CPV-2, has a demonstrated efficacy against CPV-2a, CPV-2b and CPV-2c (Spibey et al., 2008), however other studies have shown that the virus neutralising titres are lower in dogs vaccinated with CPV-2 based vaccines rather than vaccines based on later variants (CPV-2a, CPV-2b or CPV-2c) (Decaro et al., 2020).

46. A major impediment to successful vaccination against CPV-2 is the presence of maternally derived antibodies in young puppies which can neutralise CPV-2 vaccines. These antibodies are inefficiently carried across the placenta and provide some protection against CPV-2 infection, depending on the titre of antibodies present (Decaro et al., 2005a). Maternal antibody titre in puppies declines over time and is depleted by 15 weeks of age at the latest (Decaro et al., 2020). Sufficient titres of maternal antibodies in puppies can neutralise vaccine strains of CPV-2 prior to seroconversion, interfering with effective immunisation (Decaro et al., 2005a; Decaro et al., 2020). Maternally derived antibodies are thought to be a major cause of immunisation failure against CPV-2, contributing to a so-called "immunity gap" where maternal antibodies provide insufficient protection against infection, but the maternal antibodies are sufficient to impact on vaccine efficacy (Decaro et al., 2005a; Decaro et al., 2020). Vaccination protocols recommend re-vaccinating puppies at 2-4 week intervals (2-3 doses total by 16 weeks) to ensure adequate opportunities for vaccines to effectively overcome this immunity gap.

3.5.5 Stability and decontamination methods

47. As a small, non-enveloped DNA virus, CPV-2 is highly stable and resistant to many disinfectants and environmental conditions (McGaving, 1987). The most effective method of decontamination is 30 minutes exposure to bleach (sodium hypochlorite) concentrations greater than 0.37% (Cavalli et al., 2018). Organic materials, such as soil, blood or faeces, interfere substantially with effective decontamination of CPV-2. Therefore effective decontamination is best achieved by cleaning surfaces prior to treatment with bleach (Cavalli et al., 2018).

48. CPV-2 remains viable at a range of temperatures. At 100°C, CPV-2 is completely inactivated within 2 minutes, but viable CPV-2 can still be recovered after 7 hours at 80°C and after 3 days at 56°C (McGaving, 1987). At room temperature (20-25°C), CPV-2 can persist for at least 6 months under laboratory conditions (McGaving, 1987) and between 5 and 7 months in the environment, depending on light exposure (Gordon and Angrick, 1986).

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

4.1 The genetic modifications

49. The parent strain (CPV-154) is a vaccine strain derived from a field isolate of a CPV-2 outbreak in Britain in 1980 (Churchill, 1987). The field isolate strain was passaged in cell lines to attenuate the strain, generating CPV-154.

50. Some information about the construction and testing of the GMO has been declared Confidential Commercial Information (CCI) under Section 185 of the Act. Under Section 187 of the Act, this information must not be disclosed except where it is made available to the Commonwealth or a Commonwealth Authority, a State agency of the Gene Technology Technical Advisory Committee in the course of carrying our their duties or functions under the Act or under corresponding State law.

51. The GMO (CPV-630a) is a recombinant live vaccine based on CPV-154 and aims to induce an immune reponse against multiple strains of CPV-2 in the presence or absence of maternally derived antibodies. The vaccine strain, called CPV-630a, was constructed as a plasmid in a multistep process to replace the CPV-154 capsid with the capsid from a circulating CPV-2c strain. The CPV-2c capsid has been further modified with two amino acid substitutions present in the CPV-154 capsid that are thought to attenuate the virus (Pearce et al., 2023). The mechanism of attenuation has not been characterised.

52. Compared with CPV-154, the GMO contains the same non-structural protein sequences as the parent strain with an attenuated CPV-2c capsid sequence. It is expected that the modification in the GM CPV-630a strain will generate a robust immune response to all currently circulating CPV-2 strains in dogs inoculated with the GM vaccine.

4.2 Characterisation of the GMO

4.2.1 Growth kinetics and virulence

53. Attenuated CPV-2 strains have been shown to replicate in intestinal mucosa and be shed in the faeces for up to four weeks post vaccination (Decaro et al., 2007; Decaro et al., 2020). CPV-154 is shed from vaccinated dogs for up to two weeks post vaccination, usually correlating with clearance of the vaccine (Churchill, 1987; Decaro et al., 2014).

54. No significant difference was observed in the growth kinetics between the GMO and the CPV-154 parent strain *in vivo*. Rectal swabs from inoculated puppies demonstrated that CPV-630a is shed in faeces for up to two weeks post administration, from 2-6 days post administration, (Pearce et al., 2023), comparable with the parent CPV-154 strain (Churchill, 1987), suggesting that there is no difference in the growth between the parent strain and the GMO.

55. Puppies and kittens inoculated with the GMO show a transient drop in white blood cell counts between day 3 and 6 post vaccination (Pearce et al., 2023).

56. The GMO was shown to be attenuated as puppies inoculated with the GMO showed no clinical symptoms of CPV disease and maintained expected body weight increases (Pearce et al., 2023). In the same study, vaccinated and unvaccinated puppies were challenged with wild type CPV-2c three days post vaccination. All vaccinated puppies exhibited no clinical signs of disease while all unvaccinated puppies showed symptoms of CPV disease from four days after CPV-2c challenge without recovery (Pearce et al., 2023). Similar experiments with the full vaccine (containing CPV-630a and attenuated CDV) showed similar results with no increased virulence resulting from vaccinating puppies with two other commercially available live viral vaccine strains (Pearce et al., 2023).

57. To meet the requirements set out in the *European Pharmacopeia Monograph 0964 - Vaccines for Veterinary Use – Canine parvovirus vaccine (live)*, an overdose study with the GMO was performed (Pearce et al., 2023). Puppies vaccinated with a 10x overdose of the full vaccine (CPV-630a and attenuated CDV) showed no clinical symptoms of CPV disease and no serious adverse reactions. Some

puppies had a local reaction at the injection site that resolved without intervention within 3 days (Pearce et al., 2023).

4.2.2 Bio-distribution, shedding and transmission

58. As mentioned above, the GMO DNA is mainly detected in rectal swabs, resulting from the high level of CPV-2 replication in intestinal tissue. In studies where puppies are vaccinated with the GMO subcutaneously, viral DNA is detected in rectal swabs from 2 days after vaccination, showing that the GMO has a similar tropism to the parent organism (Pearce et al., 2023).

59. The GMO was administered to kittens subcutaneously and via the oronasal route to determine the capacity of the GMO to infect non-target hosts (Pearce et al., 2023). Five sentinel kittens were also housed with the vaccinated kittens to determine whether the shed vaccine could naturally infect naïve kittens. Vaccinated kittens showed no clinical symptoms of disease throughout the study and most vaccinated kittens shed the vaccine between day 3 and 5 post vaccination (Pearce et al., 2023). Vaccine shedding was detected in one sentinel kitten 11 days post vaccination, suggesting that sufficient viral vaccine is shed to be transmitted between animals.

60. The GMO was administered subcutaneously to ferrets, who showed no sign of clinical CPV disease, no adverse reaction to the GMO and no shedding of the GMO was detected in faeces, serum or tissues. Sentinel ferrets housed with vaccinated ferrets remained seronegative to CPV by day 21 after vaccination, indicating that infective viral shedding was either limited or absent. Similar results were obtained in studies using mice and chickens.

4.2.3 Phenotypic and genomic stability

61. To meet requirements set out in the *European Pharmacopeia Monograph 0964- Vaccines for Veterinary Use – Canine parvovirus vaccine (live)*, a reversion to virulence study was carried out in puppies. CPV-630a was administered to the first group of puppies subcutaneously. Faecal samples were collected for 2-6 days post administration to re-isolate CPV-630a, which was then administered to a subsequent group of puppies by the oronasal route. The GMO was passaged in this way 5 times. No clinical signs of disease and no reversion to virulence was observed in this study. In virus isolated from the final group of puppies, no sequence differences were observed from CPV-630a.

62. The parent strain, CPV-154, has not demonstrated reversion to virulence in the three decades that it has been in use (Decaro et al., 2020). The applicant has performed two reversion-to-virulence studies using CPV-154, one with seven serial passages and one with three serial passages. In both studies, CPV-154 showed no reversion to virulence, suggesting that the parent strain is genetically stable.

4.2.4 Efficacy

63. The efficacy of the GMO in protecting dogs from CPV disease has been assessed in naïve puppies and in puppies with high levels of maternal antibodies (Pearce et al., 2023).

64. In the naïve puppies challenged with wild type CPV-2c three days after vaccination with CPV-630a, no clinical manifestation of CPV disease was observed, while all unvaccinated control puppies developed clinical CPV disease (Pearce et al., 2023). Serological analysis showed that vaccinated puppies developed antibodies against CPV-2 three days after vaccination, with very high antibody levels developed by day 6. In contrast, unvaccinated puppies did not develop antibodies until day 5-6 after the wild type CPV-2c challenge, at which point disease progression was severe (Rabbani et al., 2021; Pearce et al., 2023).

65. In puppies with maternally derived antibodies, puppies were vaccinated with CPV-630a at approximately 4 weeks of age (Pearce et al., 2023). All vaccinated puppies produced high levels of CPV-2 antibodies between 8 and 51 days post vaccination, while unvaccinated control puppies showed a decline in maternal antibodies over the same period (Pearce et al., 2023). Subsequent challenge with wild type CPV-2 was not assessed in this study.

4.2.5 Manufacture of the GMO and quality testing

66. The GMO will be manufactured overseas under Good Laboratory Practices consistent the requirements in *European Pharmacopeia Monograph 0964- Vaccines for Veterinary Use – Canine parvovirus vaccine (live)*.

67. The presence of residual plasmid in the final vaccine product is within acceptable limits as defined by the World Health Organisation (WHO) and the Food and Drug Administration (FDA) of less than 10 nanograms (ng) per dose (Vernay et al., 2019; Zheng et al., 2019).

4.2.6 Decontamination of the GMO

68. Methods to decontaminate CPV-2, which have been described in Section 3.5.5, would also be effective against the GMO.

69. The applicant performed decontamination studies using formaldehyde fumigation (6 hours with a minimum of 3000 ppm) to validate that this method can be used to decontaminate rooms housing animals vaccinated with CPV-630a. Rooms that had housed vaccinated puppies for five days were cleaned then fumigated with formaldehyde over two consecutive fumigation cycles. Naïve dogs were introduced to the rooms after the formaldehyde was measured at safe levels. Blood samples, rectal swabs and faecal samples were all negative for CPV-630a or CPV antibodies in samples collected on day 7 and day 21. This study shows that CPV-630a can be decontaminated using this decontamination method.

70. Additional decontamination studies using common cleaning agents Virkon S® and Presept™ found that these cleaning agents were insufficient for decontaminating CPV-630a.

Section 5 The receiving environment

71. The receiving environment forms part of the context for assessing risks associated with dealings with 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. Relevant information about the receiving environment includes state and local council requirements relevant to domestic dogs; waste management practices; related viral species in the environment; and potential hosts in the environment.

5.1 Site of vaccination

72. The intended primary receiving environment would be domestic dogs, administered by qualified veterinarians within clinics Australia wide. The mode of administration would be subcutaneous injection in the scruff of the neck. To use other methods of administration (i.e. oronasal administration), the applicant would also need to seek a registration from the APVMA to authorise these modes of administration.

73. The principal route by which the GMO may enter the wider environment following vaccination is via shedding. Further, GMO may also enter the environment via accidental spills of the vaccine and residual GMO on contaminated surfaces (floors, shoes, hands etc).

5.2 Dog breeders

74. Australian requirements for licensing of veterinary hospitals or other facilities offering dog breeding services are imposed by States and Territories, with additional requirements imposed by their respective legislation (Table 1). Vaccination is not required under any state or territory legislation but is recommended under standards and guidance for breeders Australia wide. States and territories strongly recommend that puppies remain with the breeder until after 8 weeks of age.

Table 1 State and territory requirements for dog breeders in Australia.

State	Legislation	Additional requirements
Australian Capital Territory (ACT)	Domestic Animals Act 2000 and Animal Welfare Act 1992	Mandatory registration. No vaccination requirements.
New South Wales (NSW)	Companion Animals Act 1998	Mandatory registration. Standards set out in *Animal Welfare Code of Practice Breeding Dogs and Cats*. Vaccinations required prior to sale or transfer of ownership under Code of Ethics (not legislatively required).
Northern Territory (NT)	Animal Protection Act 2018	Registration encouraged. No vaccination requirements.
Queensland (QLD)	Animal Management (Cats and Dogs) Act 2008	Mandatory registration. Welfare standards set out in the *Queensland Animal Welfare Standard and Guidelines for the Breeding of Dogs and their Progeny (Oct 2018).* Vaccination recommended.
South Australia (SA)	Dog and Cat Management Act 1995	Mandatory registration. Welfare standards set out in *South Australian Standards and Guidelines for Breeding and Trading Companion Animals 2017*. Vaccination recommended.
Tasmania (TAS)	Dog Control Act 2000 and Animal Welfare (Dogs) Regulations 2016	Mandatory registration. Vaccination status must be disclosed prior to rehoming.
Victoria (VIC)	Domestic Animal Act 1994 and Domestic Animals Amendment (Puppy Farms and Pet Shops) Act 2017	Mandatory registration. Vaccination required prior to sale or transfer of ownership under Code of Practice for the Operation of Breeding and Rearing Businesses 2014 (not legislatively required).
Western Australia (WA)	Dog Act 1976	Mandatory registration. Vaccination recommended.

5.3 Domestic dogs

75. In 2021, it was estimated that 69% of Australian households have a pet, with 6.3 million domestic dogs registered Australia wide (Animal Medicines Australia, 2021).

76. Domestic dogs must be registered, except in NT, and this is enforced by states and territories under their respective legislation (Table 1).

5.4 Canine recommended vaccination schedule

77. Vaccines for dogs in Australia follow the recommendations defined by the World Small Animal Veterinary Association (WSAVA) Vaccination Guidelines Group (VGG) (Day et al., 2016). The VGG defines vaccines as core and non-core, with the recommendation that all dogs should be vaccinated with core vaccines while non-core vaccines should only be used as necessary.

78. All vaccines must be administered by a qualified veterinarian, who are trained to administer vaccines via multiple routes, including subcutaneously using sharps.

79. Vaccination protocols and labels typically recommend only vaccinating healthy animals and avoiding live vaccines in immunocompromised animals (Day et al., 2016).

80. The core vaccines include CPV-2, CDV and canine adenovirus (CAdV), with a preference for modified live or recombinant vaccines, if available. Administration of core vaccines is recommended between 6-8 weeks of age, with additional vaccination 2-4 weeks apart until 16 weeks of age. Attenuated live and recombinant vaccines are generally considered protective after one dose. Boosters are recommended at 1 year old then at intervals of three years thereafter (Day et al., 2016). CPV-2 vaccination is not associated with a period of immunosuppression, however a brief period of immunosuppression is expected following vaccinations containing a modified live CDV component, which rarely causes clinical complications (Day et al., 2016).

81. Non-core vaccines include Parainfluenza virus*, Bordatella bronchisceptica* and *Leptospira interrogans* as modified live virus or attenuated bacterial vaccines, respectively. Non-core vaccines may be administered within similar time frames to core vaccines, depending on veterinary assessment of individual health risks to puppies or dogs. Non-core vaccines are administered when the risk of exposure to each disease is identified based on regional outbreaks, lifestyle, and expected socialisation with other dogs (Day et al., 2016).

82. Vaccines are not mandatory in any states or territories, however veterinary associations, veterinary clinics, national breeder associations and state and territory departments responsible for biosecurity strongly advocate for vaccination of all domestic dogs. These bodies further recommend that puppies have limited environmental exposure until 2 weeks after the completion of their vaccination schedule, and that, in known outbreak areas, unvaccinated dogs should be vaccinated and isolated for two weeks (Day et al., 2016).

83. Overall vaccine coverage of dogs in Australia is not known, however studies overseas have shown that owned dog populations are vaccinated against CPV-2 at a rate of 86-98.5% while stray or surrendered dogs in shelters are vaccinated at a rate of 67-84% (Decaro et al., 2020).

84. While not mandatory, standard practices for animal shelters and animal care facilities (animal daycare and long stay services) require all animals to be vaccinated to limit disease spread. Shelters and care facilities must be designed for effective cleaning and disinfection which must be carried out at least daily using disinfectants that are effective against canine pathogens.

5.5 Biosecurity

85. Each state and territory have their own biosecurity regulations and legislation. The following state departments are responsible for the biosecurity for each state and territory:

- Environment, Planning and Sustainable Development Directorate – Environment (ACT);

- Department of Primary Industries (NSW);
- Northern Territory government (NT);
- Department of Agriculture and Fisheries (QLD);
- Department of Primary Industries and Regions (SA);
- Department of Natural Resources and Environment Tasmania (TAS);
- Agriculture Victoria (VIC); and
- Department of Primary Industries and Regional Development (WA).

86. Biosecurity considerations includes the following: import of animals for domestic or commercial purposes; management of animal diseases (including vaccination and risk of transmission); and animal welfare. Australia also has a national *Biosecurity Act 2015* and a website for managing and reporting national pest and disease outbreaks, that is managed by the Department of Agriculture, Fisheries and Forestry (DAFF).

5.6 Presence of related viral species in the receiving environment

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

88. Twenty-one live attenuated CPV-2 vaccines are registered for use in Australia, including CPV-154. However, CPV-2 remains endemic in Australia with a range of CPV-2 capsid variants detected between 2015 and 2019 (Woolford et al., 2017; Kwan et al., 2021). Detected variants were predominantly CPV-2b (54%), CPV-2a (43%) and CPV-2 (2.5%) (Kwan et al., 2021), with CPV-2c detected in a small number of dogs in a separate study (Woolford et al., 2017) . Kwan et al. (2021) also identified CPV-2 variants with a high level of similarity to Asian variants and CPV-2 with capsid mutations similar to FPV, showing a high diversity in circulating CPV-2 in Australia. The National Pest and Disease Outbreaks website, has no current listed outbreaks of CPV-2 (as of April 2024).

89. Other parvoviruses also circulate in Australia and are highly host specific, including Porcine Parvovirus (infecting pigs), FPV, human parvovirus B19, human bocavirus 1 and a range of adeno-associated viruses (AAV). Species in the family Parvoviridae infect many different animals across invertebrates and vertebrate animals, with naming often linked to the specific host (e.g. rat parvovirus, turkey parvovirus etc)(Du et al., 2019). Recombination between different species of parvoviruses has been observed under field conditions, most often within the same genera that share similar cell tropism (Shackelton et al., 2007; Wang et al., 2012).

90. Approximately half of adults in Australia are estimated to have immunity to human parvovirus B19, based on the seroprevalence of antibodies across several population groups (Faddy et al., 2018). Human parvovirus has different cell tropism and transmission to CPV-2, primarily spread through respiratory routes and targeting red blood cells and bone marrow (Pudasaini et al., 2023). Clinical manifestation is also distinct from CPV-2, with a characteristic rash and arthritic symptoms (Pudasaini et al., 2023).

5.7 Presence of similar genetic material in the environment

91. The balance of an ecosystem 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.

92. The GMO was derived from naturally occurring CPV-2c and a vaccine strain already used in Australia, hence similar genetic material would already be present in the environment.

5.8 Potential hosts in the environment

93. The potential for CPV-2 to infect other susceptible hosts that may be present in rural or urban areas is considered in the risk assessment (Chapter 2). The primary host for CPV-2 is dogs and other canids. CPV-2 disease in cats, ferrets and other carnivores is rarely reported (see Chapter 1, Section 3.5.1).

94. Australia has wild canines, including feral dogs, dingoes (*Canis lupus dingo*, or *Canis familiaris dingo*) and red foxes *(Vulpes vulpes*)(Van Arkel et al., 2019). CPV-2 cases have been detected in both red foxes and dingoes, with similar disease pathology to that observed in dogs (Zourkas et al., 2015; Van Arkel et al., 2019).

95. There is extensive spatial overlap between populations of wild dogs and domestic dogs in Australia (Van Arkel et al., 2019). Given the prolonged survival of CPV-2 in the environment, there is likely bi-directional transmission of CPV-2 between wild and domestic dogs which contributes to the ongoing circulation of CPV-2 in Australia (Van Arkel et al., 2019).

96. Wild dogs typically move over larger areas than domestic dogs, with dingoes having the largest estimated home range of 10 to 60 km^2 (Van Arkel et al., 2019).

97. Dingoes are primarily active at dusk and dawn, with activity varying between searching (hunting) behaviour and exploratory (social) movement (Harden, 1985; Thomson, 1992). Packs of dingoes usually consist of a mated pair and their offspring from the current breeding season with distinct territories that have little overlap with neighbouring territories (Harden, 1985; Thomson et al., 1992). The breeding season is estimated to occur between March and June, with denning and whelping occurring from June to August (Thomson, 1992; Thomson et al., 1992). Dingo litters range from 1-10 pups, with an average of two pups surviving to adulthood (Thomson et al., 1992). The pups leave the den periodically between 3 and 8 weeks of age within a range of 2.5 km (Thomson, 1992). The pups become independent between 3-6 months of age and will leave the pack at 10 months of age (Thomson et al., 1992).

Section 6 Previous authorisations

98. This GM vaccine has not been previously authorised for commercial supply in Australia.

99. This GM vaccine has been authorised for use in the European Union by the European Medicines Agency (EMA/531403/2020) since 2021.

100. This GM vaccine has been authorised for use by the Philippines Food and Drug Administration (VR-4383) since 2022.

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.

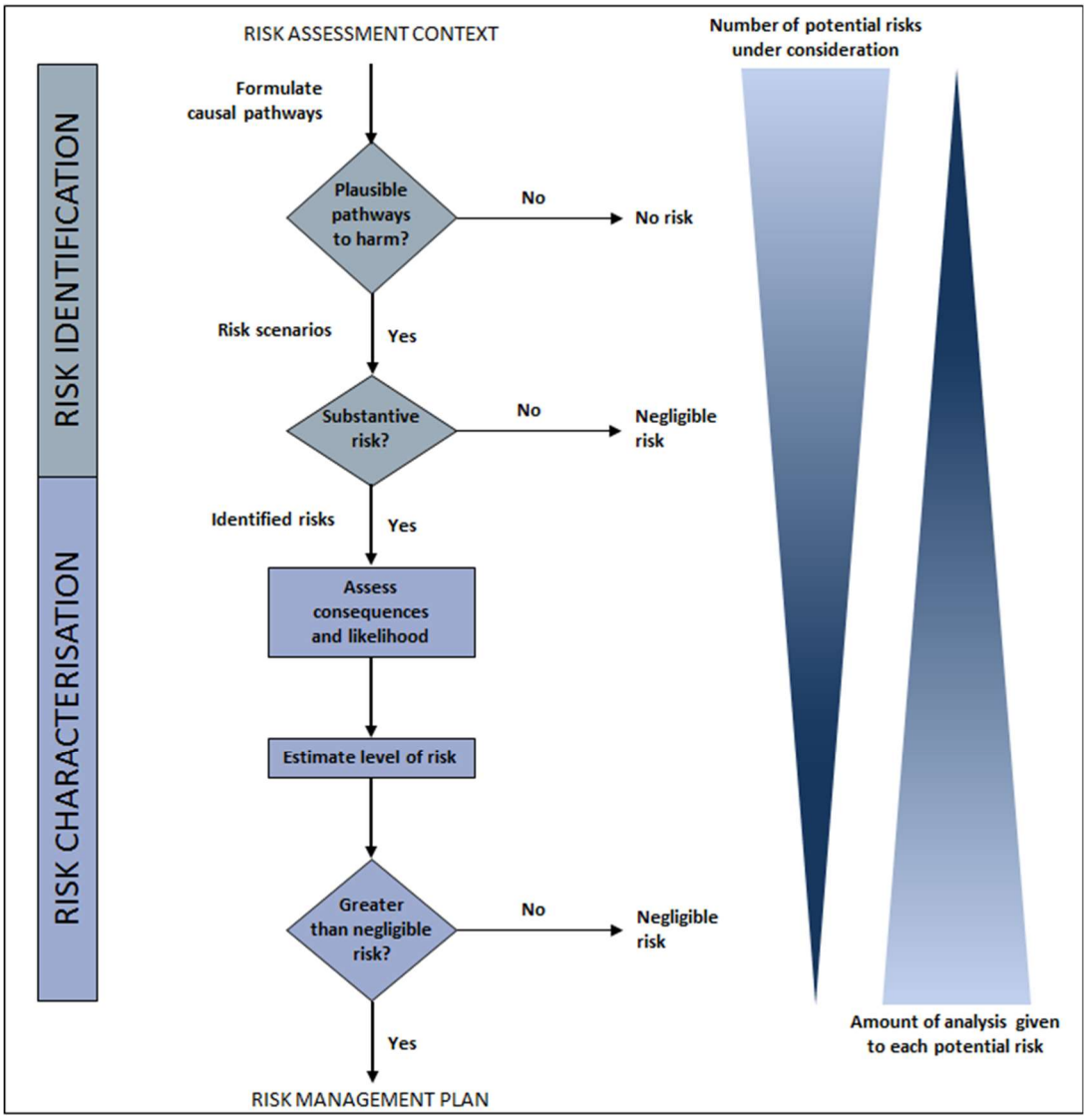

Figure 4: The risk assessment process

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 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.

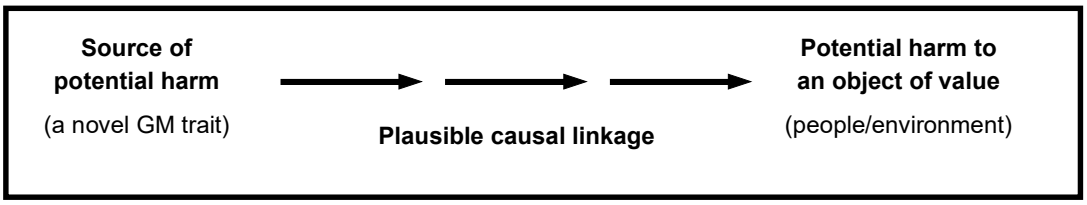

Figure 5: Components of a risk scenario

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 is an infectious canine parvovirus type 2 (CPV-2) vaccine strain. Details of the pathogenicity and transmissibility of CPV-2 is discussed in Chapter 1. Infection is the result of direct contact with infected dogs or indirect contact with surfaces contaminated with infected faeces. Canines vaccinated with the GMO could transmit the GMO to uninfected canines or other susceptible carnivore species (e.g. cats, wild dogs and dingoes).

109. The sources of potential harms can be the intended novel GM traits associated with the genetic modification, or unintended effects arising from the use of gene technology.

110. As discussed in Chapter 1, Section 4.1, the GMO has been modified by replacing the vaccine strain capsid protein with an attenuated CPV-2c capsid protein. This modification is considered further as a potential source of risk.

111. Unintended effects can arise through horizontal gene transfer (HGT) which is the stable transfer of genetic material from one organism to another without sexual reproduction. As discussed in Chapter 1, Section 4.2, there is a possibility that the GMO could recombine with other field or vaccine strains resulting in a novel trait. The novel trait may result in negative, neutral or positive effects on the fitness of the recipient organism. This pathway is further considered as a potential source of risk.

112. Infection with CPV-2 could result in significant shedding into the environment via faeces of infected dogs and increase the period of viral persistence and transmission. Therefore, this pathway is further considered as a potential source of risk.

113. CPV-2 is not known to integrate into the host DNA as discussed in Chapter 1, Section 3.3. Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

114. CPV-2 is known to have a very limited host range and not shown to be able to infect and cause disease in non-carnivore species. In the event of exposure of other animals to the GMO, it is highly unlikely that it would lead to any harm to those animals. Therefore, this pathway will not be further discussed.

115. CPV-2 attenuated vaccines have not demonstrated a reversion to virulence in three decades of use. Therefore, this pathway will not be further discussed.

116. The vaccine contains GM CPV-2 and attenuated CDV and is likely to be administered with other viral vaccines. However, CPV-2 does not undergo recombination with CDV or other viruses that are not parvoviruses. Therefore, this pathway is not discussed further.

117. The GMO will be administered with a CDV component and can be expected to induce a brief period of immunosuppression between 3 and 10 days post administration. However, other live attenuated combination vaccines containing CPV-2 and CDV are already widely used in Australia and are not associated with severe clinical outcomes for dogs or cats. Therefore, this pathway is not discussed further.

118. The current assessment focuses on risks posed to people and to the environment, including long term persistence of the GMO, which may arise from the transport, storage or disposal of the GMO.

2.2 Causal pathway

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

- the proposed dealings, which are transport or disposal of the GMO and possession (including storage) in the course of any of these dealings,
- regulations in placed for the 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,
- potential for transmission,
- potential effects of the genetic modification on the properties of the organism,
- 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 (e.g. tolerance to temperature, UV irradiation and humidity),
- potential risk of revertant/novel strains due to HGT,
- practices before and after administration of the GMO including veterinary practices.

120. Although these factors are taken into account, some are not included in the risk scenarios because they are regulated by other agencies, have been considered in previous RARMPs or are not expected to give rise to substantive risks (see Sections 2.4.1 to 2.4.2 below).

121. The APVMA regulates the quality, safety and efficacy, and trade risks associated with the GM vaccine under the AgVet Code, as mentioned in Chapter 1, Section 1.1. This includes safety and efficacy of the vaccine; environmental risks; and recommended practices for the use, transport, storage and disposal of the GM vaccine. Therefore, risk scenarios in the current assessment focus primarily on risks posed to people and to the environment from the GMO, and not the intended vaccine recipients (dogs).

122. 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.

2.3 Potential harms

123. Potential harms from the GM vaccine include:

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

2.4 Postulated risk scenarios

124. Three risk scenarios were postulated and screened to identify substantive risk. These hypothetical scenarios are summarised in Table 2.

125. In the context of the activities proposed by the applicant and considering both the short and long term, two of the three risk scenarios did not give rise to any substantive risks that could be greater than negligible (discussed in depth in sections 2.4.1-2.4.2; this chapter). One risk scenario was identified as posing substantive risk which warranted further assessment (characterised in Section 3; this chapter).

Table 2 Summary of hypothetical risk scenarios from dealings with GM vaccine

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GM CPV-2	Exposure of people to the GMO via fomites or needle stick: <u>During:</u> (a) preparation and administration of the GMO; (b) handling waste from vaccinated dogs; (c) unintentional spills; and (d) transport, storage or disposal of the GMO and waste associated with GMO.	Disease in people	No	• The vaccine is transported in sealed single dose vials, therefore exposure to the GMO from spills or needlestick injury would be in small volumes. • Vaccination would be conducted by registered veterinarians who are trained in the appropriate use of sharps. • Other CPV-2 vaccines have a history of safe use with no adverse effects in people from direct exposure. • CPV-2 has a very narrow

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		⬇ Infection of people with the GMO.			host range, is not a human pathogen and is not expected to cause disease, toxicity or allergenicity in people.
2	GM CPV-2	Exposure of other animals to the GMO via transmission from vaccinated dogs or shedding the GMO into the environment ⬇ Infection of other animals (e.g. wild, feral, pest, native or pet/household animals). ⬇ Disease in susceptible animals; or vaccination of susceptible feral animals	Disease in domestic or native animals or Increased numbers of feral/pest animals	No	• Animals previously exposed to CPV-2 or CPV-2 vaccines are unlikely to be infected with the GMO. *Domestic animals* • Exposure is minimised due to recommended vaccination protocols. Considering that most domestic dog owners are conscious of preventing disease in pets, they are likely to follow recommendations. • Most puppies receive their first vaccines while in the care of a breeder, limiting their exposure to other susceptible dogs and the environment. • GMO is unlikely to cause disease in susceptible animals housed with the vaccinated dog due to attenuation of the virus. *Native and Feral animals* • GMO is unlikely to cause disease in wild dogs, including foxes and dingoes due to potential prior exposure. • Native non-canid animals, such as marsupials, birds and reptiles, are not known to be infected by CPV-2. Serious outbreaks in native animal with circulating strain of CPV-2 have never been reported.
3	GM CPV-2	Vaccination of dogs with the GMO.	Disease in dogs or other	Yes	• CPV-2 vaccines have a known history of recombination with field

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		⬇ Infection of cells by GMO. ⬇ a) Transduced cells co-infected with circulating CPV-2 strain. OR b) Shed GMO infects susceptible animal infected with a parvovirus ⬇ Homologous recombination with CPV-2 (field or vaccine strains). ⬇ Generation of recombinant CPV-2 or parvovirus strains. ⬇ Infection of dogs and/or other susceptible animals with recombinant CPV-2.	susceptible species		strains resulting in novel strains that could infect and cause disease in susceptible species or alter host range. • See Section 3 for risk characterisation

2.4.1 Risk scenario 1

Risk source	GM CPV-2
Causal pathway	Exposure of people to the GMO via fomites, contact with contaminated faeces and needle stick: <u>During:</u> (a) preparation and administration of the GMO; (b) handling waste from vaccinated dogs; (c) unintentional spills; and (d) transport, storage or disposal of the GMO and waste associated with GMO. ⬇ Infection of people with the GMO
Potential harm	Disease in people

Risk source

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

Causal Pathway

127. People conducting the dealings could be exposed to the GMO in several ways. The GMO could be transmitted indirectly by contaminating clothes and hands during an unintentional spill of the GMO or during the preparation and administration of the GMO. Transmission could also occur through a needle stick injury during subcutaneous injection of the GMO. People handling waste containing the GMO could be exposed to the GMO via contact (e.g. hands, clothing). This exposure could potentially result in infection with the GMO that could lead to disease.

Exposure during preparation and administration of the GMO

128. As discussed in Chapter 1, Section 2.1, the GMO would be supplied as a freeze-dried vaccine in sealed vials, which would need to be reconstituted prior to use. There is the potential for exposure of people involved in the administration of the GMO from breakage/spillage of GMO onto surfaces during preparation and administration or via needle stick injury.

129. The GM vaccine would be prepared and administered by a qualified veterinarian who is trained in the use of sharps and vaccine administration.

130. Based on the current registration for approved live CPV-154 vaccines, the APVMA registration of veterinary vaccines would include a label indicating the dosage; method of administration; precautions; personal protective equipment (PPE) requirements; and instructions relating to first aid, storage, and disposal of the GMO. Compliance with these behavioural practices by veterinarians would reduce the likelihood of unintended exposure of people to the GMO.

131. The existing work practices mentioned above would minimise the potential exposure of people to the GMOs during preparation and administration of the vaccine.

Exposure during handling of waste from vaccinated dogs

132. As mentioned in Chapter 1, Section 3.5.2, CPV-2 is mainly transmitted by direct contact with infected dogs or indirect contact with surfaces contaminated by waste from infected dogs. This could occur as a result of vaccinated dogs defecating in public or in private spaces or in care facilities such as kennels. People cleaning up faeces may be exposed to the GMO. However, cleaning of dog faeces is typically done with limited direct contact through the use of gloves, plastic bags, shovels or high-pressure hoses. This limits the potential exposure of people to the GMO through the waste from vaccinated dogs.

Exposure via unintentional spill

133. If the GM vaccine was unintentionally/accidentally spilled or lost during transport or storage, this could result in exposure to people transporting or storing the GMO via contamination of surfaces.

134. As described in Chapter 1, Section 2.1, the GMO would be packaged in sealed vials and subsequently packaged into a cardboard box prior to import and transport. This would lower the likelihood of unintended dispersal of the GMOs.

135. The packaged final product will be stored at Schedule 4 licensed distribution centres prior to transportation to veterinarian clinics. The current APVMA registered CPV-2 vaccines include storage instructions (in refrigerators).

136. The transport and storage procedures discussed above would meet the containment requirements of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*, which ensures that the GM vaccine would be properly contained for transport and storage. This would mitigate exposure due to spills of the GMO during these dealings.

Exposure during disposal of the GMO and waste contaminated with the GMO during administration

137. Individuals may be inadvertently exposed to GMOs while disposing of used, expired, or unused vials of the GM vaccine.

138. As mentioned in Chapter 1, Section 2.1, the applicant has stated that all residual vaccine and associated waste which has come into contact with the GM vaccine (such as syringes and vials) would be discarded in waste disposal streams at veterinary clinics. As mentioned in Chapter 1, Section 3.5.5, CPV-2 is a non-enveloped virus that is resistant to many disinfectants. However, veterinary clinics have strict cleaning protocols using appropriate disinfectants for veterinary pathogens. Current registered CPV-2 vaccines have disposal instructions on their labels to discard the vial/container in designated biological containers.

139. The disposal and decontamination procedures discussed above would minimise the likelihood of exposure of people that could be associated with conducting these dealings with the GMOs.

Potential harm

140. As mentioned in Chapter 1, Section 3.5.1, CPV-2 has a very narrow host range and is not known to cause disease in humans. Non-attenuated CPV-2 strains are currently present in the Australian environment, and live attenuated CPV-2 vaccines are widely used in Australia. Therefore, it is highly likely that people are currently exposed to various strains of CPV2 with no reports of disease, infection (clinical or subclinical), toxicity or allergic reactions.

Conclusion

141. The exposure of people to the GMO resulting in disease is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

2.4.2 Risk scenario 2

Risk source	GM CPV-2
Causal pathway	Exposure of other animals to the GMO via transmission from vaccinated dogs or shedding the GMO into the environment ⬇ Infection of animals (e.g. wild, feral, pest, native or pet/household animals). ↙ Disease in susceptible animals ↘ vaccination of susceptible feral animals
Potential harm	Decreased numbers of susceptible animals Or Increased numbers of susceptible feral/pest animals

Risk Source

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

Causal Pathway

143. Other animals (e.g. wild, feral, pest, native or pet/household animals) may be exposed to the GMO via transmission from dogs vaccinated with the GMO or contamination in the environment via shedding in faeces either a) in the home of the vaccinated dog or b) outside the home in kennels, dog parks, or gardens.

a) Exposure and infection of animals in the home

144. CPV-2 has a narrow host range and is known to infect dogs and cats. Other domestic animals such as ferrets, mice, rats or birds are not known to be infected by CPV-2 and are therefore not considered to be susceptible to CPV-2 or the GMO.

145. Animals in the home could be exposed to the GMO directly via transmission from a vaccinated dog. For other dogs in the home, it could be other puppies from the same litter or another litter if the vaccinated dog is housed in a breeder facility. Some of these puppies may have been vaccinated at the same time or they may be younger and awaiting vaccination. It is likely that, if these animals have been vaccinated against CPV-2, their pre-existing immunity against CPV2 makes them unlikely to be infected with the GMO. If, however, they have not yet been vaccinated, maternal antibodies may reduce the symptoms associated with a CPV-2 infection. For older dogs, as the immunity provided by vaccination is lasting, those would be unlikely to be infected with the GMO.

146. Cats living with the vaccinated dog may become infected with and shed the GMO.

b) Exposure and infection of animals outside the home

147. Animals outside the home include other domestic animals, and feral and native animals. CPV-2 is known to infect dogs, foxes, dingoes and cats. Native animals, such as marsupials, reptiles and birds, are not known to be infected by CPV-2 and infection is considered unlikely due to the narrow host range of CPV-2.

148. The GMO is expected to be shed in faeces of vaccinated dogs for a period after vaccination. Animals outside the home, including other dogs, cats, wild dogs, dingoes, feral cats and foxes, are unlikely to come into direct contact with vaccinated dogs if vaccination protocols are reasonably

adhered to. However, due to the environmental persistence of the GMO, these animals may be exposed to GMO shed into the environment in the faeces of vaccinated dogs. This could occur if, during the post-vaccination isolation period, the vaccinated dog is exercised outside the home, housed in a kennel, or toilets outside in spaces accessible to feral animals.

149. Vaccination protocols recommend that animals vaccinated for the first time are not taken out into the environment to limit their exposure to disease until the vaccine has taken effect. Kennels also restrict the housing of animals to those that have completed their vaccination schedule. Many pet owners are conscious of the health of their animals and are likely to adhere to the recommendations. In addition, States and Territories can issue fines for failing to pick up dog faeces in public spaces. Therefore, the likelihood of the potential spread of the GMO in the environment is reduced.

150. As described in Chapter 1, Section 3.5.1, CPV-2 could potentially infect other canids and felids such as feral foxes, wild dogs or cats, or native dingoes. Wild dogs, dingoes and foxes that have previously been exposed to CPV-2 are unlikely to be infected by the GMO due to the sterilising immunity against CPV-2 strains.

151. As mentioned in Chapter 1 in Section 3.5.4, vaccination against or prior exposure to CPV-2 produces sterilising immunity against all strains of CPV-2 in dogs. Therefore, most susceptible canines (domestic or wild) would likely be less than 6 months of age.

Potential harm

152. If susceptible animals are exposed and infected with the GMO, they are unlikely to develop CPV-2 disease due to the attenuation of the virus. As mentioned in Chapter 1, Section 4.2, the vaccine did not cause any clinical disease in puppies even at 10 times the dose or after multiple doses (2 doses, one week apart). The vaccine also did not cause disease when administered as a full dose to cats, chickens, mice or ferrets. It is unknown whether native birds, marsupials or reptiles would be susceptible to the GMO, however it is highly unlikely due to the narrow host range of the GMO.

153. Susceptible animals are more likely to be less than 6 months of age because they have not been previously exposed to CPV-2 or a vaccine. As mentioned in Chapter 1 Section 5.8, dingo pups move over a much more limited range than adults, therefore reducing the likelihood of encountering the GMO in the environment. Adult dingoes or foxes caring for pups may have been previously exposed to CPV-2 or a vaccine and are unlikely to shed the GMO if infected due to sterilising immunity. For adults not previously exposed to CPV-2 or a vaccine, they may become infected with the GMO and shed the GMO in close proximity to their den.

154. Alternatively, as the GMO was shown to offer protection to vaccinated puppies from CPV-2 infection, exposure of wild/feral animals (e.g. dogs, foxes and cats) could also potentially result in immunity towards CPV-2. This could inadvertently result in increased numbers of wild dogs, foxes and cats as these feral species could be vaccinated via an exposure to the GMO, increasing their survival in the event of an outbreak due to a more pathogenic strain of CPV2. However, for this scenario to lead to harm to the environment, many wild dogs, foxes and cats have to become infected with the GMO, and CPV-2 circulating viruses would need to be an important factor limiting the populations. As mentioned in Chapter 1, Section 5.8, CPV-2 already circulates within wild populations of dogs and foxes, and these animals are likely to encounter a number of live non-GM vaccine strains in their lifetimes. This reduces the likelihood of the GMO coming into contact with a significant number of naïve animals. This impact has not been observed thus far with the large number of live attenuated vaccines already available in Australia.

155. As mentioned in Chapter 1, Section 5.8, there are native dingoes in Australia. If dingoes are exposed to the GMO, disease is highly unlikely as the GMO does not cause disease in canines, and wild CPV-2 already circulates in dingo populations, reducing the likelihood of the GMO encountering a naïve animal.

Conclusion

156. The potential of direct or indirect exposure of susceptible or feral animals to the GMO via transmission from vaccinated dogs or from shedding of the GMO into the environment is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

Section 3 Risk characterisation

157. Three risk scenarios were postulated and evaluated, as summarised in Table 2. The third risk scenario was identified as posing a substantive risk which warrants further assessment. This section provides more detail on the evaluation of this scenario.

3.1 Risk Scenario 3

Risk source	GM CPV-2
Causal pathway	Vaccination of dogs with the GMO ⬇ Infection of cells by GMO ⬇ a) Transduced cells co-infected with another CPV-2 strain (field or vaccine strains) OR b) Shed GMO infects susceptible animal infected with a parvovirus ⬇ Homologous recombination with CPV-2 or other parvovirus ⬇ Generation of recombinant CPV-2 or parvovirus strains ⬇ Infection of dogs and/or other susceptible animals
Potential harm	Disease in dogs and/or other susceptible species

Risk source

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

Causal Pathway

159. An animal containing the GMO could be co-infected with another CPV-2 strain, or other parvovirus, which recombines to generate a novel CPV-2 or parvovirus strain that causes disease in dogs or other susceptible species.

Likelihood assessment

160. The probability of recombination occurring in viruses is dependent on co-circulation of different viruses in the same geographical area, genetic similarity between the viruses, rate of co-infection of a host with both viruses and viral population size within the infected host cell. For recombination between the GMO and a strain of CPV-2 or another parvovirus to occur, both strains would need to be present and replicating in the same cell at the same time. This could occur if:

i. the dog vaccinated with the GMO is exposed to another strain of CPV-2 before or after vaccination;

ii. two different live attenuated CPV-2 vaccines are administered at the same time; or

iii. a susceptible animal is infected by a parvovirus and infected by the GMO following exposure to a vaccinated dog or from GMO shed into the environment.

Potential for recombination between the GMO and another strain of CPV-2

161. Dogs may be exposed to field strains of CPV-2 immediately prior to or after vaccination with the GMO. This could occur if dogs are housed with other animals that can move freely between the home and the environment, or if dogs are taken out into the environment within the period immediately prior to vaccination with the GMO or before onset of immunity from the vaccine (3 days, discussed in Chapter 1). As the GMO and wild-type CPV-2 share similar cell tropism, co-infection is highly likely to occur in the same cell and result in recombination. As discussed in Chapter 1, Section 3.4, bioinformatic studies have shown that recombination occurs between vaccine strains and circulating strains of CPV-2.

162. Many puppies are vaccinated within 4 to 8 weeks old while still in the care of a breeder and are typically isolated from other proximal dogs. Any other dogs likely to encounter those puppies in a breeder environment are likely to have already been vaccinated against CPV-2.

163. Puppies not vaccinated while in the care of the breeder are likely to be vaccinated shortly after being bought, with the recommendation that puppies are kept in the home until vaccinations are complete (Chapter 1, Section 5.4). This reduces the likelihood of puppies being infected with field strains of CPV-2 before being vaccinated. Vaccination of dogs with the GMO or other available CPV-2 vaccines should also generate immunity towards circulating strains, minimising the window in which naïve dogs would be infected with the virus to around 4 to 8 weeks old.

164. As discussed in Chapter 1, CPV-2 causes symptomatic disease in young dogs within 2 days after exposure. The APVMA has registered several live attenuated CPV2 vaccines and has issued recommendations about their use. This includes the recommendation to only vaccinate healthy puppies. This recommendation reduces the likelihood that puppies will be co-infected with the GMO and a field strain of CPV-2.

165. Vaccination protocols recommend that animals vaccinated for the first time are not taken out into the environment to limit their exposure to disease until the vaccine has taken effect. As mentioned in Risk scenario 1, many pet owners are conscious of the health of their animals and are likely to adhere to the recommendations, therefore reducing the likelihood a vaccinated puppy being exposed to field strains of CPV-2 after vaccination.

166. The vaccination of dogs with the GMO would confer protective immunity against circulating strains of CPV-2, reducing the likelihood of co-infection with multiple strains outside of the two-week post-vaccination period. Vaccination protocols and practices recommend that vaccinated dogs have limited environmental exposure. Adherence to the recommendations limits the likelihood of a dog being exposed to a field strain of CPV-2 before the onset of immunity.

Potential for recombination between the GMO and other CPV-2 vaccine strains

167. Recombination between two vaccine strains of CPV-2 could occur if a dog is exposed to two different CPV-2 vaccine strains within a small temporal window. This could occur by administering another CPV-2 vaccine strain at the same time as the GMO, by administering the GMO while another vaccine strain has not been cleared from the dog, or by being vaccinated with the GMO then exposed to another vaccine strain that has been shed into the environment.

168. All animal vaccines approved for administration by injection in Australia must be administered by a qualified veterinarian. Veterinary protocols recommend only vaccinating with one strain of a given live attenuated vaccine, reducing the likelihood of two CPV-2 vaccines being administered concurrently.

169. A dog could be vaccinated with the GMO while still infected with a different CPV-2 vaccine strain or vice versa. This could occur if a puppy is vaccinated while in the care of a breeder and then vaccinated again after being re-homed. As discussed in Chapter 1, vaccine strains are typically cleared within two weeks. Australian vaccination schedules recommend at least two weeks between vaccine administrations for young puppies, reducing the likelihood of a dog being infected with two different vaccine strains of CPV-2.

170. Several APVMA registered CPV-2 vaccines also include recommendations to administer vaccine doses at least two weeks apart.

171. For both adult domestic and wild dogs, the likelihood of previous exposure to CPV-2 or a vaccine against CPV-2 is high, therefore limiting the potential for co-infection with the GMO and a second strain of CPV-2 in the environment due to existing immunity.

172. Several live attenuated CPV-2 vaccines are already in use in Australia, and several strains of wild type CPV-2 are already circulating in Australia. To date, there are no reported instances of recombinant strains of CPV-2 or other parvoviruses with increased virulence.

173. Therefore, based on the information discussed above and assuming reasonable adherence to vaccination guidelines, the likelihood that both the GMO and other CPV-2 are present in the same host/cells for recombination to occur is likely. However, the likelihood of recombination events leading to an established novel pathogenic CPV-2 strain is **unlikely**.

Potential for recombination between the GMO and other parvoviruses

174. For recombination to occur, both the GMO and another strain of CPV-2 or a similar parvovirus must be present and replicating in the same cell at the same time.

175. It is expected that the GMO will be shed in the faeces of vaccinated dogs for up to 10 days post vaccination. While the environmental stability of the GMO has not been tested, it is likely similar to the parent strain. The GMO could persist on contaminated surfaces or in the environment for an extended period. As described in Chapter 1 Section 5.8, there is significant spatial overlap in the habitats of wild dogs and urban dogs, increasing the likelihood of animals encountering surfaces or environment where the GMO has been shed in faeces.

176. Animals exposed to the GMO on contaminated surfaces or in the environment would not be expected to adhere to an isolation period, and therefore may also encounter field strains of CPV-2 or similar parvoviruses such as FPV, thereby leading to potential recombination events.

177. As mentioned in Chapter 1, Section 5.6, sequence analysis shows that parvovirus species can recombine with each other. Many parvoviruses already circulate in Australia, however cases of co-infection with different parvovirus species have not been reported. CPV-2 has not been reported in non-canid and non-felid vertebrates, and cases of infection with a parvovirus that is not CPV-2 has not been reported in dogs. Therefore, it is **highly unlikely** that the GMO and another parvovirus species would co-infect dogs or wild animals simultaneously resulting in the generation of novel recombinant strains that could cause disease.

Consequence assessment

Recombination of the GMO with field CPV-2 strains or vaccine CPV-2 strains

178. If recombination occurred between the GMO and either a field strain or a vaccine strain of CPV-2, the likely result would be a recombinant GMO with a wild type capsid, or a wild type strain with an attenuated capsid. In either case, the recombinant GMO would have similar characteristics to the vaccine strain or the already circulating wild type CPV-2. The recombination between the GMO and other strains of CPV-2 (field or vaccine) would result in either vaccination against CPV-2 or clinical disease that is not more severe than wild type CPV-2. Therefore, the consequence to susceptible species would be **marginal** (minimal or no increase in harm to desirable components of the environment).

Generation of novel recombinant CPV-2 or parvovirus

179. If recombination between the GMO and other CPV-2 strains or parvoviruses were to occur, it could result in the generation of a novel strain of CPV-2. As discussed in Chapter 1, CPV-2 is genetically highly similar to FPV, with the greatest variation occurring in the capsid sequence. Therefore, the likely result of recombination is a recombinant GMO with a wild type parvovirus capsid or a wild type parvovirus with an attenuated capsid. However, even with the presence of several live attenuated vaccines used in Australia and the circulation of several CPV-2 strains in Australia, novel, more virulent strains have not been reported. It is highly unlikely that the GMO would recombine with other strains of CPV-2 at a greater rate than other strains already present in Australia, or that the resulting strain would be more virulent. In the event of a recombinant strain emerging, it would only cause serious disease in the small number of animals which have not been either vaccinated or exposed to CPV . Therefore, the consequence of resulting in a novel CPV-2 is **marginal**.

Risk estimate

180. The risk estimate is based on a combination of the likelihood and consequence assessments, using the Risk Estimate Matrix (see Chapter 2, Section 1), as described in the Regulator's Risk Analysis Framework 2013.

181. The potential consequence of recombination of the GMO and other strains of CPV-2 in dogs/other susceptible species is considered **marginal**, with a probability of **highly unlikely**. The overall risk is therefore estimated to be **negligible** (risk is of no discernible concern and there is no present need to invoke actions for mitigation).

182. The potential consequence of the generation of novel CPV-2 more pathogenic than the parent organism via homologous recombination in dogs/other susceptible species are considered **marginal**, with a probability of **unlikely**. The overall risk is therefore estimated to be **negligible**.

Section 4 Uncertainty

183. Uncertainty is an intrinsic part of risk analysis[2]. 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.

[2] 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.

184. 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.

185. 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.

186. For DIR-202 uncertainty is noted in relation to several points, including:

- the ability of the GMO to persist in the environment;
- the potential of the GMO to recombine and generate novel pathogenic strains; and
- the length of the protection from CPV-2 conferred by the GM vaccine.

187. The uncertainties outlined above have been accommodated by taking a conservative approach to the risk analysis.

Section 5 Risk evaluation

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

189. 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.

190. Three risk scenarios were identified whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people and animals can be exposed to the GMO while conducting the dealings or in the environment and whether there is a potential for recombination of the GMO with other CPV-2 strains. The potential effects of releasing the GMO into the environment was also considered.

191. 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.

192. In the context of the range of measures already in place, including the operating guidelines and requirements of the other regulatory agencies, and considering both the short and long term, one of these scenarios was identified as representing a substantive risk requiring further assessment.

193. The likelihood and consequences of the substantive risk was characterised (Chapter 2, Section 3), and the level of risk estimated using the Risk Estimate Matrix, as described in the *Regulator's Risk Analysis Framework 2013* (see Chapter 2, Section 1).

194. The risk due to recombination of GMO with other CPV-2 strains, with the potential for transmission of recombinant CPV-2 to other susceptible animal species resulting in disease was estimated as posing a negligible risk to the environment. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment[3].

195. Control measures are likely to be imposed by the APVMA during the registration process to manage those risks. Control measures for administration of other live attenuated CPV-2 vaccines are currently imposed under other APVMA registrations. However, since this product is yet to be registered with the APVMA, additional measures to maintain critical elements of the risk context are considered in Chapter 3

[3] 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. However, the Regulator has allowed up to eight weeks for the receipt of submissions from prescribed experts, agencies and authorities and the public.

Chapter 3 Risk management plan

Section 1 Background

196. 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.

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

198. 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 are also required to be reported to the Regulator.

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

Section 2 Risk treatment measures for substantive risks

200. The risk identification process led to identification of one substantive risk, which involves the GMO recombining with other CPV-2 strains, with the potential for transmission of the recombinant GMO to other susceptible animals resulting in disease. This risk was characterised in Chapter 2, Section 3.

201. Some of the current APVMA registered CPV-2 vaccines have warning statements on their labels to ensure that:

- CPV-2 vaccines are available by prescription only;
- Only healthy dogs should be vaccinated following adequate clinical examination; and
- A minimum period of two weeks should lapse between vaccination courses.

202. To maintain critical elements of the risk context, prior to APVMA registration, the draft licence imposes conditions requiring that the vaccine may only be administered to healthy dogs, only one live CPV-2 vaccine should administered at a time, and that a minimum period of two weeks should lapse between vaccinations. This is to manage the risk of recombination between CPV-2 vaccine or field strains circulating in the environment.

Section 3 General risk management

203. 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
- access for the purpose of monitoring for compliance
- other modes of administration.

3.1 Applicant suitability

204. 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.

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

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

3.2 Testing methodology

207. If a licence were issued, Intervet Australia Pty Ltd would be required to provide a method to the Regulator for the reliable detection of the GMO, and the presence of the introduced genetic materials in a recipient organism. This methodology would be required prior to conducting any dealings with the GMO.

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

208. If a licence were issued, any person, including the licence holder, could conduct any permitted dealing with the GMO.

3.4 Modes of administration

209. The applicant has proposed one mode of administration (subcutaneous injection). The risks associated with this method of administration has been included in the risk assessment for DIR 202.

3.5 Reporting requirements

210. If issued, the licence would oblige 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.

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

212. 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).

213. If issued, the licence would also require the licence holder to notify the Regulator of the following authorisations by the APVMA:

- inclusion on the Public Chemicals Registration Information System (PubCRIS); and
- any amendments to the registration.

3.6 Monitoring for compliance

214. 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.

215. 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

216. 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.

217. For the current application for a DIR licence, the Regulator is including 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. If a licence was issued, this ongoing oversight would be 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

218. 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

219. 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.

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

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

222. The characterisation of the risk scenarios discussed in Chapter 2 identified the risk of recombination as a risk that could be greater than negligible. Therefore, it was considered a substantive risk that warranted further detailed assessment. Further assessment determined that this risk was not greater than negligible. No specific indicators of harm have been identified in this RARMP for application DIR 202. However, specific indicators of harm may also be identified during later stages, e.g. following the consideration of comments received on the consultation version of the RARMP, or if a licence were issued, through either of the other components of PRR.

223. 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

224. 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. In the case of a veterinary vaccine where the APVMA is the primary regulatory body overseeing the vaccine, any review of the RARMP or licence would likely only be initiated in consultation with APVMA.

Section 5 Conclusions of the consultation RARMP

225. The risk assessment concludes that the proposed commercial release of this GM CPV-2 vaccine poses negligible risks to the health and safety of people and a negligible risk to the environment as a result of gene technology.

226. The risk management plan concludes that the identified negligible risks can be managed to protect the health and safety of people and the environment by imposing risk treatment measures. Licence conditions are proposed to prevent the concurrent administration of vaccine with different CPV-2 strains, mandate the time lapse between two live vaccines to be a minimum of 2 weeks and restrict the vaccination to healthy dogs. General conditions were also included in the draft licence to ensure that there is ongoing oversight of the GM vaccine.

Chapter 4 Draft licence conditions

Section 1 Interpretations and Definitions

1. In this licence:

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

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

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

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

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

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

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

2. In this licence:

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

‘**Annual Report**’ means a written report provided to the Regulator by the end of September each year containing all the information required by this licence to be provided in the Annual Report.

‘**GM**’ means genetically modified.

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

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

‘**OGTR**’ means the Office of the Gene Technology Regulator.

‘**Regulator**’ means the Gene Technology Regulator.

Section 2 Licence conditions and obligations

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

4. The licence holder is Intervet Australia Pty Ltd.

5. Any person, including the licence holder, may conduct any authorised dealing(s) with the GMO.

6. The dealings authorised by this licence are:

    (a) Import the GMO;

    (b) transport of the GMO;

(c) disposal of the GMO;

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

Note: Use of the GMO for veterinary purposes is not covered by the Gene Technology Act 2000 and therefore this licence is not required to authorise such use. The GMOs are also subject to regulation by other federal and state departments and agencies, including the Australian Pesticides and Veterinary Medicines Authority and the Department of Agriculture, Fisheries and Forestry. These other departments and agencies may impose further requirements for, or limitations on, the use of the GMO or these dealings.

7. This licence does not apply to dealings with the GMO conducted as a Notifiable Low Risk Dealing (NLRD) or pursuant to another authorisation under the Act.

Note: Dealings conducted as an NLRD must be assessed by an Institutional Biosafety Committee (IBC) before commencement and must comply with the requirements of the Regulations

8. Dealings with the GMO may be conducted in all areas of Australia.

9. Dealings described in Condition 6(a) must not occur unless authorised by registration with the APVMA.

10. The licence holder must ensure that end users of the GMO are informed that the GMO:

(a) is not to be given concurrently with any other live CPV-2 vaccines;

(b) is not to be given within two weeks of administration with any other live CPV-2 vaccines; and

(c) is to be given to healthy dogs only.

11. The licence authorises dealings with the GMO described in **Attachment A**.

12. To the extent that the conditions of any prior licence authorising dealings with the GMOs are inconsistent with the conditions of this licence, the conditions of this licence will prevail.

2.1 Obligations of the Licence Holder

13. The licence holder must immediately notify the Regulator if any of its contact details change.

Note: Please address correspondence to OGTR.M&C@health.gov.au

Prior to issuing a licence, the Regulator considers suitability of the applicant to hold a licence. The following conditions address ongoing suitability of the licence holder.

14. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.

15. The licence holder must:

(a) inform the Regulator immediately in writing, of:

i. any relevant conviction of the licence holder; and

ii. any revocation or suspension of a licence or permit held by the licence holder under a law of the Australian Government, a State or a foreign country, being a law relating to the health and safety of people or the environment; and

iii. any event or circumstances that would affect the capacity of the holder of this licence to meet the conditions in it; and

(b) provide any information related to the licence holder's ongoing suitability to hold a licence, if requested, within the stipulated timeframe.

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

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

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

(c) the surrender of the licence.

2.2 Provision of new information to the Regulator

Licence conditions are based on the risk assessment and risk management plan developed in relation to the application using information available at the time of assessment. The following condition requires that any new information that may affect the risk assessment is communicated to the Regulator.

17. The licence holder must inform the Regulator if the licence holder becomes aware of:

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

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

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

Note: The Act requires, for the purposes of the above condition, that:

(a) the licence holder will be taken to have become aware of additional information of a kind mentioned in paragraph 17 if he or she was reckless as to whether such information existed; and

(b) the licence holder will be taken to have become aware of contraventions, or unintended effects, of a kind mentioned in paragraph 17, if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

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

18. If the licence holder is required to inform the Regulator under condition 17, the Regulator must be informed without delay.

Note: An example of informing without delay is contact made at the time of the incident via the OGTR free call phone number 1800 181 030, which provides emergency numbers for incidents that occur out of business hours.

19. If at any time the Regulator requests the licence holder to collect and provide information about any matter to do with the progress of the dealings authorised by this licence, including but not confined to:

(a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 17(a);

(b) any contraventions of the licence by a person covered by the licence, whether or not the licence holder has provided information to the Regulator under condition 17(b);

(c) any unintended effects of the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 17(c);

(d) research, including by way of survey, to verify predictions of the risk assessment, or for any purpose related to risks to the health and safety of people, or to the environment;

(e) scientific literature and reports in respect of the GMO authorised by this licence, for a nominated period;

(f) details of any refusals of applications for licences or permits (however described) to deal with the GMO made pursuant to the regulatory laws of a foreign country;

and the request is reasonable, having regard to consistency with the Act and relevance to its purpose, then the licence holder must collect the information and provide it to the Regulator at a time and in the manner requested by the Regulator.

Note: The Regulator may invite the licence holder to make a submission on the reasonability of a request by the Regulator to collect and provide information relevant to the progress of the dealings with the GMO.

2.3 Obligations of persons covered by the licence

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

Section 3 Reporting and Documentation Requirements

3.1 Notification of authorisations by the Australian Pesticides and Veterinary Medicines Authority

21. If the GMOs are included on the Public Chemical Registration Information System (PubCRIS), the licence holder must notify the Regulator in writing and include information of how Condition 10 is met, within 14 days of registration.

22. The licence holder must notify the Regulator in writing of any subsequent amendments to the conditions of the PubCRIS registration involving the pattern of usage, handling, storage, transport or disposal of the GMOs, within 14 days of the change occurring.

3.2 Annual Report

23. The licence holder must provide an Annual Report to the Regulator by the end of September each year covering the previous financial year. An Annual Report must include:

(a) information about any adverse impacts, unintended effects, or new information relating to risks, to human health and safety or the environment caused by the GMOs or material from the GMOs;

(b) information about the numbers of GM vaccine doses distributed to each State and Territory.

3.3 Testing methodology

24. At least 14 days prior to conducting any dealings with the GMO, the licence holder must provide to the Regulator a written methodology to reliably detect the GMO, or the presence of the genetic modifications described in **Attachment A** in a recipient organism or environmental sample. The detection method(s) must be capable of identifying, to the satisfaction of the Regulator, the genetic modification event described in **Attachment A**.

Note: Please address correspondence to OGTR.M&C@health.gov.au

ATTACHMENT A

DIR No: 202

Full Title: Commercial supply of a live attenuated vaccine containing canine distemper virus and a genetically modified canine parvovirus (Nobiva Puppy DP Plus) for dogs

Organisation Details

Postal address: Intervet Australia Pty Ltd

PO Box 2800

Bendigo Delivery Centre

VIC 3554

Accreditation No: Accr 073

GMO Description

GMO covered by this licence

The vaccine contains live attenuated canine distemper virus and GM canine parvovirus (CPV-2) CPV-630a. The GM component was produced introducing the capsid (viral envelope) of a circulating CPV-2 strain into the existing attenuated vaccine strain CPV-154.

Parent Organism

Common Name: Canine parvovirus

Scientific Name: *Carnivore protoparvovirus 1*

Modified traits

Category: Vaccine – attenuated

Description: CPV-630a has been genetically modified to reduce virulence and induce an immune response against circulating strains of CPV-2, for use as live attenuated vaccine.

Purpose of the dealings with the GMO

The purpose of the dealings is commercial supply of the GM vaccine against CPV-2 Australia-wide to provide protection against CPV-2 infection. Therefore, the permitted dealings under this licence are import, transport, storage and disposal of the GM vaccines.

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Appendix A: Summary of submissions

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

Submission	Summary of issues raised	Comment
1	As this has been approved by the European Medicine Authority no issues are raised. I do not have an issue.	Noted.
2	Information noted.	Noted.
3	Does not have the required expertise to assess this application or provide meaningful comment. Therefore, are unable to support nor challenge this application.	Noted.
4	No objections to the application.	Noted.
5	No comments to provide	Noted
6	No issues at this time.	Noted.
7	Do not have specialist veterinary qualifications so does not plan to make any comment on the application.	Noted.
8	It is noted that the risk scenarios presented appear to pose negligible effect to both environmental and human health. We do not have any policy in place opposing gene technology	Noted.
9	Accepts that, overall, Intervet Australia Pty Ltd's application has negligible risks to the health and safety of people and the environment. Is satisfied that the measures taken to manage the short and long term risks from the proposal are adequate.	Noted.
10	Advised to consider the following in the preparation of the RARMP: • Clarification of the mechanism of attenuation of the parent CPV strain, if known; • Whether the circulating CPV-2 strain used for the capsid protein is circulating in Australia; • The genetic diversity of circulating strains of CPV-2 in Australia; • Clarification on how the GMO was constructed;	Noted. The raised issues have been addressed in the RARMP prepared by the Regulator and are discussed in Chapter 1 and 2.

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

Submission	Summary of issues raised	Comment
	• The frequency of recombination between field strains of CPV-2; • Has the GMO been tested in immunocompromised animals; • Potential shedding of the GMO from vaccinated animals; and • Whether the applicant will be seeking an import permit from DAFF.	
11	Advised to consider the following in preparation of the RARMP: • The relative risk of the GMO to human health from needlestick injuries compared to non-GM CPV-2 vaccines; • The relative risk of the GMO reverting to virulence compared with non-GM CPV-2 vaccines; • The relative risk of the GMO causing disease in animals in contact with vaccinated animals compared with non-GM CPV-2 vaccines; and The risk of recombination leading to virulent strains of CPV-2 that cause disease in animals.	Noted. The raised issues have been addressed in the RARMP prepared by the Regulator and are discussed in Chapter 1 and 2.
12	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 GMO to be harmful to the environment and potential for complementation or recombination with other CPV strains.	Noted.
	Recommended seeking clarification on the methods used to detect residual plasmid and the sensitivity of the assay used; the potential for reversion to virulence; and the potential response of dingoes in Australia to the GMO.	Risks associated with residual plasmid, reversion to virulence and potential response of dingoes in Australia to the GMO are discussed in Chapter 1 and 2 (Risk scenario 2 and 3).
13	No advice or comments on the RARMP for DIR 202.	Noted.