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VMDA

Submission to the Legislative and Governance Forum on Gene Technology Regarding Overlap in the Regulation of Vaccines Produced using Gene Technology

Reducing the cost of regulatory compliance by eliminating duplication

Live veterinary vaccines created using gene technology are subject to regulation as veterinary medicines and also as products of gene technology. The purpose of both regulatory regimes is to evaluate potential risks arising from the use of the product and to specify conditions that mitigate any identified risks where appropriate.

The sale or experimental release for field trials of veterinary vaccines is regulated by Australian Pesticides and Veterinary Medicines Authority. The APVMA manages the risk of harm to people, to the intended target animal and to animals or plants in the environment, posed by agricultural and veterinary chemicals (including immunobiologicals such as vaccines). This is achieved by registering products for sale only after extensive evaluation of data on safety and efficacy, and by placing conditions on manufacture (GMP) to ensure consistent quality.

Regulation of AgVet Chemicals

The *Agricultural and Veterinary Chemicals (Administration) Act 1992* calls for demonstration that the product is safe for people and the environment, as well as safe and effective in the target organism. Specifically, *Category 2 applications for registration of a new product or Category 23 applications for research permits must satisfy the criteria of section 112 of the Agvet Code, that the proposed use:*

- *would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues; and*
- *would not be likely to have an effect that is harmful to human beings; and*
- *would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment; and*
- *would not unduly prejudice trade or commerce between Australia and places outside Australia; and*
- *would be effective for the intended purpose.*

These criteria must be satisfied by the provision of data generated in laboratory studies

and field trials performed to standards specified in the relevant monographs (such as European Pharmacopoeia, British Pharmacopoeia or US Code of Federal Regulations, 9CFR).

The *Agricultural and Veterinary Chemicals (Administration) Act 1992* requires the APVMA to consult with the Gene Technology Regulator and take into account the advice of the Regulator when making a decision on the approval, registration or reconsideration of products that have been created using gene technology.

Regulation of Genetically Modified Organisms

Where gene technology has been used to create a live vaccine organism, the *Gene Technology Regulator* has responsibility under the *Gene Technology Act 2000* to manage risks to people and the environment arising from the use of the technology. The object of the Act is:

> *"to protect the health and safety of people, and the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with genetically modified organisms (GMOs)."*

For laboratory studies, this regulation takes the form of a Notification that Low Risk Dealings (NLRD) are being performed in appropriate facilities certified by the OGTR, or a licence for Dealings Not Involving Release (DNIR) stipulating conditions to manage the exposure of people to novel organisms, and to prevent release of the organism into the environment. For a candidate vaccine organism, following the completion of laboratory studies to produce evidence of efficacy and safety for product registration (with the APVMA), a separate licence application to the OGTR is required for approval of Dealings involving Intentional Release (DIR) of the organism into the environment for field trials or for commercial release.

Overlap between APVMA and OGTR Regulation and Risk Assessments

There is considerable overlap between the *Gene Technology Act 2000* and the *Agricultural and Veterinary Chemicals (Administration) Act 1992* in considering the risks to people and to the environment posed by the release into the environment of a live veterinary vaccine created using gene technology. The overlap between these two regulatory regimes may be demonstrated by comparing the scientific data requirements for a field trial permit or for product registration by the APVMA, and for the issue of a licence for Dealings involving Intentional Release (DIR) by the Gene Technology Regulator.

Both regulators require information regarding the good character of the applicant and the capacity of the applicant to comply with any conditions imposed on the registration or the licence. These administrative requirements are similar and will not be discussed in detail.

Comparison of data assessed by the APVMA and OGTR

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The APVMA has a set of standard data requirements across all agricultural and veterinary products (including pharmaceuticals, chemicals and pesticides) and subsets of these are required according to the circumstance. The data parts required for vaccines are specified in *'Guideline for the registration of new veterinary vaccines'*, which highlights data that are appropriate to consideration of live vaccine organisms. The data required for consideration during approval of a DIR licence for release into the environment of an organism that is defined as a GMO by the *Gene Technology Regulations* is mainly captured in the application form for the licence as this includes all data required. An alternative would be to survey completed Risk Assessment and Risk Management Plans for vaccine organisms, however these are few in number and may be out of date.

Table 1 matches the data required for APVMA approval of a field trial or for registration of a vaccine produced using gene technology, with the data requested in the DIR licence application form. This comparison serves to identify the overlap and any differences within the sets of data considered by each regulator. In the case of the DIR application form, the data requirements have been created to cover a wide range of products and need to be interpreted in a way most relevant to veterinary vaccines.

Each part of the *'Guideline for the registration of new veterinary vaccines'* is discussed below with reference to the extent to which the data evaluated by APVMA matches the data evaluated as part of the Risk Assessment and Risk Management consideration of OGTR.

Part 2 Chemistry and Manufacture

For registration by the APVMA data must be provided regarding the chemistry and method of manufacture of the vaccine to demonstrate that the raw materials and the production process are of a type that will ensure continuing product quality, safety and efficacy. Detailed descriptions of the manufacturing facility, formulation of the product and the origin and quality of starting materials must be provided. Similar information is requested for a DIR licence application in questions 7.5 and 7.6. Data are required for description of the Master Seed organism under *Production, control and testing of starting materials*, including the taxonomy of the parent organism to the strain level, the environmental distribution of the organism, and the date and location of the isolation of the organism from the field. These data correspond closely with the data required by the DIR licence application, *Part 9: Risk assessment information – the parent organism(s)*, and serve the same purpose in the risk assessment. Characterisation of the parent organism/master seed provides the basis for identifying the potential for harmful or unintended events that could occur as a result of the release of a live vaccine organism into the environment, irrespective of whether the organism has been created using gene technology or conventional methods (such as passage in eggs or cultured cells).

Part 3 (Human safety) Toxicology data

Toxicity data are not normally required for registration of immunobiological products by the APVMA, however they may be required where a modified organism expresses a novel protein, or otherwise results in the presence of a novel substance in the final product that presents a risk of toxicity or allergenicity following exposure to the vaccine during handling. If there is a reasonable expectation of harm to people occurring, based either on the known properties of any novel proteins or other substance present in the formulated product, or on experience of adverse events recorded during the development of the vaccine organism, the risk should be assessed against the criteria listed in the *Scheduling Policy Framework for Medicines and Chemicals* published by the National Coordinating Committee on Therapeutic Goods. If there is an identified risk sufficient to require scheduling as a *Prescription Animal Remedy* (Schedule 4) or as a poison (Schedules 5, 6, or 7), toxicity data suitable to allow assessment for scheduling must be provided to the APVMA.

This issue is considered in *Part 11: Risk assessment information – risks GMO(s) may pose to the health and safety of people* of the DIR application, specifically at 11.1, which considers the expression of novel toxic or allergenic proteins.

Part 4 Metabolism and Kinetics

Part 4 addresses the rate of degradation and elimination of toxins from the organism. It is relevant to chemical medicines, and possibly to genetically modified organisms that produce a potentially toxic substance as a result of the modification. As noted, for vaccines, it is usually considered in conjunction with *Part 5 Residues and Trade* and the capacity of the vaccine organism to persist within the animal.

In this area, the DIR application requires information on the production and possible concentration of harmful metabolites produced by the GMO as a result of the genetic modification. The relevance to vaccine organisms that are likely to be present transiently in a food producing animal is not clear, and this information would seem to be more appropriate to organisms such as genetically modified plants consumed directly by humans or used as stock feed.

Part 5 Residues and Trade

While residues would normally refer to chemical residues, a food producing animal containing live vaccine organisms requires a withholding period during which the organism should decline to the point where it is undetectable. This is true of conventional vaccines as well as those modified by gene technology, to avoid the exposure of people to replication competent micro-organisms, or violation of the biosecurity arrangements (including restrictions on products of gene technology) of another country.

The DIR application requires information on the fate of animals used in a trial of a

genetically modified vaccine organism (*Part 17 Additional information – live GM vaccine for use in animals*), obliquely addressing the issue of whether the organism is present at the time of slaughter or disposal.

Part 7 Environment

Assessment of potential negative impact on the environment forms a large part of the consideration of agricultural and veterinary chemicals under the *Agricultural and Veterinary Chemicals (Administration) Act 1992*. For conventional vaccine organisms, where the same organism is already present and causing disease in the environment, consideration of the environmental impacts has not generally been considered necessary. However a genetically modified organism would be considered to be a new introduction into the environment and therefore subject to environmental risk assessment. The specific guideline for registration of new veterinary vaccines does not provide substantial guidance on the data requirements for environmental assessment, and the requirements listed by the general guideline for veterinary chemicals are not appropriate to biological products. Instead, the European Agency for the Evaluation of Medicinal Products (EMEA) guideline *Environmental Risk Assessment for Immunological Veterinary Medicinal Products* (EMEA/CVMP/074/95) is listed as a Supplementary Guideline. In summary, this guideline considers:

A) Hazards due to the:

- Capacity of live organisms to transmit to non-target species
- Shedding of live product organisms (route, numbers, duration)
- Capacity to survive, establish and disseminate
- Pathogenicity to other organisms
- Potential for other effects of live product organisms
- Toxic effects of the product components
- Toxic effects of excreted metabolites

B) The likelihood of the hazard being manifested.

Issues including climatic, geographical and soil conditions, demographic considerations, the types of fauna and flora in the potential receiving environment that could contribute to manifestation of the hazard should be identified and assessed, and the magnitude and exposure of any viable organisms to the environment.

C) Assessment of the consequence of a hazard occurring

D) Assessment of level of risk

E) Selection and assignment of appropriate control measures (risk management)

This assessment informs the decision as to whether any risks posed by the product are such that the product should not be registered, or whether an *environmental protection statement*, describing how the product should be handled to avoid environmental harm, should be included on the label. The provision of information on safe use and environmental protection through labelling, and the reporting of any adverse environmental effects, are the means of controlling any environmental risk for a commercial release. Processes to use these means are well established for controlling similar risks due to conventional vaccine organisms by the APVMA. Any use in contravention of a label direction resulting in actual or potential harm to people or the environment may lead to prosecution under State and Territory legislation governing human health, animal health or environmental health.

The DIR application form requires information on the scale and consequences of environmental exposure in *Part 10: Risk assessment information – interaction between the GMO(s) and the environment* and *Part 12: Risk management information.* The first requires information about the survival and likely dispersal of the organism, its interaction with organisms in the environment, and the resulting undesirable effects, including competitive advantage or pathogenesis. The information required by *Part 12: Risk management information* regards proposals for monitoring and limiting the release of the organism. Disposal of unused product is considered in *Part 17: Additional Information – live GM vaccine for use in animals*. It is clear that the data considered in assessing risk to the environment during evaluation of a DIR licence application is the same as that considered under the APVMA/EMEA guidelines, considering the likely exposure of animals or plants that may experience harm, given the scale of the release and the rate at which the GMO degrades, and assessing the potential magnitude of any harm. This should not be surprising, as the risks posed by conventional and genetically modified vaccine organisms are essentially the same.

Part 8 Efficacy and Safety

The *Gene Technology Regulator* does not consider efficacy, or the potential benefit provided by an organism, when deciding whether to issue a licence. Furthermore, in considering a live vaccine organism, only the safety of people or animals other than those targeted for treatment should be considered. In particular, any potential increase in virulence should only be considered where the host range of the vaccine organism includes animals in the environment, and not the targeted animal, as this is the responsibility of the APVMA. Hence the consideration of Efficacy and Safety by the *Gene Technology Regulator* covers only a subset of the issues considered by the APVMA registration process.

Where overlap does occur, is in consideration of issues that are specific to live vaccine organisms, such as the likelihood that the vaccine organism may directly or indirectly (by altering the behaviour of pathogenic organisms in the environment) cause harm to non-target animals or people.

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The APVMA guidelines consider five issues specific to live vaccine organisms. These are;

- spread to non-vaccinates,
- spread to non-target animals,
- dissemination in the host,
- reversion to virulence and
- recombination.

Transmission from vaccinated to non-vaccinated animals is not necessarily a safety risk, although it may contribute to selection of more virulent genetic variants and hence the evolution of increased virulence (reversion to virulence). Experimental protocols are specified in monographs (European Pharmacopoeia, British Pharmacopoeia or US 9CFR) which aim to satisfy reversion to virulence. Another important issue common to live vaccines, whether produced using gene technology or conventional means, is the potential for genetic recombination with other pathogenic organisms replicating within the host, resulting in an organism with increased ability to cause harm. Assessing the likelihood of recombination requires an assessment of the biology of the vaccine organism, and of other pathogens circulating within the host population that may have the potential to recombine with the vaccine organism. Spread to non-target animals is considered under Part 8 Safety and Efficacy as well as under Part 7 Environment, of the APVMA requirements. These considerations closely follow the issues addressed in the EMEA *Guideline on Live Recombinant Vector Vaccines for Veterinary Use* (EMA/CVMP/004/04), which provides more detailed guidance on the data required to assess risks posed by modified vaccine organisms.

The DIR licence application requires data addressing these issues in *Part 10: Risk assessment information – interaction between the GMO(s) and the environment*, including whether the inserted genetic trait will be able to be transferred to other organisms (recombination) and any possible adverse effects of the transfer including any advantage that an affected organism is likely to have over members of the species that do not contain the transgene, and any environmental risks posed. Note that the DIR application assumes that the modified organism has been modified by the addition of genetic material from another organism, and this need not apply to a vaccine organism that demonstrates a decrease in virulence as a result of the *deletion* of genetic material. The data requirements for a licence application need to cover a wide range of organisms, and are often difficult to interpret for vaccine organisms that require the presence of a suitable host to persist.

Further information more directly applicable to vaccine organisms is required by *Part 17: Additional information – live GM vaccine for use in animals,* which broadly follows the data requirements listed in the EMEA *Guideline on Live Recombinant Vector Vaccines for Veterinary Use.*

Part 10 Special Data Requirements (GMOs)

Any licence issued by the GTR for the organism proposed for release in field trials or for sale must be provided in the application to the APVMA. The need to first obtain approval from the Gene Technology Regulator prior to seeking approval from the APVMA may result in extensive delays between the completion of laboratory studies and the commencement of field trials. However any vaccine organism created using gene technology must be assessed by the OGTR for a licence application, or by an Institutional Biosafety Committee for notification to the OGTR as a Notifiable Low Risk Dealing, during pre-clinical development and testing in the laboratory. This is the case even where inserted foreign DNA, such as a selectable marker gene, has been fully removed from the final vaccine organism and no foreign DNA remains. This is important as it triggers the requirement for environmental assessment, which is not required for a conventional live vaccine organism, and excludes the product from provisions allowing the conduct of small scale trials without approval from the APVMA (PER7250).

Consequences of Regulatory Duplication

The *Agricultural and Veterinary Chemicals (Administration) Act 1992* administered by the APVMA includes consideration of human safety and risk to the environment , fully encompassing the consideration of human safety and risk to the environment as required under the *Gene Technology Act 2000* administered by the OGTR. While these issues are typically only given high level consideration in the case of conventional live vaccine organisms, as the virulent organism must already be present in the environment for registration of the vaccine to be considered, detailed consideration is required for a vaccine organism produced using gene technology, whether or not the final organism is a Genetically Modified Organism.

The data requirements for registration or release under a field trial permit by the APVMA or licencing by the OGTR are comparable, differing in the specific questions asked rather than in the fundamental risk issues that those questions address. They differ in that the APVMA requires empirical data derived from studies of the phenotypic properties of the vaccine organism so as to assess the absolute risk posed by the organism as a whole. The APVMA requirements are tied to international standards and guidelines (VICH, European Pharmacopoeia, US 9CFR) that are used to direct the studies performed during product development, and provide clear acceptance criteria for demonstrating an acceptable risk. The OGTR assesses the potential for an increase in harm as a result of the genetic changes, relative to the parent organism. It is considerably more difficult to design an experiment to provide such data, and hence the OGTR data requirements must be answered by extrapolating from studies performed for other purposes, or from published data. It is unlikely that such studies would usually be performed to directly address OGTR data requirements as these requirements are not clearly specified and are

not linked to international standards describing acceptable experimental protocols or acceptance criteria. This means that approval from the Gene Technology Regulator must be sought after the completion of laboratory studies intended to support registration and before application can be made to the APVMA for a Permit to perform field trials. That is, assessment of the likelihood that the genetic modifications may result in increased harm occurs after the vaccine has been demonstrated to be safe for the target species, people and the environment. While appropriate prior to experiments demonstrating safety in the laboratory, it is clear that at the point where a field trial permit or product registration is sought, the DIR licence process does not add to the management of any risks posed by a vaccine organism.

Although the issues considered and the data required are the same, the data formats for application to the APVMA and to the OGTR are not sufficiently similar that a single data submission can be supplied to both regulators. This effectively doubles the time and work involved in gaining approval to release a vaccine organism for field trials or for sale, adding greatly to the cost of bringing a new product to market.

The timeframe for application and approval by the GT Regulator may further add to the time and cost involved in developing and marketing a vaccine. While shorter than the timeframe for APVMA approval, the timeframe for OGTR assessment (150 days for a field trial licence or 255 days for commercial release) may increase substantially where additional data are sought. As the precise data requirements are not well specified in the DIR application process, there is considerable regulatory uncertainty involved in the development of novel vaccines using biotechnology. This additional cost and regulatory uncertainty explains why there are currently no live veterinary vaccines developed using gene technology available on the Australian market.

Recommendations

The analysis above demonstrates the following:

- The assessment of risk to people and to the environment is duplicated by the APVMA permit/registration and OGTR DIR licence approval processes.
- The APVMA process is linked to international standards appropriate to live veterinary vaccine organisms, which provide clear guidance on data requirements.
- The OGTR licence process introduces additional cost and regulatory uncertainty that acts as a significant barrier to the development of novel vaccines using biotechnology.

It follows from these points that allowing the APVMA to take responsibility for the evaluation of all veterinary vaccine organisms would not increase the minimal risks associated with the release of such organisms into the environment, and would reduce the cost to industry of developing new vaccines. This would increase the number of vaccines available on the Australian market to the benefit of end users.

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Table 1. Comparison of data requirements

OGTR Data Requirements DIR Licence	APVMA data requirements for Veterinary Vaccines
Part 7: About the dealings with the GMO(s)	
7.1 Details of: (i) the number of sites for proposed release; and (ii) the area of land to be used (if applicable); and (iii) the location of the proposed release(s), including identification of the local government area(s) in which any release will take place and the geographical location, grid references and GPS coordinates of the site(s)	*The location of trial sites would be provided to the APVMA for a field trial permit. This information is not relevant for a commercial release covering the whole of Australia*
7.2 Details of the reasons for the choice of location(s) for the release(s)	**Application Overview (Part 1)**
7.3 Details of the number of different types (events, lines, species, etc) of GMO(s) that will be released	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism
7.4 Details of how the GMO(s) will be released	Method of administration would be determined by methods used in Safety and Efficacy trials
7.5 Details of the methods to be used to test for batch to batch consistency, if large scale production is required to produce the GMO(s) for release	**Chemistry and Manufacture (Part 2)** GMP status of the manufacturing facility Production, control and testing of starting materials In-process control tests during production Control tests on the finished product (*Regulation of these are issues is the responsibility of the APVMA*)
7.6 Details of the measures that have been taken, or will be taken, in the production process to ensure quality and purity of the GMO(s) intended to be released	
7.7 Details of the arrangements for conducting any other dealing(s) in association with the proposed release(s), such as importation of a GMO(s) and transportation of a GMO(s), to or from a release site(s)	*This is relevant to compliance with the GT Act and Regulations. It is not relevant to scientifically assessing risks associated with a vaccine intended for trial or commercial release*
7.8 Details of proposed uses of the GMO(s), or of things derived or produced from the GMO(s), following release into the environment	**Residues (Part 5a)** A transgenic or zoonotic live veterinary vaccine administered to food producing animals would require assessment of the presence of the vaccine organism in food products
Part 8: Description of the GMO(s)	
8.1 Details of the modified trait(s) and how the modification will change the phenotype of the organism(s) to be released, including information to demonstrate the effects of the modification(s)	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism – biological characteristics *(These details form part of the history and characterisation of the vaccine master seed.)*
8.2 Identity of the gene(s) responsible for the modified trait(s), including a description of gene combinations in the GMO(s) (if any)	
8.3 Details of the origin(s) of the DNA to be inserted	
8.4 If the inserted DNA will come from an organism that causes disease or other ill-health in humans, animals, plants or fungi, details of the effects	
8.5 Details of the genetic modification(s) that have been or will be made, including details of the steps involved in its construction	
8.6 Details of the stability of the genotype(s) of the GMO(s), including a statement on whether it has a potentially unstable genotype	**Safety and Efficacy (Part 8)** Recombination Reversion to Virulence
8.7 Details of the extent to which the genetic modification(s) has been characterised (that is, the DNA sequenced, and the potential gene products understood)	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism – biological characteristics These details, to the extent that they are relevant to a vaccine organism that may not have inserted foreign DNA, form part of the history and characterisation of the vaccine master seed.
8.8 Details of the location of the inserted DNA and the number of copies that will be present in the final construct	

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8.9 Is the site of integration of the inserted DNA, within the host genome, known?	Master Seed Organism – biological characteristics Efficacy and Safety - recombination
8.10 Details of the markers or sequences that will enable the GMO(s) to be identified in the laboratory and under field conditions	
8.11 Details of the type of vector used in the transfer (including a description of the vector), showing the position of the inserted DNA and any other control sequences or markers in the vector	
8.12 Details of whether the vector has the ability to transfer to other hosts and, if so, details of the host range	
8.13 Details of whether the recombinant vector will be present in the final construct and if not, how it will be removed	
8.14 If no vector will be involved, details of how the DNA will be introduced and how many copies of the gene will be inserted	
8.15 Details of secondary genetic effects that may be anticipated	
8.16 Details of the intrinsic genetic features, if any, of the GMO(s) that will regulate survival in the environment, including a statement on how stable those features are	
8.17 Details of the genetic changes, if any, that will be included in the GMO(s) to limit or eliminate any capacity to reproduce or transfer genes to other organisms	
Part 9: Risk assessment information – the parent organism(s)	
9.1 Details of the common name of the parent organism(s)	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master seed organism •origin, date of isolation •the genus and species •strain/serotype
9.2 Details of the scientific name of the parent organism(s). If a GMO(s) is the result of a crossing event between more than one species, please include relevant information	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master seed organism •the genus and species •strain/serotype
9.3 Details of the strain(s), cultivar(s) etc to be released. If a GMO(s) is the result of a crossing event between more than one strain, cultivar etc, please include all relevant information	
9.4 Details of whether the parent organism(s) has an extended history of safe use in agriculture or other industries	**Application Overview (Part 1)** **Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism – biological characteristics
9.5 Details of whether the parent organism(s) is capable of causing disease or other ill-health in people, plants or animals and, if so, the possible effects	
9.6 Details of the natural habitat of the parent organism(s), and its range	**Application Overview (Part 1)**
9.7 Details of the location where the parent organism(s) was originally isolated for the purpose of the proposed dealing(s)	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master seed organism •origin, date of isolation
9.8 Details of the distribution of the parent organism(s), and closely related organism(s), in Australia and in particular its distribution at or near the site of proposed release, including details if the parent organism(s) is exotic to Australia	**Application Overview (Part 1)** *Usually covered in the description of the disease to be treated, except in the case of a transgenic vectored vaccine. A vaccine vector (such as the canary pox vector for the equine influenza vaccine) would need to be approved by DAFF if exotic to Australia.*

9.9 Details of any known predators, parasites, pests or diseases of the parent organism(s) in Australia	*Unlikely to be relevant to a vaccine organism*
Part 10: Risk assessment information – interaction between the GMO(s) and the environment	
10.1 Details on whether the proposed release of the GMO(s) could prejudice any beneficial function of the parent organism(s) in the environment	**Efficacy and Safety (Part 8)** spread to non-vaccinates spread to non-target animals
10.2 On the basis of contained experiments, details of: (i) the survival times of the GMO(s) in habitats relevant to the release; and (ii) the growth rate (or generation time) of the parent organism(s) and GMO(s) in the ranges of environmental conditions characteristic for the place and date of release; and (iii) the frequency of reversion or loss of the genetic change	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines includes, spread to non-vaccinates, spread to non-target animals, recombination and reversion to virulence *See also:* **Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products** (EMEA/CVMP/074/95) which considers: a. Capacity of live organisms to transmit to non-target species b. Shedding of live product organisms (route, numbers, duration) c. Capacity to survive, establish and disseminate d. Pathogenicity to other organisms e. Potential for other effects of live product organisms f. Toxic effects of the product components g. Toxic effects of excreted metabolites
10.3 Details of the capability of the GMO(s) to disperse from the release area(s), and, if any, the dispersal mechanism	
10.4 Is the GMO(s) likely to be able to establish in the environment outside the release site(s)? If so please provide details	
10.5 Is the GMO(s) able to form long-term survival structures, such as seeds or spores? If so please provide details	
10.6 Details of whether the inserted genetic trait(s) will be able to be transferred to other organism(s) found at the release site and surrounding environment and, if so: (i) the organism(s) the trait(s) can be transferred to and the frequencies at which it can be transferred, including information about the species that have been tested for transfer and the rationale for selecting the test species; and (ii) the transfer mechanisms involved; and (iii) the techniques that have been used to demonstrate transfer; and (iv) any possible adverse effects of the transfer including: (a) any advantage that affected organism(s) are likely to have over members of the species that do not contain the transgene(s); and (b) environmental risks posed by such an advantage	
10.7 Details of whether interactions between pathogens and the transgene(s) are possible (for example, gene silencing) and, if so: (i) the incidence and distribution of relevant pathogens; and (ii) possible effects of interaction	
10.8 Details of whether the GMO(s) is likely to show any competitive advantages over its unmodified parent(s) in mixed populations under the conditions at the release site(s), and if so the nature of the advantages	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines includes spread to non-vaccinates and spread to non-target animals (*in the context of a vaccine organism, the rate of new infections is the trait that is subject to selection or competitive advantage*) *See also:* **Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products** (EMEA/CVMP/074/95)
10.9 Details of whether the modified trait(s) will confer a selective advantage on the GMO(s) under certain conditions, if so the conditions, including data on growth rates with and without selective pressure	
10.10 Details of features of the physical environment of the release site(s), particularly features that may minimise or exacerbate any undesirable effects of the GMO(s)	**Environment (Part 7)** *The site of use (for example; veterinary surgery, farm shed or paddock) must be discussed in determining the likely exposure of the environment to the product.* *See also:* **Environmental Risk Assessment for**
10.11 Details of the proximity of the release site(s), to population centres, centres of agricultural activity, or	

the habitat of biota that might affect, or be affected by, the proposed release	**Immunobiological Veterinary Medicinal Products** (EMEA/CVMP/074/95)
10.12 Details of whether the GMO(s) is expected to remain in the environment after release, and if so: (i) the period of time; and (ii) any environmental risks posed by the GMO(s) during that period	**Environment (Part 7)** Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products (EMEA/CVMP/074/95)
10.13 Details of any other environmental risks that may be posed by the GMO(s)	
10.14 Information about: (i) whether the GMO(s) produces metabolites that may have deleterious effects on other organisms, including human beings; (a) directly; or (b) indirectly, through concentration in the food chain, and if so, the likely effect	**Metabolism and Kinetics (Part 4)** Considered with respect to residues below **Residues and Trade (Part 5)** Withholding period is relevant for a product which contains live zoonotic organisms **Environmental Risk Assessment for Immunobiological Veterinary Medicinal Product**s (EMEA/CVMP/074/95)
Part 11: Risk assessment information – risks GMO(s) may pose to the health and safety of people	
11.1 Details of any allergens or toxins that may be expressed by the proposed GMO(s) that are not found in the parent organism(s)	**Toxicology data (Part 3)** Toxicology assessment is required where there is sufficient risk of harm to meet criteria listed in the *Scheduling Policy Framework* (SPF) developed by the National Coordinating Committee on Therapeutic Goods (NCCTG) **Occupational Health and Safety (Part 6)**
11.2 Details of any pathogenic properties in the GMO(s) that are not found in the parent organism(s)	**Efficacy and Safety (Part 8)** *See also:* **Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products** (EMEA/CVMP/074/95)
11.3 Details of any occupational health and safety risks to personnel dealing with the GMO(s) and safety risks to the wider community	**Occupational Health and Safety (Part 6)**
Part 12: Risk management information	
12.1 Details of measures proposed for restricting the dissemination or persistence of the GMO(s), or its genetic material, in the environment, including details of proposed measures for disposing of the GMO(s) when the release is complete and any waste deriving from the GMO(s)	**Environment (Part 7)** Requires data on extent of exposure of the product, its active constituents or relevant metabolites to the environment, and proposed disposal methods for unused or waste product *See also:* **Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products** (EMEA/CVMP/074/95)
12.2 Details of measures proposed for monitoring the release including monitoring for: (i) the survival or presence of the GMO(s), or transferred genetic material, beyond the proposed release site(s), including specificity, sensitivity and reliability of detection methods; and (ii) impacts on the characteristics, or abundance, of other species; and (iii) transfer of the introduced gene(s) to other species; and (iv) any other hazards or deleterious effects the survival or presence of the GMO(s) after the release is completed	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines includes, spread to non-vaccinates, spread to non-target animals, recombination and reversion to virulence *See also:* **Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products** (EMEA/CVMP/074/95)
12.3 Details of the methods that will be used to minimise the effects of any transfer of the modified genetic trait(s) to other organisms	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines include Recombination
12.4 Details of the specific experimental methods proposed for detecting the presence of the GMO(s), or transferred genetic material, in the recipient organism(s)	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines include dissemination in the host, and methods would be part of this data. Methods used would comply with the US **Code of Federal Regulations Title 9: Animals and Animal Products**

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12.5 Details of proposed release site supervision procedures and, if necessary, any relevant safety procedures designed to protect staff, including a description of procedures for on-site supervision of the release if the release site(s) is located at some distance from the location of the applicant	The Schedule 4 signal heading (***PRESCRIPTION ANIMAL REMEDY*** (is required for all live-virus veterinary vaccines (except poultry vaccines, pigeon pox vaccine and scabby mouth vaccine). Products so labelled must be used under the supervision of a veterinary practitioner.
12.6 Details of measures proposed for: (i) informing persons covered by the licence of any licence conditions; and (ii) informing the public about the proposed dealing(s)	*These are regulatory considerations related to administrative compliance with rather than to scientific assessment of risk.*
12.7 Details of proposed procedures for auditing, monitoring and reporting on compliance with any conditions imposed by the Regulator	
12.8 Details of any contingency measures that will be in place to rectify any unintended consequence if an adverse effect becomes evident during the course of the release(s)	*APVMA's legislation requires registrants to provide any new information that they become aware of including adverse experience information relating to human health, harm to animals, damage to plants, property or the environment, and lack of efficacy when the product is used according to the label directions*
Part 13: Information about current and previous assessments or approvals	
13.1 Details of any related current application under consideration by a Commonwealth, State or overseas government authority or regulator	**Application overview (Part 1)** Requires data on registration status overseas, as well as any previous evaluation by a regulatory body, the outcome and any evaluation reports.
13.2 Details of results of any applications made for approval or use of the GMO(s), or any derived GM products, by any other regulator in Australia or overseas, including information about whether the application was successful or unsuccessful and details of conditions (if any) attached to the approval	**Special data: genetically modified organisms (Part 10)** *Where a DNIR licence or assessment as an NLRD by an Institutional Biosafety Committee has been required for laboratory work leading to the creation of the vaccine master seed, and for laboratory experiments to generate safety and efficacy data, this should be stated. Licence conditions or IBC assessment should be made available to the APVMA.* *Having been proven safe in the laboratory, application to the OGTR for further risk assessment should not be necessary.*
13.3 Details of any previous applications (whether successful or unsuccessful) under the Act, or to the Genetic Manipulation Advisory Committee, for a dealing with the GMO(s), or of a notification of a dealing under the Act, from which the work in the present application has developed	
13.4 If the GMO(s) has been previously released in Australia or overseas, details of any adverse consequences of the release, including identifying references and reports of assessments	
13.5 A list of Commonwealth and State government authorities that have been consulted about the proposed dealings with the GMO(s)	
13.6 For an imported GMO(s) – the date of importation or intended importation, including, if possible, a copy of documentation of clearance or assessment from the Australian Quarantine and Inspection Service (AQIS)	
Part 17: Additional information – live GM vaccine for use in animals	
17.1 Identification of the disease to be treated, or prevented, by use of the vaccine	**Application Overview (Part 1)**
17.2 Identification of the host species on which the vaccine is to be used	
17.3 Details of the host range of the parent organism from which the vaccine is constructed	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism – biological characteristics
17.4 Details of the level, and duration, of immunity produced in the host species after administration of the vaccine	**Efficacy and Safety (Part 8)** *These issues should not be assessed by the OGTR as they do not constitute risks to people and the environment*
17.5 Details of the potential for the generic material of the vaccine GMO to become incorporated in whole, or	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials

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in part, into the genome of any cells of the vaccinated host	Master Seed Organism – biological characteristics *Integration is a property of the parent organism*
17.6 Details of the period over which the vaccine GMO will be detectable in a test animal, or its excretions or secretions	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines include dissemination in the host and presence in excretions or secretions
17.7 If the GMO is a viral vaccine, information about the potential for the nucleic acid of the virus in the vaccine to be rescued, or to be restored to wild type, by recombination or complementation with intracellular viruses	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines include Recombination and Reversion to Virulence.
17.8 Details of any deleterious effects the vaccine GMO may have on a pregnant animal	**Efficacy and Safety (Part 8)** Safety studies include reproductive effects
17.9 Details on whether the vaccine GMO has a teratogenic effect on a foetus at any stage of gestation	
17.10 Details on whether the use of the vaccine GMO is likely to: (i) preclude its use for vaccination against other diseases subsequently; or (ii) affect its usefulness for other vaccinations	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism – biological characteristics **Efficacy and Safety (Part 8)** Requires data on immunological effects and interactions with other known products
17.11 Details on whether the vaccine GMO is resistant to desiccation	**Chemistry and Manufacture (Part 2)** Production, control and testing of starting materials Master Seed Organism – biological characteristics
17.12 A list of sterilising and anti-microbial agents (if any) that are active against the GMO	
17.13 Details on whether the vaccine GMO is susceptible to ultraviolet or ionising radiation	
17.14 Details of: (i) the potential for the vaccine GMO to spread from vaccinated to unvaccinated animals (of the same or other species including human beings); and (ii) if the potential exists, the likely mechanism and frequency of such spread	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines includes spread to non-vaccinates and spread to non-target animals
17.15 Details of whether the susceptibility of the host to the vaccine GMO could be affected by: (i) the state of the host at the time of vaccination (for example, immunosuppression, or superimposition of other disease); or (ii) other treatments, such as drugs	**Efficacy and Safety (Part 8)** *These issues should not be assessed by the OGTR as they do not constitute risks to people and the environment*
17.16 Details of proposed methods for disposing of waste containing the vaccine GMO	**Environment (Part 7)** Applicant's proposed directions for storage and disposal
17.17 Details of the intended fate of vaccinated animals at the end of the trial	**Residues (Part 5a)** A transgenic or zoonotic live veterinary vaccine administered to food producing animals would require assessment of the presence of the vaccine organism in food products. *This is only relevant if the vaccine organism is present*.
17.18 Information about whether the live vaccine GMO will be carried by an animal at the end of the trial and, if so: (i) the potential for dissemination of the live vaccine the GMO through the animal's family contact, or to the general population of the species; and (ii) measures intended to be taken to minimise the potential for dissemination; and (iii) the potential for the GMO to cross the placenta of a pregnant animal	**Efficacy and Safety (Part 8)** Special data requirements for live virus vaccines includes spread to non-vaccinates and spread to non-target animals