AUSTRALIAN QUARANTINE POLICY AND REQUIREMENTS FOR THE IMPORTATION OF LIVE AND NOVEL VETERINARY BULK AND FINISHED VACCINES

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Glossary

Effective sterilisation refers to treatment by a properly validated process to inactivate all conventional extraneous agents including viruses and providing a sufficient safety factor

- as prions have been shown to remain infectious in the face of treatments that would inactivate conventional micro-organisms, AQIS requires that raw materials used for the production of live vaccines are not sourced from countries in which relevant transmissible spongiform encephalopathies occur

- AQIS accepts the following procedures for the purpose of effective sterilisation: autoclaving at 121^{o}C for 15 minutes; dry heat at 160°C for 2 hrs; 5 MRad irradiation or other treatment validated to AQIS satisfaction to provide at least a 6 log reduction in titre of each potential contaminant

    .. European Pharmacopoeia (Eu. Pharm) (1997) 5.1.1 should be used as a guide however applicants should note that AQIS does not accept treatment at 2.5 MRad, as recommended by the Eu. Pharm, as this treatment does not achieve a 6 log reduction in titre of many viruses of quarantine concern

- treatment must provide a safety factor of at least $10^{6.}$

    .. this means that treatment must provide at least a 6 log reduction in titre of each potential contaminant

    .. a larger reduction in titre will be required where there is reasonable likelihood of contamination (eg if an average titre of 10^2 organisms would be expected to be present in a product, to be considered “effective” the treatment should achieve ≥8 log (ie 6+2) reduction in titre)

- all sterilisation procedures should be validated, verified for the product, container type, configuration and volume and be supported by GMP standards and procedures

    .. for example, in the case of autoclaving of culture media and other substrates, the autoclaving conditions should be validated for each media, for each container type and for each autoclave load configuration.

Master seed is a collection of aliquots of a preparation, for use in the production or testing of a product, distributed into containers in a single operation and processed together in such a manner as to ensure uniformity, and processed and stored in such a manner as to ensure stability.

Working seed is a collection of aliquots of a preparation consisting of a passage level between Master Seed and the last passage that forms the finished product, for use in the preparation of finished product, distributed into containers in a single operation and processed together in such a manner as to ensure uniformity, and processed and stored in such a manner as to ensure stability.

Primary cell cultures are cultures of cells essentially unchanged from those in the animal tissues from which they have been prepared and being no more than 5 *in vitro* passages to production level from the initial preparation from the animal tissue.

High risk ingredients refer to products of animal origin which may not be effectively sterilised prior to use in the manufacture of vaccines. Examples of such products include serum, serum albumin and enzymes (eg trypsin).

Nutritive factors refer to serum, foetal serum, serum albumins and other serum products which are used for cell line maintenance and growth. They may also be used for the growth of leptospira and certain other organisms. Nutritive factors are considered high risk products because they undergo only minimal processing/treatment prior to use.

Manufacturing facility is a production entity which can be considered separate and independent from the surrounding environment by independent buildings, ventilation and staff and other physical and sanitary measures.

Novel vaccines refer to synthetic peptide and biosynthetic subunit vaccines, DNA vaccines, genetically modified live vaccines, live vector vaccines and live vaccines against parasites and poisons or used for immuno-sterilisation or growth and metabolic modification.

SPF flocks/eggs used in the production of the vaccine must meet the requirements of the Eu. Pharm (1997). and must be free from other avian pathogens listed in Annex 3. Importers should also be aware that they may be required to meet additional requirements specified by the NRA.

Australian Quarantine Import Policy and Requirements for Live and Novel Veterinary Vaccines in Bulk or Finished Form

1. INTRODUCTION

Mission

The mission of the Australian Quarantine and Inspection Service is to protect Australia's animal and plant health environment, including our native fauna and flora, while facilitating improved market access for products, including veterinary vaccines and immuno-biologicals. AQIS's objective is to prevent the introduction and establishment of exotic pathogens and exotic strains of endemic pathogens.

Scope of policy

This statement of policy presents the quarantine conditions relating to production and testing under which AQIS will permit the importation of live and novel veterinary vaccines into Australia. It also applies to the importation of vaccine seed material and live and novel veterinary vaccine antigen in bulk form for use in vaccine production in Australia. This document complements and should be read in conjunction with AQIS's "Guidelines for the Production and Control of Inactivated Veterinary Vaccines in Australia and Guidelines for Submissions to Import Veterinary Vaccines" (November 1994) and "Specific Requirements for the Importation of Inactivated Veterinary Vaccines" (December 1997).

Policy on Imports

Australia maintains a conservative approach to the management of quarantine risk. This is particularly important in the case of veterinary vaccines, which could bring about the widespread dissemination of unwanted diseases, because they are not subjected to microbiologically lethal treatment during production. AQIS considers that imported live vaccines present inherently high quarantine risks due to the direct exposure of live animals to these products. A decision to permit imports depends upon a detailed and rigorous technical assessment of the raw materials, their processing and the testing of final product. The production of imported vaccines must be strictly controlled and products must be tested for pathogens of quarantine concern using sensitive methods.

AQIS has previously permitted the importation of vaccine seed organisms for the production of vaccine in Australia. However, 'one-off' importation of a seed organism is considered of lesser quarantine significance than the importation of live vaccine in bulk or finished form. Such imports have not previously been permitted.

Under this policy, AQIS intends to permit the importation of live vaccine on the basis of batch by batch quarantine assessment. If AQIS's assessment confirms that an exporting company has implemented appropriate controls to ensure that the source of raw ingredients and processing of batches would remain unchanged, AQIS may permit the importation of several batches of vaccine under a single permit. Moreover, AQIS may permit the importation of multiple batches of novel vaccines on a single permit where the quarantine assessment confirms that the importation presents an acceptable quarantine risk.

Consultation

AQIS will consult widely with State governments and relevant industry and professional organisations on proposals to import live vaccines which AQIS considers may have a significant impact on the agricultural industry and/or the environment or have a high risk of reversion to virulence or genetic reassortment. In relation to such assessments AQIS will work closely with the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) which is responsible for ensuring the efficacy and safety of biological products.

AQIS may grant dispensations to the public consultation process and certain technical requirements if it is necessary to expedite an application in the case of an exotic disease emergency.

2. POLICY ON THE IMPORTATION OF LIVE AND NOVEL VETERINARY VACCINES

2.1 General

2.1.1 AQIS will assess applications for permission to import live vaccines on a case by case basis.

2.1.2 Unless otherwise specified by this policy, AQIS will not permit the importation of live conventional viral and bacterial vaccines unless the vaccine has a well-established safety record

- there have been many examples, including recent examples, of live vaccines being contaminated, despite modern manufacturing methods and quality controls
- they are considered high quarantine risk products
- while the use of a contaminated veterinary vaccine could have grave biological and economic consequences for Australia, the use in livestock species has the most serious potential consequences
- a well-established safety record is defined as use in a significantly large number of animals in a country or countries with appropriate veterinary services, diagnostic capabilities and adverse reaction reporting mechanisms
- in determining what constitutes a significant number of animals, AQIS will take into consideration, on a case by case basis, factors such as vaccine type, target species or genotype, contamination history of similar vaccines, reporting mechanisms in countries of use and diversity of use[1].

2.1.3 AQIS will conduct a process of public consultation for live vaccines, including live vector vaccines which AQIS considers will have a significant impact on the agricultural industry and/or the environment or have a high risk of reversion to virulence or genetic reassortment

- as much of the information provided by manufacturers is considered commercial-in-confidence, only information relevant to the quarantine assessment will be released to the public
- AQIS may summarise information, removing commercially sensitive matters, in consultation with the manufacturer/importer
- AQIS will conduct a process of public consultation for the initial application and in the case where there are significant changes to the production process which could change the quarantine risk presented by the vaccine

[1] Diversity of use refers to how widespread a vaccine is used. For example, use of a poultry vaccine in an isolated population such as a single flock or in a small geographical area would not be considered significant, regardless of numbers.

- a joint AQIS/NRA public consultative process may be undertaken subject to agreement between AQIS, NRA and the manufacturer/importer

- AQIS may convene an expert working group to review public comment and provide expert advice to AQIS on quarantine issues associated with an application.

2.1.4 If determined as necessary by AQIS on assessment of the application, the final batch of the live virus vaccine will be tested by inoculation into live animals at the Australian Animal Health Laboratory (AAHL) to confirm the absence of specified pathogens based on AQIS's assessment of factors such as the country of origin and species of origin of each master seed virus (MSV), master cell seed (MCS) and substrate

- AQIS may also require that vaccines other than live virus vaccines be tested at AAHL or another AQIS-approved laboratory[2] if this is considered necessary

- AQIS may permit the testing of vaccines by *in vitro* procedures as an alternative to *in vivo* procedures subject to advice from AAHL confirming the effectiveness of such procedures

- if the first 3 batches tested according to AQIS's conditions at AAHL meet quarantine requirements, the Director of Quarantine may agree to reduce testing requirements and/or may permit tests to be conducted at another AQIS-approved laboratory, either in Australia or overseas.

2.1.5 AQIS will not permit the importation of live vaccines which incorporate cell lines, serum, meat extracts and other materials derived from bovine animals that were born or lived in BSE-affected countries or derived from sheep or goats that were born or lived in scrapie-affected countries, except that:

- cell lines created at least 6 years prior to the first reported case of BSE or scrapie in the country of origin are acceptable provided all other quarantine requirements are met

- AQIS will not permit the importation of live vaccines that incorporate material derived from the CNS (eg brain/heart infusion) of any species that is susceptible to transmissible spongiform encephalopathy regardless of the country of origin of such CNS-derived materials

- these conditions are generally consistent with international medical restrictions on the use of human and bovine products and reflect Australia's concern that the risk attributable to prion contamination of vaccines is still largely unknown. They will however be subject to review as more information concerning prion diseases becomes available.

[2] An AQIS-approved laboratory would normally be a national or an OIE reference laboratory for the pathogens under consideration or a laboratory of equivalent standard.

2.1.6 AQIS will not permit the importation of live vaccines that were produced using primary cell cultures unless the cultures were derived from specific pathogen free (SPF) animals[3].

2.1.7 Embryonated eggs, avian cell lines and other components of avian origin which are not effectively sterilised, used for the production of live vaccines must be derived from specific pathogen free (SPF) flocks.

2.1.8 AQIS may approve the importation of viral vaccines, including live viral vector vaccines, provided that any substrate of animal origin that has only undergone minimal processing[4] (eg cell lines, serum, serum albumin, trypsin) has been derived from countries (or OIE defined regions) that are free from specified List A diseases (refer Annex 1) for the relevant species of origin.

2.1.9 AQIS may approve the importation of live bacterial vaccines, including live bacterial vector vaccines, provided that ingredients of animal origin used in production were derived from countries (or OIE defined regions) that are free from specified List A diseases (refer Annex 1) for the relevant species of origin or were sterilised effectively prior to use.

2.1.10 For the purpose of approving importation, AQIS will require, as a minimum, that the vaccine, master seeds, cell line or culture media, substrates and all material of animal origin used in production of the vaccine are free from all pathogens of quarantine concern as specified in Annex 3 based on country of origin, processing, treatment and/or testing as specified in Appendix 1.

2.1.11 In order to assess an application for permission to import, AQIS will require documentation that would support an effective audit of production methods/controls, from the source of animals to the final product for each batch/lot of serum, trypsin and other substrates/materials of animal origin which are not subjected to an effective process of sterilisation

- such documentation may include export health certificates, transport manifests and vaccine production sheets

- AQIS requires original documents or good quality, legible, authenticated copies.

2.1.12 AQIS will not permit the importation of a live vaccine if the country and species of origin of any serum, serum albumin or animal-derived enzyme cannot be substantiated as described above

- this requirement applies to any animal-derived material used in the production of the vaccine that is not subjected to a process of effective sterilisation.

2.1.13 AQIS will not permit the importation of mammalian vaccine if the facility in which it is produced holds or uses live mammalian pathogens listed in Annex 1.

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[3] A SPF herd or flock must meet Eu. Pharm requirements or other requirements specified by AQIS.

[4] Cell lines, serum, serum albumin and animal-derived enzymes are not usually subjected to processing that would be sufficient to fully address quarantine concerns.

2.1.14 AQIS will not permit the importation of avian vaccine if the facility in which it is produced holds or uses any of the following live viruses:

- Avian influenza virus (virulent strains)
- Newcastle disease virus (virulent strains)
- highly virulent strains of Infectious Bursal Disease virus.

2.1.15 If the facility holds other pathogens or manufactures vaccines against other pathogens, the vaccine must be tested and shown to be free of these pathogens or the manufacturer must, by other means, satisfy AQIS that cross-contamination has not occurred.

2.1.16 An AQIS-approved auditor with appropriate expertise in quarantine assessment of biological products will audit on a full cost recovery basis the manufacturing facility, process and documentation prior to the initial approval of a live vaccine

- where possible, audits will be conducted in cooperation with NRA

- for live viral vaccines, physical audits will be conducted every 2 years or more frequently if considered appropriate by the Director of Quarantine.

2.1.17 AQIS may call on expert advice to assist with the assessment of quarantine risks associated with the vaccine (eg reversion to virulence and genetic recombination/reassortment)

- as part of this process of assessment AQIS may require the manufacturer and/or importer to demonstrate the safety of the product by presenting the results of appropriate innocuity and transmission field trials

  .. such trials would normally be conducted overseas.

2.1.18 AQIS will issue import permits for live viral vaccines on a batch by batch basis only.

2.1.19 Import permits for vaccines other than live viral vaccines may cover multiple batches.

2.1.20 AQIS will fully assess all applications for the renewal of import permits for live vaccines

- all relevant information including the application for renewal should be resubmitted and all information must be current

- the importer should provide a declaration to the effect that the production process, country of origin of raw materials, testing and other procedures as provided in the previous application have not changed

  .. any changes should be summarised, to assist the process of reassessment and approval.

- permits for the importation of vaccines to be tested or used in trials in Australia will require approval from the NRA.

2.2 Live Conventional Viral Vaccines

2.2.1 The importation of the following live viral vaccines will be considered:

a) vaccines for use in response to an exotic disease incursion (refer 2.6);

b) vaccines for use in exotic disease contingency planning;

d) c) vaccines for use in dogs, cats and other non-livestock species where there is no significant risk of infecting non-target species;vaccines manufactured using master seed viruses, substrates and cell lines which originated from and/or have been used in Australia for the production of vaccines;

e) other vaccines which have a demonstrated and well documented safety record involving use in a significant number of animals *(refer 2.1.2)*.

2.2.2 Applications to import live viral vaccines in category 2.2.1(e) will be subject to public consultation as described in 2.1.3.

2.3 Live Conventional Bacterial Vaccines

2.3.1 Bacterial vaccines are usually produced using sterile culture media and fermentation broths. The risk of contamination with exotic agents is much lower than with viral vaccines, however, AQIS will require evidence as to the purity of the final vaccine. Applications will be considered for the following:

a) vaccines for use in response in an exotic disease incursion (refer 2.6);

b) vaccines for use in exotic disease contingency planning;

c) vaccines for use in dogs, cats and other non-livestock species where there is no significant risk of infecting non-target species;

d) vaccines for the importation of vaccines manufactured using master seed bacteria which originated from and/or have been used in Australia for the production of vaccines;

e) vaccines where all media have been sterilised by autoclaving at 121^{o}C for 15 minutes, 5 MRad irradiation or other effective sterilisation treatments;

f) other vaccines which have a demonstrated and well documented safety record involving use in a significant number of animals *(refer 2.1.2)*.

2.3.2 Applications for bacterial vaccines in categories 2.3.1(f) will be the subject of public consultation as described in 2.1.3.

2.4 Novel Vaccines

2.4.1 ***Synthetic peptide and biosynthetic subunit vaccines*** and other novel vaccines which do not contain live organisms present a significantly lower quarantine risk than live vaccines. However

- the purification process to inactivate or eliminate potential contaminants in the growth system must be validated
- carrier molecules, if used, will also be the subject of quarantine assessment
- assessment will be conducted according to the AQIS "Specific Requirements for the Importation of Inactivated Veterinary Vaccines".

2.4.2 ***DNA Vaccines*** which do not contain live organisms present a lower quarantine risk than live vaccines

- assessment will be based on the AQIS "Specific Requirements for the Importation of Inactivated Veterinary Vaccines" with variations as necessary to address the novel nature of the vaccine
- AQIS may seek advice from the Genetic Manipulation Advisory Committee (GMAC) and other agencies as appropriate
- AQIS will require information that demonstrates the absence of genomic integration with the host germinal cells and freedom from viable particles and other infective contaminants.

2.4.3 ***Genetically Modified Live Vaccines*** (ie vaccine agents containing gene deletions, modifications or insertions, marker genes, etc):

- AQIS will require evidence that the modification would reliably prevent undesirable events such as reversion to virulence
- AQIS will consider applications for permission to import as described under sections that deal with live conventional viral and bacterial vaccines
- AQIS may seek advice from GMAC and other agencies as appropriate.

2.4.4 ***Live Vector Vaccines*** generally present a lower quarantine risk in regard to reversion to virulence, introduction of exotic strains of endemic pathogens and reassortment and recombination. However quarantine risks potentially associated with contamination are the same as for conventional live vaccines. Consequently

- assessment will be based on live vaccine policy and guidelines requirements with appropriate variation to address the novel nature of the vaccine
- AQIS will require evidence showing that the expression vector is non-pathogenic to humans, target and in-contact species and is not exotic to Australia
- the importation of immune stimulators/modulators will also undergo quarantine assessment

- AQIS may seek advice from GMAC and other agencies as appropriate.

- the application will be subject to public consultation if there are significant quarantine and environmental concerns with the vector used.

2.4.5 ***Live Vaccines Against Parasites and Poisons, or Used for Immuno-sterilisation or Growth and Metabolism Modification*** will be assessed in accordance with one of the above (ie 2.2, 2.3, 2.4.1, 2.4.2, 2.4.3 or 2.4.4) depending on the nature of the vaccine.

2.5 Vaccines Manufactured in Australia from Imported Materials

2.5.1 All Australian vaccine manufacturing facilities that use imported material of animal origin must be Quarantine Approved Premises under the *Quarantine Act 1908*

- as part of the approval process, AQIS approval must be obtained for the use, *in vivo,* of imported material of animal origin

2.6 Vaccines for Use in an Outbreak of an Exotic Animal Disease

2.6.1 AQIS may grant dispensations with respect to public consultation and other requirements if necessary to expedite the importation of vaccines for use in an outbreak of an exotic disease

- this includes diseases such as Newcastle disease and clinical bluetongue, the respective viruses of which are present in Australia but do not normally cause outbreaks of disease

- AQIS may permit the importation of mammalian vaccine if the facility in which it is produced holds or uses live mammalian pathogens listed in Annex 1

- AQIS may permit the importation of avian vaccine if the facility in which it is produced holds or uses any of the following live viruses:

  .. Avian influenza virus (virulent strains)
  .. Newcastle disease virus (virulent strains)
  .. highly virulent strains of Infectious Bursal Disease virus.

2.6.2 AQIS will however establish that the vaccine meets a minimum standard of quarantine safety

- minimum standards are described in the Bureau of Resource Sciences document "Quarantine risk analysis - Emergency Exotic Disease Live Vaccines" Dec 1997.

3. GENERAL REQUIREMENTS

3.1 Requirements for an Import Permit

3.1.1 Live vaccines must comply with these general requirements except as otherwise stated in the specific requirements sections.

3.1.2 Prospective importers must obtain an import permit from AQIS before importing any vaccine or related biological product. The NRA is responsible for ensuring the efficacy, potency, toxicity as well as storage and labelling requirements for vaccines and other biological products. The quarantine assessment and the assessment of safety and efficacy by NRA may be conducted concurrently.

3.2 Standards for Manufacturing Plants

3.2.1 Standards of Good Manufacturing Practice (GMP)

3.2.1.1 AQIS requires documentation showing that the production facility complies with relevant GMP requirements in the country of manufacture. The production facility and the product intended for export to Australia must be approved by AQIS and compliance with the relevant requirements regularly audited by the relevant regulatory authority.

3.2.1.2 AQIS requires that the manufacturer applies the principles of quality assurance to the production of vaccines and biological products for export to Australia. This helps to confirm the safety, in quarantine terms, of the product at every step of production from the sourcing, processing, treatment and testing of all materials of animal origin, including the testing of the final product.

3.2.1.3. AQIS requires that production plant(s) do not store or handle viruses listed in Annex 1.

3.2.2 Standards for Production, Control and Testing

3.2.2.1 AQIS requires that the production, control and testing of the vaccine and all components used in production meet the requirements set out in the following documents:

. *Guidelines for the Production and Control of Inactivated Veterinary Vaccines in Australia* AQIS (1994)[5] and

. Eu. Pharm (1997) with particular reference to 1997:0062 (*Vaccines for Veterinary Use*) and Section 5.2 (*General texts on vaccines*) and

. Specific Requirements for the production and control of the following products as detailed in *The Rules governing Medicinal Products in the European Union Vol VII* - (Committee for Veterinary Medical Products 1994)

[5] This document is consistent with and based on the *General Requirements for the Production and Control of Inactivated Mammalian Bacterial and Viral Vaccines for Veterinary Use* in "The Rules governing Medicinal Products in the European Union" Vol VII (1994)

- Avian Live and Inactivated Viral and Bacterial Vaccines
- Bovine Live and Inactivated Viral and Bacterial Vaccines
- Pig Live and Inactivated Viral and Bacterial Vaccines
- Ovine and Caprine Live and Inactivated Viral and Bacterial Vaccines
- Equine Live and Inactivated Viral and Bacterial Vaccines
- Avian Live and Inactivated Viral and Bacterial Vaccines
- Live and Inactivated Viral and Bacterial Vaccines for Dogs and Cats
- Live and Inactivated Viral and Bacterial Vaccines for Fish.

3.2.2.2 Where the Eu. Pharm or other relevant guidelines specified above do not specify testing requirements, AQIS requires the adoption of appropriate testing procedures such as may be specified by AQIS or in the USDA Code of Federal Regulations (9CFR 113) in addition to relevant Eu. Pharm requirements.

3.3 Freedom from Extraneous Agents - General Requirements

3.3.1 Master and working seeds, cell lines, substrates, and other materials of animal origin must be free from extraneous agents. AQIS will base its assessment on the country of origin and the processing, treatment and testing of the vaccine.

3.3.2 Annex 1 lists pathogens exotic to Australia which pose such a major economic and social threat that sourcing of potentially contaminated products from affected countries (or OIE defined regions) will not be considered unless the product is effectively sterilised.

3.3.3 Importers must provide evidence showing that products have been effectively sterilised. Appropriate evidence includes a clear demonstration of the lethality of processing, usually expressed in terms of titre reduction or kinetic studies of the process for the most resistant class of micro-organism(s) (other than prions) which may potentially contaminate the product.

3.3.4 Annex 2 lists the prion diseases, scrapie and bovine spongiform encephalopathy (BSE). These agents are difficult to detect and normally extremely resistant to inactivation. AQIS will not permit the importation of vaccines produced from products derived from the relevant species in countries (or OIE defined regions) affected by BSE/scrapie. The importation of vaccines containing neurological material of any species known to be susceptible to transmissible spongiform encephalopathies will not be approved regardless of the country of origin.

3.3.5 Annex 3 lists other animal diseases which are either exotic pathogens other than those listed in Annex 1 or exotic strains of an endemic pathogen or are potential contaminants of economic or social concern to Australia. During assessment, AQIS may also identify other potential contaminants of concern.

3.3.6 All raw materials of animal origin used in the production of vaccines to be exported to Australia must be shown to be free of extraneous agents. They must be tested for bacteria, fungi and mycoplasma using sensitive and accurate techniques. Unless effectively sterilised, they must also be tested for the viruses listed in Annexes 1 and 3 as appropriate to the species of origin (see Appendix 1). AQIS requires the results of

such testing or confirmation of effective sterilisation for every batch of raw material utilised in the manufacture of the vaccine to be imported.

3.3.7 AQIS or the NRA may also require evidence that the vaccine to be imported is free from pathogens additional to those listed in Annexes 1-3.

3.4 Country of Origin of Raw Materials

3.4.1 All materials of animal origin used to produce vaccines to be imported into Australia must be sourced from countries with high standards of animal health and veterinary services.

3.4.2 The source of all materials of animal origin used during production must be certified. This certification must preferably be issued by the government of the source country. Manufacturer's certification may be accepted as an alternative to government certification for low risk products (ie those that will be effectively sterilised prior to use). Manufacturer's certification may also be accepted for other substrates except nutritive factors (eg serum) and animal enzymes (eg trypsin) provided the manufacturer is operating under a quality assurance system accepted by AQIS as adequate to ensure compliance with Australian quarantine requirements on sourcing. The certificate must specifically apply to each batch of vaccine to be imported. There must be an audit trail from the country of origin of the source animals to the batch of finished vaccine destined for Australia.

4 INFORMATION TO BE PROVIDED WITH THE APPLICATION

4.1 General

4.1.1 Information should be presented in a format consistent with these requirements or as a summary document cross-referenced to registration dossiers and/or drug master files which should also be submitted.

4.1.2 For live vaccines, the information provided with the application should relate to the batch of vaccine to be imported. A fully documented audit trail must be in place for each high risk ingredient of the vaccine batch being assessed, details of batch numbers, Certificates of Analysis (CoA), health certification, import permits, etc for all batches to be imported.

4.1.3 Where the vaccine has a short-term shelf life and subject to prior AQIS approval, AQIS may perform an initial assessment on historical data from a representative batch. However, permission to import will be subject to satisfactory review of relevant information for the batch to be imported.

4.2 Registration and Approvals

4.2.1 The importer should submit copies of all relevant approvals of the production facility, registrations and approvals of the product by the country of manufacture and other importing countries. Copies of any relevant current import and/or export permits should also be provided.

4.2.2 Details of doses used commercially in other countries for each target species should be provided in support of the application.

4.3 Flow-chart of Production Process

4.3.1 Each major step of the production process should be shown in a flow-chart diagram. Each step on the flow-chart should be cross-referenced to the application, which should contain details of the materials used and results of tests conducted.

4.4 Testing Standards

4.4.1 AQIS will normally accept the procedures to test for pathogens that are specified in the Code of Federal Regulations (9CFR 113). Standards other than those set out in the 9CFR may also be acceptable (eg Australian Standard Diagnostic Techniques). Details of all testing protocols should be submitted with the application.

4.4.2 AQIS may require additional treatment or testing of products to address quarantine concerns.

4.4.3 AQIS will not permit the importation of any master seed or bulk vaccine found to be contaminated with any organism. Other products, such as substrates and cell lines, found to be contaminated with any organism will not be approved for use in the production process.

4.5 Standard Operating Procedure (SOP)

4.5.1 The manufacturer's GMP must include standard operating procedures (SOPs) and/or specifications of the approved source, sterilisation procedure (if applicable) and pathogen testing applied to each product. Adherence to SOPs should be verified in the course of regular GMP inspections.

4.5.2 The importer (or manufacturer) must provide copies of test results and SOPs relevant to the AQIS's requirements; test results must be demonstrate compliance with the relevant SOP.

4.6 Materials of Biological Origin

4.6.1 The manufacturer must provide detailed information on all components of biological origin used directly or indirectly in production of the vaccine. Such components include viral/bacterial seeds, cell lines, trypsin, nutritive factors (eg serum), fermentation broths/culture media and excipients. Every ingredient of animal origin contained in or used in the production of the component must also be listed and the country and species of origin, approximate date of collection, processing/treatment and testing specified.

4.7 Certification and Audit Trails

4.7.1 AQIS requires information on the basis of which audits of the country, species and date of origin of <u>each product</u> of animal origin used in production of the vaccine may be conducted.

4.7.2 Such audits will involve correlating batches of finished product with all raw ingredients. The manufacturer must provide copies of relevant certification for all products imported into the country of vaccine manufacture (refer 3.4.3) and documentation relevant to all steps where batch numbers change or products are combined.

4.8 Other Pathogens Held and Vaccines Produced at the Facility

4.8.1 All pathogens held and vaccines produced within the vaccine manufacturing facility must be listed. Details must be provided of other activities on the same site (eg vaccine research involving challenge trials, veterinary pathology and diagnostic services, etc) and on neighbouring sites (eg intensive livestock production, abattoirs, animal research facilities, etc).

4.9 Sterilisation of Components of Animal Origin

4.9.1 Because of the risk of contamination, the use of components of animal origin which cannot be effectively sterilised should be minimised. If used, these components will be subject to more comprehensive controls on sourcing and testing.

4.9.2 Sterilisation procedures must be validated and a copy of the appropriate SOP submitted with the application.

4.9.3 Because processing, treatment and testing procedures can sometimes fail or not be satisfactorily completed, ingredients of animal origin should not be sourced from countries (or OIE defined regions) with major exotic diseases relevant to the species of origin. This is especially the case with the following:

- bovine material from FMD, rinderpest and BSE affected countries
- ovine/caprine material from FMD, rinderpest, peste des petits ruminants, ovine/caprine pox and scrapie affected countries
- porcine material from FMD, SVD, CSF and ASF affected countries
- equine material from African horse sickness affected countries.

4.10 Adverse Reaction Reporting

4.10.1 A summary of records of reported adverse reactions and subsequent investigations should be submitted. This should be supported by the total number of doses sold. These records may be used as a possible indicator of contamination with or freedom from extraneous agents. They may also provide support in the form of a safety history especially for vaccines where the MSV and MCS have an incomplete history.

5. SPECIFIC TESTING REQUIREMENTS

5.1 Master Seed Virus (MSV)

5.1.1 A well documented history of the master seed must be available. The origin, date of isolation, passage history, reversion to virulence, purity and identity confirmation studies must be provided. Details of cell lines and nutritive media used for the transport, storage and propagation of the master seed virus should also be provided.

5.1.2 For MSV created many years ago, detailed information on the initial nutritive factors used may not be available. In this situation, it may be possible in some circumstances to establish the safety of the MSV by additional testing and a history of safe use over many years in live vaccines. Extensive pathogen testing over many years may also provide an additional level of quarantine confidence.

5.1.3 All MSVs must be tested for

a) bacterial and fungal contamination as per 9CFR 113.27(c) or Eu. Pharm (1997) 2.6.1; and

b) mycoplasmas as per 9CFR 113.28 or Eu. Pharm (1997) 2.6.7; and

c) extraneous viruses as per 9CFR 113.55 and 113.300; or as per Eu. Pharm - Vaccines for Veterinary Use (1997:0062)[6]; and

d) pathogens listed in Annex 1 and 3 which are pathogenic to or carried by the species[7]
   -- from which the virus was originally isolated
   -- from which all cell lines used for propagation and maintenance since original isolation of the virus were derived
   -- from which all nutritive factors of animal origin previously used with these cell lines were derived
   -- for which the vaccine is intended; and

e) any other pathogen determined by AQIS during assessment of the application to be a potential contaminant.

5.1.4 The following methods should be used when testing the MSV for pathogens listed in 5.1.3(d) and (e): (see Appendix 2)

General method 1- for specifically neutralised master seed

AND either

[6] To avoid duplication, testing for a particular pathogen using a Eu. Pharm procedure is not required if already tested for that pathogen in accordance with a 9CFR procedure and vice versa.

[7] Note: AQIS may take into consideration countries of origin and potential for contamination before and after any processing or treatments.

Specific method 1 or Specific method (embryonated eggs) 2.

5.1.5 The strain/serotype/genotype of master seed virus used must be either endemic in Australia or a recognised attenuated or naturally apathogenic strain considered safe for release in Australia.

5.2 Working and Production Seed Viruses

5.2.1 All working and production viruses must be tested for potential pathogens as per relevant 9CFR or Eu. Pharm requirement or as determined by AQIS on assessment of the application.

5.2.2 Where required by AQIS or under a specific monograph for that vaccine, virus testing using the general method and/or specific methods as described in 5.1.4 may be necessary.

5.3 Master and Working Cell Seeds

5.3.1 A well documented history of the master cell seed must be available. The country, species, date of creation and number of passages of the master cell seed since its creation must be specified. Identity and karyological studies must have been undertaken. The country and species of origin of each nutritive factor used since its creation should also be specified.

Because viral contamination in cell lines frequently goes undetected despite testing, it is essential that manufacturers make every effort to use cell lines with a detailed history and that the cell line and all nutrient factors used have been sourced from countries with high standards of animal health (eg free of diseases listed in Annex 1 for the species of origin).

5.3.2 For cell lines created many years ago, detailed information on the initial nutritive factors used may not be available. In this situation, it may be possible in some circumstances to establish the safety of the cell line by additional testing and a history of safe use over many years in live vaccines. Extensive pathogen testing over many years may also provide an additional level of quarantine confidence.

5.3.3 The use of primary cells is discouraged and will only be considered by AQIS if there is no alternative cell line and if the primary cells are derived from specific pathogen free herds or flocks.

5.3.4 The country (or OIE defined region) of origin of the cell line must have been free of major exotic OIE List A pathogens (refer Annex 1) for the relevant species of origin at the time of creation of the cell line.

5.3.5 If the cell line is of ovine or caprine origin, the country of origin must not be scrapie-affected at the time of or within the 6 year period after the creation of the cell line.

5.3.6 If of bovine origin, the country of origin must not be BSE-affected at the time of or within the 6 year period after the creation of the cell line.

5.3.7 The general standards for the testing of cell lines and primary cells are as described in the Eu. Pharm (1997) Chapter 5.2.4 *(Cell cultures for the production of veterinary vaccines).*

5.3.8 All cell lines must be tested for

a) bacterial and fungal contamination as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1; and

b) mycoplasmas as per 9CFR 113.28 or Eu. Pharm (1997) 2.6.7; and

c) extraneous pathogens as per 9CFR 113.51 for primary cell lines and as per 9CFR 113.52 for master and production (working) cell lines; and

d) extraneous pathogens as per Eu. Pharm - Vaccines for Veterinary Use (1997:0062 and 5.2.4) [8]; and

e) bluetongue virus and pestiviruses; and

f) all other pathogens listed in Annex 1 and Annex 3 which are pathogenic to or carried by the species[9]
   -- from which the cell line was originally isolated
   -- from which all nutritive factors of animal origin previously used on the cell line since its creation were derived unless that nutritive factor was effectively sterilised[10]
   -- for which the vaccine is intended; and

g) any other pathogen determined by AQIS during assessment of the application to be a potential contaminant.

5.3.9 Testing as described below should be carried out on a culture of the MCS, WCS or on cells from the WCS at the highest passage level used for production and derived from a homogenous representative sample:

[8] To avoid duplication, a specific test using a Eu. Pharm procedure is not required if already tested for that pathogen in accordance with a 9CFR procedure and vice versa.

[9] Note: AQIS may take into consideration countries of origin and potential for contamination before and after any processing or treatments.

[10] For cell lines with an inadequate history of nutritive factors used since its creation, country of origin of the nutritive factors used cannot be taken into consideration. The cell line should be tested free from all pathogens listed in Annex 1 and Annex 3 relevant to the species of origin of all probable nutritive factors used since its creation. The cell line should also have a history of safe use in vaccine production and/or frequent pathogen testing over many years.

	MCS	WCS	cells from WCS at highest passage level
general microscopy	+	+	+
bacteria/fungi	+	+	-
mycoplasma	+	+	-
viruses	+	+	-
identification of species	+	-	+
karyology	+	-	+
tumorigenicity	+	-	-

5.3.10 The following methods should be used when testing the cell lines for pathogens listed in 5.3.8 (e), (f) and (g): (see Appendix 2)

Either General method 1 for lysate from the master cell seed and at least two subsequent passages or General method 2;

AND either

Specific method 1 or Specific method (embryonated eggs) 2.

5.4 Master Seed Bacteria

5.4.1 A well documented history of the master seed must be available. The species, origin, date of isolation, passage history and purity and identity confirmation studies must be provided. Details of culture media used for transport, storage and propagation of the bacteria since its isolation should also be provided.

5.4.2 For master seed bacteria created many years ago, detailed information on the initial culture media used may not be available. In this situation, it may be possible in some circumstances to establish the safety of the master seed by additional testing and a history of safe use over many years in live vaccines. Extensive pathogen testing over many years may also provide an additional level of quarantine confidence.

5.4.3 All master seed bacteria must be tested for

a) identity and purity such that the master seed is shown to contain only the species and strain of bacterium stated *(Demonstration of freedom from bacterial and fungal contamination as per 9CFR 113.27(d) and mycoplasmas as per 9CFR 113.28 is recommended)*; and

b) all pathogens listed in Annex 1 and bacterial pathogens listed in Annex 3 which occur in the country of origin of and are pathogenic to or carried by the species[11]
-- from which the master seed bacteria was originally isolated; and

[11] Note: AQIS will take into consideration countries of origin and potential for contamination before and after any processing or treatments.

-- from which all culture media ingredients of animal origin used since original isolation of the bacteria were derived unless effectively sterilised prior to use

Viral testing to be performed using the general method and either specific method 1 or 2 as described in 5.4.4; Bacterial testing to use media capable of detecting the relevant potential bacterial contaminant;[12] and

c) other viral pathogens using only the general method as described in 5.4.4; and

d) any other pathogen determined by AQIS on assessment of the application to be a potential contaminant.

5.4.4 Virus tests referred to in 5.4.3 (b) and (c) are as follows: (see Appendix 2)

General method 1for master seed, specifically neutralised if appropriate;

AND either

Specific method 1 or Specific method (embryonated eggs) 2.

5.4.5 The strain of master seed bacteria used must be either endemic in Australia or a recognised attenuated strain considered safe for release in Australia.

5.5 Working and Production Bacteria

5.5.1 All working and production bacteria must be tested for potential pathogens as per relevant 9CFR or Eu. Pharm requirement or as determined by AQIS on assessment of the application.

5.6 Nutritive Factors

5.6.1 Nutritive factors include blood, serum, foetal serum, serum albumins and other serum products used for cell line maintenance and growth. They may also be used for the growth of leptospira and certain other organisms. Fresh or an inadequately sterilised blood is sometimes mixed with culture media (ie blood agar) for bacterial vaccine production. The country and species of origin, processing and any pathogen testing must be detailed with the application. Appropriate government health certification and other documentation providing an audit trail from country of origin to final vaccine must be provided.

5.6.2 Government certification of origin is essential for all animal serum and serum products used in production. Additional pathogen testing may be required by AQIS depending on the country and species of origin and confidence in the certification.

5.6.3 The country (or OIE defined region) of origin must be free of major exotic OIE List A pathogens relevant to the species of origin. Refer to Annex 1.

[12] . AQIS may require the use of appropriate bacterial controls if the media used is inconsistent with Eu. Pharm. requirements.

5.6.4 If of ovine or caprine origin, the country of origin must not be scrapie-affected.

5.6.5 If of bovine origin, the country of origin must not be BSE-affected.

5.6.6 If information is not available as to the origin of serum and other nutritive factors used on cell lines prior to the cell line's acquisition by the manufacturer, the worst case scenario must be assumed and the cell line tested accordingly.

5.6.7 Serum and other nutritive factors must be tested for

a) bacterial and fungal contamination as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1; and

b) mycoplasmas as per 9CFR 113.28 or Eu. Pharm (1997) 2.6.7; and

c) extraneous pathogens as per 9CFR 113.53 or Eu. Pharm (1997:0062) [13]; and

d) pathogens listed in Annex 1 which are pathogenic to the species of origin of the nutritive factor; and

e) bluetongue virus if derived from bovines, ovines, caprines or other susceptible species (regardless of country of origin); and

f) pestiviruses using methods and reagents which detect pestiviruses of all known types; and

g) all other pathogens listed in Annex 3 which are pathogenic to the species of origin of the nutritive factor[14]; and

h) any other pathogen determined by AQIS during assessment of the application to be a potential contaminant.

5.6.8 Virus tests carried out on serum and other nutritive factors as specified in 5.6.7 (d) - (h) must use the following methods: (see Appendix 2)

General method 1- for the nutritive factors;

AND either

Specific method 1 or Specific method (embryonated eggs) 2

5.7 Trypsin and Other Enzymes of Animal Origin

[13] To avoid duplication, testing for a particular pathogen using a Eu. Pharm procedure is not required if already tested for that pathogen in accordance with a 9CFR procedure and vice versa.

[14] Note: For Annex 3 diseases, AQIS may take into consideration disease occurrence in the country of origin and potential for contamination before and after any processing or treatments.

5.7.1 Enzymes of animal origin used in vaccine manufacture frequently undergo only minimal processing and are therefore considered a high quarantine risk. The country and species of origin, processing and any pathogen testing must be detailed with the application. Appropriate government health certification and other documentation providing an audit trail must be provided.

5.7.2 The country (or OIE defined region) of origin must be free of the major exotic OIE List A pathogens relevant to the species of origin (refer Annex 1) unless the product will be effectively sterilised prior to use[15].

5.7.3 If of bovine origin, the enzyme must not be from a BSE-affected country.

5.7.4 Trypsin and other enzymes of animal origin must be tested for

a) bacterial and fungal contamination as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1; and

b) mycoplasmas as per 9CFR 113.28 or Eu.Pharm (1997) 2.6.7; and

c) extraneous pathogens as per 9CFR 113.53 or Eu. Pharm (1997) 5.2.5; and

d) if of porcine origin[16]:
- porcine parvovirus,
- porcine pestivirus (CSF)[17],
- porcine reproductive and respiratory syndrome (PRRS) virus,
- transmissible gastroenteritis (TGE) virus and
- Aujeszky's disease (pseudorabies) virus; and

e) if of bovine origin[18]:
- bovine parvovirus,
- bovine pestivirus (BVD),
- vesicular stomatitis virus, and
- infectious rhinotracheitis virus; and

f) pathogens listed in Annex 1 which are pathogenic to the species of origin of the enzyme *(only required if AQIS considers the certification submitted does not provide complete assurance as to origin*); and

g) other pathogens listed in Annex 3 which are pathogenic to the species of origin of the enzyme[19]; and

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[15] For example, if of porcine origin, the product must not be sourced from foot and mouth disease (FMD), swine vesicular disease (SVD), classical swine fever (CSF) or African swine fever (ASF) affected countries. It should be noted that SVD is extremely resistant to pH changes and irradiation. If of bovine origin, it must not be from FMD or rinderpest affected countries.

[16] Testing for PRRS, TGE or Aujeszky's disease virus is not required if the country of origin of the animals from which the product was derived AND the country of production of the enzyme are free of the respective virus.

[17] Although the country of origin must be free from classical swine fever (CSF), the virus is a high risk contaminant. Consequently, the product must be tested if there are any deficiencies in the audit trail.

[18] Testing for VS or IBR virus is not required if the country of origin of the animals from which the product was derived AND the country of production of the enzyme are free of the respective virus.

h) any other pathogen determined by AQIS during assessment of the application to be a potential contaminant.

i) virus tests carried out on trypsin and other animal enzymes as specified in 5.6.7(d)-(h) must use appropriate methods as detailed in 5.6.8.

Note: For d) - h), irradiation at ≥ 5 MRad is an option instead of testing. Freezing prior to irradiation may reduce damage to the product however manufacturers are advised to conduct trials before adopting the procedure commercially.

5.8 Fermentation Broths and Culture Media

5.8.1 All ingredients used in the fermentation broth/production culture media must be listed in the import application.

5.8.2 Country and species of origin of each ingredient of animal origin must be specified along with details of any processing, treatments or testing of either the ingredients or the final culture media/fermentation broth.

5.8.3 Unless effectively sterilised prior to use, meat extracts must not be sourced from countries (or OIE defined regions) affected by diseases listed in Annex 1 for the relevant species of origin. Additional testing will also be required by AQIS for the relevant Annex 1 pathogen(s) if sourced from such countries.

5.8.4 Meat extracts and other ingredients of ovine or caprine origin must not be sourced from scrapie-affected countries.

5.8.5 Meat extracts and other ingredients of bovine origin must not be sourced from BSE-affected countries.

5.8.6 Unless effectively sterilised prior to use, either the individual ingredient of animal origin or the final fermentation broth/culture media must be tested for

a) bacterial and fungal contamination as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1; and

b) mycoplasmas as per 9CFR 113.28 or Eu. Pharm (1997) 2.6.7; and

c) extraneous pathogens as per 9CFR 113.53 or Eu.Pharm (1997) 5.2.5; and

d) pathogens listed in Annex 1 and Annex 3 which are pathogenic to the species of origin of any fermentation/culture ingredients of animal origin[20]; and.

e) any other pathogens determined by AQIS to be a potential contaminant.

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[19] Note: AQIS may take into consideration confidence in certification of origin, disease occurrence in the country of origin and potential for contamination before and after any processing or treatments.

[20] Note: AQIS may take into consideration countries of origin and potential for contamination before and after any processing or treatments.

5.9 Components of Avian Origin and Embryonated Eggs

5.9.1 The importation of live avian viral vaccines derived from embryonated eggs will be considered in the following situations:

a. the vaccine has a demonstrated and well-documented safety record involving use in a significant number of animals (*refer 2.2.1*)[21]; or

b. if SPF eggs of Australian origin are used for production; or

c. if the importation is required to combat an exotic disease incursion.

5.9.2 Avian cell lines and other components of avian origin used for production which are not effectively sterilised must be derived from specific pathogen free (SPF) flocks. SPF flocks must be under veterinary supervision and approved by the relevant government authority in the country of origin. Vaccination of the SPF flock against any disease including ND or AI must not be practised.

5.9.3 The SPF flocks must meet the procedures and testing requirements as described in Eu. Pharm (1997) Chapter 5.2.2 (*Chicken flocks free from specified pathogens for the production and quality control of vaccines*). They must also be testing for other avian pathogens listed in Annex 3.

5.9.4 Avian cell lines and other components/ingredients of avian origin must be sampled and tested for extraneous avian pathogens listed in Eu. Pharm (1997) Chapter 5.2.2 and Annex 3.

5.9.5 Avian cell lines and components of avian origin (unless effectively sterilised) must also be tested for bacteria, fungi, mycoplasma, salmonella and extraneous viruses as per 9CFR 113.26, 113.28, 113.30, 113.31, 113.34[22].

5.9.6 Applications must be accompanied by the relevant government health certificate along with copies of the current test results of the testing program.

5.9.7 Components of avian origin and eggs must be tested for any other pathogens determined by AQIS during assessment of the application to be a potential contaminant.

[21] Applications to import egg derived live avian vaccines will be subject to public consultation as described in 2.1.3.

[22] To avoid duplication, testing for a particular pathogen using a 9CFR 113 procedure is not required if already tested for that pathogen in accordance with a Eu.Pharm procedure.

5.10 Other Material of Animal Origin

5.10.1 The country and species of origin, processing and any pathogen testing must be detailed with the application. Appropriate government health certification and other documentation providing an audit trail should be provided.

5.10.2 Material of animal origin must not be sourced from countries (or OIE defined regions) affected by diseases listed in Annex 1 for the relevant species of origin unless effectively sterilised. Additional testing will also be required by AQIS for the relevant Annex 1 pathogen(s) if sourced from such countries.

5.10.3 Material of ovine or caprine origin must not be sourced from scrapie-affected countries.

5.10.4 Material of bovine origin must not be sourced from BSE-affected countries.

5.10.5 All other material of animal origin must be either effectively sterilised or be tested for

a) bacterial and fungal contamination as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1; and

b) mycoplasmas as per 9CFR 113.28 or Eu. Pharm (1997) 2.6.7; and

c) extraneous pathogens as per 9CFR 113.53 or Eu. Pharm (1997) 5.2.5; and

d) pathogens listed in Annex 1 and Annex 3 which are pathogenic to the species of origin[23]; and

e) any other pathogen determined by AQIS during assessment of the application to be a potential contaminant.

5.11 Final Product Testing - Viral Vaccines

5.11.1 Every batch of the live final bulk (or final container) viral vaccine must be sampled and tested in general in accordance with either 9CFR 113.300 or Eu. Pharm 1997:0062.

5.11.2 Every batch of the live final bulk (or final container) viral vaccine must be sampled and tested for bacterial and fungal sterility as per 9CFR 113.27; or Eu. Pharm (1997) 2.6.1.

5.11.3 Every batch of the live final bulk (or final container) viral vaccine must be sampled and tested for freedom from mycoplasma as per 9CFR 113.28 or as per Eu. Pharm (1997) 2.6.7.

[23] Note: AQIS may take into consideration countries of origin and potential for contamination before and after any processing or treatments.

5.11.4 Every batch of the final bulk (or final container) viral vaccine must be sampled and tested for freedom from extraneous pathogens by the following:

a) as per the Eu. Pharm (1997) monograph for the specific live viral vaccine; or

b) inoculation of vaccine specifically neutralised by monospecific antiserum onto an appropriate range of cell lines known to be sensitive to viruses pathogenic to the target species and testing for cytopathic agents, inclusion bodies and haemadsorbing agents; or

c) by any other method determined appropriate by AQIS.

5.11.5 In addition, every batch of the final bulk (or final container) live avian viral vaccine must be sampled and tested for freedom from the following:

a) avian leucosis viruses as per either Eu. Pharm (1997) 2.6.4 or 9CFR 113.31; and

b) extraneous viruses using cell cultures as per Eu. Pharm (1997) 2.6.5; and

c) extraneous viruses using fertilised eggs as per Eu. Pharm(1997) 2.6.3 or 9CFR 113.34; and

d) extraneous agents using chicks as per Eu. Pharm (1997) 2.6.6 or 9CFR 113.36[24]; and

e) salmonellae as per either 9CFR 113.30 or other method determined appropriate by AQIS.

5.11.6 Additional testing may be necessary as determined by AQIS on assessment of the application.

5.11.7 If deemed as necessary by AQIS, prior to release from quarantine, each batch of live viral vaccine must be tested at the Australian Animal Health Laboratory (AAHL) or another AQIS-approved laboratory for any relevant OIE List A pathogens and any other pathogen considered by AQIS to be a potential contaminant of quarantine concern.

5.12 Final Product Testing - Bacterial Vaccines

5.12.1 Every batch of the live final bulk (or final container) bacterial vaccine must be sampled and tested in general in accordance with either 9CFR 113.64 or Eu. Pharm 1997:0062.

5.12.2 Every batch of the live final bulk (or final container) bacterial vaccine must be sampled and tested for bacterial and fungal sterility as per 9CFR 113.27 or Eu. Pharm (1997) 2.6.1.

[24] 9CFR 113.36 may be used as an alternative to Eu. Pharm 2.6.3 only if the test includes the use of serology to detect antibodies to the pathogens listed in Eu. Pharm 2.6.3.

5.12.3 If the media used in the vaccine production supports the growth of mycoplasma, every batch of the live final bulk (or final container) bacterial vaccine must be sampled and tested for freedom from mycoplasma as per 9CFR 113.28 or Eu. Pharm (1997) 2.6.7.

5.12.4 Additional testing may be necessary as determined by AQIS on assessment of the application.

5.12.5 If determined as necessary by AQIS on assessment of the application, prior to release from quarantine, the live bacterial vaccine must be tested at the Australian Animal Health Laboratory (AAHL) or another AQIS-approved laboratory for any relevant OIE List A pathogens and any other potential contaminant of quarantine concern. At AQIS's discretion, testing may be required on each batch or only the initial imported batch.

5.13 Safety and Efficacy

5.13.1 The NRA is responsible for the regulation and assessment of safety and efficacy. Efficacy testing should be carried out in accordance with any requirements specified by the NRA. In the absence of NRA specifications and subject to agreement with NRA, testing should be carried out as specified in the Eu. Pharm (1997) - Vaccines for Veterinary Use (1997:0062) and in the relevant Eu. Pharm monograph for the specific vaccine

- as Confirmatory Australian Efficacy Trials are a NRA requirement, the NRA has requested that an application to NRA for a field trial permit (NRA category 45) be made at the same time as an import application is made to AQIS.

5.13.2 The potential of the vaccine strain to spread and for reversion to virulence shall be tested using appropriate international procedures (eg Directive 81/852/EEC, as modified by Directive 92/18/EEC).

5.13.3 Safety and efficacy testing involving inoculation of live animals should be conducted overseas or alternatively in biosecure facilities following approved, controlled protocols.

5.14 Genetic Recombination

5.14.1 Where genetic reassortment or recombination has been reported, the application should include an analysis of the likelihood of such reassortment and recombination with local strains of the particular virus.

ATTACHMENTS

APPENDIX 1 - Standards for Assurances of Freedom from Microbial Contamination[25]

1. Master virus seed should be specifically tested for the presence of the viruses listed in the Annex 1 and 3, with regard to the species in the left column of the Annexes if:

   a) the seed was originally derived from that species; or

   b) the cell cultures used to produce the master virus seed were of that species; or

   c) the vaccine is intended for use in that species; or

   d) the seed has been exposed to production substrates derived from that species.

2. Animal-derived production substrates, master cell seeds, SPF eggs, and SPF donor flocks/colonies for primary cell lines must be shown to be free from bacteria, fungi and mycoplasma in all cases and from the viruses listed in Annex 1 and 3, with regard to the species in the left column of the Annexes if:

   a) the material was originally derived from that species; or

   b) the vaccine is intended for use in that species; or

   c) in the case of cell lines, the cells have been exposed to production substrates derived from that species.

3. Assurances of freedom from pathogens listed in Annex 1 (ie major exotic diseases) must include:

   a) acceptable assurances of disease-free origins (ie. country freedom from particular disease); or

   b) (i) validation of effective sterilisation of the product to eliminate all potential contaminating pathogen(s); and

   (ii) tests for freedom from the relevant pathogen(s).

   *Note: Cell lines, serum, serum albumin, animal enzymes and other products which undergo only minimal processing must comply with **both** a) and b(ii).*

[25] This list is neither mandatory nor exhaustive but a guide. Rabies virus testing for instance may be waived if the seed did not originate from a rabies endemic country and has never been handled in a laboratory which also handled rabies virus. On the other hand, additional specific tests might be required by AQIS if there were any question of possible contamination with agents not listed or if required under a monograph in a recognised pharmacopoeia. Where highly sensitive tests such as DNA probes exist, these may be used in lieu of the tests described but the sensitivity of the test method must be validated.

4. Assurances of freedom from pathogens listed in Annex 2 (ie prions) must include an acceptable assurance of disease-free origins (ie. country freedom).

5. Assurances of freedom from pathogens listed in Annex 3 (ie other diseases of concern) must include:

   a) adequate assurances of disease-free origins (ie. country or OIE defined regional freedom from particular disease); or

   b) validation of processing of production substrates as effective at eliminating the pathogen(s); or

   c) adequate assurances that cell line(s) or culture media do not support propagation of the pathogen(s); or

   d) tests for freedom from the pathogen(s) where the assurances at (i), (ii) and (iii) above are inadequate.

APPENDIX 2: Detection Methods

General method 1- inoculation onto an appropriate range of cell lines and testing for cytopathic agents, inclusion bodies and haemadsorbing agents.

General method 2 - direct examination for cytopathic agents, inclusion bodies and haemadsorbing agents.

Specific method 1 - inoculation onto an appropriate cell line and testing for specific agents. Alternatively, inoculation into a number of animals of a susceptible species which should be serologically tested pre and post inoculation.

Specific method (embryonated eggs) 2 - where applicable - inoculation of the chorio-allantoic membrane/sac, followed by post-inoculation incubation, serial passage(s), and examination of the chorio-allantoic membrane, allantoic sac and yolk sac for cytopathic effects. Chorioallantoic fluid should be tested for haemadsorption and haemagglutination inhibition and/or testing for antibodies to the pathogens of concern.

These testing standards and methods are not inflexible but any alternative proposals must be validated.

ANNEX 1 - Exotic Animal Diseases of Major Economic and Social Concern

SPECIES	OIE CODE	PATHOGEN/DISEASE
Bovine	A010 A040	Foot and mouth disease virus Rinderpest virus
Equine	A110	African horse sickness virus
Ovine/Caprine	A010 A040 A050 A100 B157	Foot and mouth disease virus Rinderpest virus Peste des petits ruminants virus Ovine/caprine pox virus Pulmonary adenomatosis
Porcine	A010 A030 A120 A130	Foot and mouth disease virus Swine vesicular disease virus African swine fever virus Classical swine fever virus
Avian	A150 A160	Clinical avian influenza virus Virulent Newcastle disease virus *Note: Use of eggs from SPF flocks in affected country may be allowed subject to additional testing for ND and AI*
Other species		As determined by AQIS on application

ANNEX 2 - Exotic Animal Prion Diseases of Major Economic and Social Concern

(Relatively low infectivity but extremely high resistance to normal inactivation processes)

SPECIES	OIE CODE	PATHOGEN/DISEASE
Bovine	B115	bovine spongiform encephalopathy
Ovine	B160	scrapie

ANNEX 3 - Other Animal Pathogens/Diseases of Economic and Social Concern

These pathogens/diseases are either exotic to Australia, potential for exotic strains of endemic pathogens or potential contaminants of concern.

SPECIES	PATHOGEN/DISEASE
Bovine	Adenovirus Akabane virus Bluetongue/EHD virus Bovine ephemeral fever virus Bovine herpesvirus 1, 2, 4 Bovine immunodeficiency virus Bovine Parvovirus Bovine respiratory syncitial virus Bovine pestiviruses (Bovine Viral Diarrhoea) *Brucella abortus* Contagious bovine pleuro-pneumonia *Coxiella burnetti* (Q-fever) Enzootic bovine leucosis virus Infectious Bovine Rhinotracheitis virus Lumpy skin disease virus Parainfluenza virus 3 Rabies virus Rift Valley fever virus Rotavirus Vesicular stomatitis virus
Equine	Contagious equine metritis Epizootic lymphangitis Equine adenovirus Equine arteritis virus Equine encephalomyelitis viruses Equine herpes virus types 1,2,3, 4 Equine infectious anaemia virus Equine influenza virus equine piroplasmosis Equine rhinopneumonitis virus Equine viral abortion Glanders Horse pox virus Pestivirus Potomac fever Rabies virus Surra Vesicular stomatitis virus

Ovine/Caprine	Adenovirus Akabane virus Bluetongue/EHD virus *Brucella melitensis* Caprine arthritis encephalitis Capripox virus Contagious agalactia Contagious caprine pleuro-pneumonia (*Mycoplasma mycoides* var *capri)* Contagious pustular dermatitis (Orf) Louping ill virus Maedi-visna virus Pestivirus Rabies virus Rift Valley fever virus Vesicular stomatitis virus
Porcine	Adenovirus Aujeszky's disease virus *Brucella suis* Haemagglutinating encephalomyelitis virus *Mycoplasma hyopneumoniae* Pestivirus (including Classical Swine Fever) Polioencephalomyelitis virus Porcine enteroviruses Porcine epidemic diarrhoea virus Porcine parvovirus Porcine respiratory corona virus Porcine respiratory and reproductive syndrome virus Post-weaning multi-systemic wasting syndrome Rabies virus Rotavirus Swine influenza virus Swine pox virus Transmissible gastroenteritis virus Vesicular stomatitis virus
Rabbit	Rabbit haemorrhagic disease virus Rabies virus Shope fibroma virus Tularaemia Treponema
Rodent	Adenovirus Ectromelia virus *(mice only)* Encephalomyocarditis virus Korean haemorrhagic fever Lymphocytic choriomeningitis (Arena virus) Rabies virus Sendai virus

Avian	Avian adenovirus Avian encephalomyelitis virus Avian leucosis virus Avian nephritis virus Chicken anaemia agent Duck viral hepatitis Duck viral enteritis EDS 76 virus Fowl pox virus Infectious bronchitis virus Infectious bursal disease virus Infectious laryngotracheitis virus *M. gallisepticum* *M. synoviae* Marek's disease virus *Ornithobacterium rhinotracheale* Reovirus Reticuloendotheliosis virus *S.* Enteritidis *S.* Gallinarum *S.* Pullorum Turkey rhinotracheitis virus
Canine/feline	Aujeszky's disease virus Bluetongue virus *Brucella canis* Canine adenovirus 1, 2 Canine distemper virus Canine parvovirus *Ehrlichia canis* Feline calicivirus Feline immunodeficiency virus Feline infectious peritonitis virus Feline leukemia virus Feline panleukopaenia virus Feline rhinotracheitis virus *Leptospira interrogans var. canicola* Pestivirus Rabies virus
Other species	As determined by AQIS on application