SPECIFIC QUARANTINE REQUIREMENTS FOR THE IMPORTATION OF INACTIVATED VETERINARY VACCINES

(AN ADDENDUM TO THE GUIDELINES FOR SUBMISSIONS TO IMPORT VETERINARY VACCINES)

December 1997

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1. INTRODUCTION

This addendum to the AQIS "Guidelines for Submissions to Import Veterinary Vaccines" and "Guidelines for Submissions to Import Veterinary Vaccines" describes specific information on the quarantine requirements for the production of imported inactivated veterinary vaccines and related products, and for the sourcing, treatment and testing of substrates and other ingredients of animal origin used in production, inactivation requirements and testing of the final product.

Prospective importers should ensure that applications to import veterinary vaccines and related products address all relevant specifications described in this addendum prior to submitting the application.

For details of general AQIS requirements and quarantine concerns, prospective importers should also refer to the "Guidelines for the Production and Control of Inactivated Veterinary Vaccines in Australia and Guidelines for Submissions to Import Veterinary Vaccines" hereafter referred to as "the Guidelines".

The Guidelines were developed based on the E.U. *General Requirements for the Production and Control of Inactivated Mammalian Bacterial and Viral Vaccines for Veterinary Use* and modified to address Australian quarantine concerns. The purpose of this Addendum is to provide clarification and specific information on the existing AQIS requirements.

Although manufacturers are expected to produce product, destined for export to Australia, which meets these requirements, this document does not preclude consideration by AQIS assessing officers of variations to these requirements provided quarantine concerns are addressed by alternative means. This may include a combination of sourcing, processing, treatment or testing overseas or within Australia prior to release from quarantine. A case by case detailed risk assessment may be required and information presented should be supported by appropriate documentation.

2. REQUIREMENTS - PRODUCTION, STANDARDS AND APPLICATION

2.1 Responsibilities

2.1.1 An import permit from AQIS is required prior to the importation of any vaccine or related product. AQIS's quarantine concerns relate primarily to ensuring imported product is not contaminated with exotic pathogens, exotic strains of endemic pathogens or endemic pathogens which could be spread further within Australia or infect other species through the use of the product. Efficacy, potency, storage, labelling, toxicity and certain other safety aspects are generally not the responsibility of AQIS. These are regulated by the National Registration Authority for Agricultural and Veterinary Chemicals (NRA).

2.1.2 Once the quarantine safety has been established and the product approved by AQIS for importation, the product must then be registered by the NRA prior to sale, distribution or use. The NRA will assess all other aspects for the normal registration process not previously addressed by AQIS. It should be noted however that there may be some unavoidable duplication especially in the area of safety testing. Product safety is one area where Australia cannot afford to make concessions.

2.1.3 Concurrent quarantine assessment by AQIS and assessment by NRA for registration is possible.

2.1.4 Quarantine assessment usually involves examining the country and species of origin of each component of biological origin to determine potential contaminants, processing, treatment and testing of these ingredients and the product at appropriate stages of production. It may also involve innocuity testing.

2.1.5 While efficacy, potency and safety testing are generally the realm of NRA, any live animal field trials or previous overseas commercial use may be considered by AQIS to be a form of innocuity testing and therefore provides an additional level of confidence.

2.1.6 AQIS import permits for inactivated veterinary vaccines are generally valid for 2 years. They may however be issued for shorter periods under certain circumstances. Imported product may be required to be accompanied by a manufacturer's declaration that the production process, including the sourcing and testing of ingredients and product being imported, has not changed from that assessed by AQIS and approved.

2.1.7 All vaccines will be reassessed prior to renewal of their import permit. All relevant information including application and dossier must be resubmitted. A declaration that the production process, sourcing, testing and other procedures as previously submitted have not changed or a summary highlighting proposed changes should streamline reassessment and approval.

2.2 Standards

2.2.1 Standards of Good Manufacturing Practice (GMP)

2.2.1.1 The production facility must demonstrate evidence of compliance with an appropriate code of GMP to provide the confidence that product is manufactured safely and consistently with appropriate emphasis on producing a quality product and maintaining necessary documentation and audit trails. Both the production facility and the product must therefore be approved and regularly audited by the relevant authority in the country of origin. Confirmation that the product is approved for export to and use within another country which AQIS considers having similar quarantine standards and concerns will add confidence to the application.

2.2.1.2 AQIS will insist on the principles of quality assurance being applied. This means that quarantine safety must be built into the product at every step of production from the sourcing, processing, treatment and testing of each ingredient of biological origin through to testing of the final product.

2.2.2 Production plant(s)

2.2.2.1 The plant(s) where the vaccine or antigen is manufactured must comply with an appropriate code of Good Manufacturing Practice (GMP) specific to the particular product. Compliance must apply for the whole period of production of batches to be imported into Australia.

2.2.2.2 The production plant(s) must be completely separate from any plant which stores or handles viruses of particular quarantine significance to Australia. Any plant handling those live OIE List A viruses listed in Annex 1, especially non-attenuated strains, will be deemed ineligible for production of vaccine for Australia.

2.2.3 Standards for production, control and testing

2.2.3.1 The minimum standard for the production, control and testing of the vaccine and sourcing and testing of all components used in production should be as specified in the following documents:

. *Guidelines for the Production and Control of Inactivated Veterinary Vaccines in Australia* AQIS (1994)[1]

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

. Specific Requirements for the production and control of the following products as detailed in *The Rules governing Medicinal Products in the*

[1] 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)

European Union Vol VII - (Committee for Veterinary Medical Products 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

2.2.3.2 Many of the standards in the Eu.Pharm and the above guidelines do not refer to specific tests. Where appropriate, testing procedures specified in the USDA's Code of Federal Regulations (9CFR 113) are generally an acceptable enhancement to the Eu.Pharm requirements.

2.2.3.3 Any additional or more stringent requirements specified by AQIS, either in these Requirements or by other communication, relating to testing, sourcing or production must also be complied with.

2.3 Extraneous Agents - General Requirements

2.3.1 Master and working seeds, cell lines, substrates, and other materials of animal origin are expected to be free of all extraneous agents. Freedom is based on assessment of the country and species of origin, processing, treatment and testing.

2.3.2 Annex 1 lists pathogens exotic to Australia which pose such a major economic and social threat to this country that sourcing of potentially contaminated products from affected countries will not be considered unless the product is effectively sterilised. In addition to country freedom, testing of certain products for pathogens listed in Annex 1 may be required especially where documentation concerning origin is unsatisfactory.

2.3.3 Effective sterilisation means treating in such a way as to completely inactivate all conventional adventitious agents including viruses

- This excludes prions which are highly resistant to treatment necessitating country freedom for the relevant species of origin

- Effective sterilisation is autoclaving at $121^{o}C$ for 15 minutes, 5 MRad irradiation or other treatments as determined by AQIS to provide a sufficient level of pathogen inactivation

- 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 higher level of titre reduction will be required where there is reasonable likelihood of contamination (eg if the average level of 2 logs of contamination in a product is expected in a product, treatment must achieve at least an 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.

2.3.4 Claims of effective sterilisation must be supported by validation data. Such validation must include a clear demonstration of the degree of the lethal effect, 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 are potential contaminants.

2.3.5 Annex 2 lists the prion diseases, scrapie and bovine spongiform encephalopathy (BSE). These agents are difficult to detect and generally extremely resistant to inactivation. Vaccines produced using products sourced from the relevant species in affected countries will not be approved.

2.3.6 Annex 3 lists other animal diseases which are either other exotic pathogens, potentially exotic strains of an endemic pathogen or are potential contaminants of economic and social concern to Australia. During assessment, AQIS may also identify other potential contaminants of concern.

2.3.7 All raw materials of animal origin used during production must be proven to be free of extraneous agents. Unless effectively sterilised (refer 2.3.3), they must be tested for bacteria, fungi, mycoplasma and for the range of viruses listed in Annexes 1 and 3 for those species as detailed in Appendix 1. Test results or confirmation of effective sterilisation must be available.

2.3.8 Importers should note that demonstrated freedom from pathogens other than those listed in Annexes 1-3 may be required to meet the safety requirements of NRA or the exporting country.

2.4 Sourcing of Ingredients

2.4.1 All materials of animal origin used in the production process must be sourced from countries with high standards of animal health and veterinary services.

2.4.2 While many treatments will inactivate major pathogens of concern and/or testing regimes will detect their presence, it is possible failures may occur in either processing, treatment or testing procedures. Some pathogens especially prion agents such as scrapie and BSE are also extremely resistant to treatment and difficult to detect. Therefore, bovine products must not be sourced from BSE

affected countries and ovine/caprine products must not be sourced from scrapie affected countries. Animal origin products must not be sourced from countries affected with Annex 1 diseases unless the product will be effectively sterilised prior to use.

2.4.3 The source of all materials of animal origin used during production must be certified. This certification must be unequivocal and preferably be issued by the government of the source country. Manufacturer's certification may be accepted provided the manufacturer is operating under a quality assurance system accepted by AQIS as adequate to ensure compliance with Australian quarantine requirements. There must be an auditable trail from the country of origin of the source animals to the batch of finished vaccine destined for Australia.

2.5 Information to be Provided with the Application

2.5.1 General

2.5.1.1 Information should be presented either as described in the Guidelines or, to minimise duplication, as a summary document dealing with all quarantine issues as described in this addendum and the Guidelines. The summary document should be cross referenced to registration dossiers and/or drug master files which should also be submitted.

2.5.1.2 The information provided with the application should relate to a recent batch of vaccine. For each high risk ingredient of the vaccine batch being assessed, details of batch numbers, Certificates of Analysis (CoA), health certification, import permits, etc should demonstrate an audit trail. AQIS must be confident that an audit trail will be possible for all future batches of vaccines.

2.5.2 Registration and Approvals

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

2.5.3 Flow-chart of Production Process

2.5.3.1 Each major step of the production process should be detailed in a flow-chart format. Each step on the flow-chart should be cross-referenced to the location in the application detailing materials used and tests conducted

2.5.4 Testing Standards

2.5.4.1.1 The test procedures to detect pathogens as specified in the Code of Federal Regulations (9CFR 113) are considered acceptable for most test procedures. Standards other than the 9CFRs may also be used if applicable (eg Australian Standard Diagnostic Techniques, etc). All test procedures used must be considered appropriate by AQIS for the product and pathogen to be detected. A copy of the relevant test protocol should also be submitted with the application.

2.5.4.1.2 Additional standards and testing may be required for certain pathogens and products as detailed in these requirements. Following quarantine assessment, AQIS may also insist on additional treatment or testing of products to address specific quarantine concerns.

2.5.4.1.3 Any master seed or bulk vaccine found contaminated with any pathogen other than the vaccine organism must be rejected and not used in the production process. Any other products (ie substrates, cell lines, etc) found contaminated with any pathogen must be rejected and not used in the production process.

2.5.4.1.4 The vaccine harvest must be tested immediately after inactivation for the presence of viable organisms (refer 2.5.10.7 and 2.5.10.8). If not completely inactivated, the inactivation procedure must be repeated and re-tested on completion. The finished vaccine should also be tested for complete inactivation (refer 2.5.10.9).

2.5.5 Standard Operating Procedures (SOP)

2.5.5.1 There must be documented standard operating procedures (SOPs) and/or specifications in place as part of the manufacturer's GMP. These SOPs should detail approved sourcing, sterilisation procedure (if appropriate), pathogen tests for each product and the inactivation process. The existence and standard of SOPs should be verified as part of the regular GMP inspections.

2.5.5.2 Copies of relevant test results must be provided and these test results must be consistent with the relevant SOP.

2.5.6 List all materials of biological origin

2.5.6.1 All components of biological origin used directly or indirectly in production must be detailed. These include virus/bacterial seeds, cell lines, trypsin, ingredients of nutritive factors (eg serum), fermentation broths/culture media, excipients, etc. If applicable, each ingredient of animal origin contained in or used in the production of the component must also be listed. Itemise country and species of origin, approximate date of collection, processing/treatment and testing for each ingredient or component of animal origin.

2.5.7 Certification and audit trails

2.5.7.1 An audit trail is essential to establish the country, species and date of origin of <u>each high risk product</u> of animal origin used in production of the vaccine. Examples of high risk products include serum and serum albumin.

2.5.7.2 The audit trail will involve the correlation of batch numbers of product from the original source of the raw ingredient through to use in the vaccine production. A copy of the official government health certification must also be provided for product imported into the country of vaccine manufacture. Appropriate documentation must also be provided for every step where the batch number is changed or products pooled.

2.5.8 Other pathogens held and vaccines produced at the facility

2.5.8.1 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).

2.5.8.2 Mammalian vaccines produced in facilities handling mammalian pathogens listed in Annex 1 will not be approved.

2.5.8.3 Avian vaccines produced in facilities handling virulent avian influenza or Newcastle disease virus will not be approved.

2.5.8.4 Vaccines produced in facilities handling pathogens listed in Annex 3 must be tested for these pathogens prior to importation and/or release from quarantine unless it can be conclusively established that cross contamination is prevented.

2.5.9 Sterilisation of components of animal origin

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

2.5.9.2 Sterilisation procedures must be validated and a copy of the appropriate standard operating procedure (SOP) submitted with the application.

2.5.9.3 Filtration (even at $< 0.1\mu$) and irradiation at lower doses (eg 2.5 MRad) are <u>not</u> considered adequate to address all quarantine concerns however such treatments may provide useful adjuncts to other treatments thus enabling AQIS concerns to be addressed.

2.5.9.4 Because processing, treatment and testing procedures can sometimes fail or not be satisfactorily completed, ingredients of animal origin should not be sourced from countries 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.

2.5.9.5 Effective sterilisation means treating in such a way as to completely inactivate all conventional adventitious agents including viruses (refer 2.3.3).

2.5.9.6 All sterilisation procedures should be validated, verified and supported by GMP standards and procedures.

2.5.10 Inactivation

2.5.10.1 The inactivating agent and inactivation procedure must be shown to inactivate the vaccine organism under conditions of vaccine manufacture.

2.5.10.2 Complete inactivation must be achieved within 2/3 of the total inactivation time.

2.5.10.3 An inactivation kinetics study must be submitted for the organism and the inactivant and must be appropriate to the particular vaccine production.

2.5.10.4 Prior to inactivation, the bulk vaccine should be an homogenous suspension free from particles which may not be penetrated by the inactivating agent.

2.5.10.5 A test for complete inactivation shall be performed on the viral harvest immediately after the inactivation procedure and, if applicable, the neutralisation or removal of the inactivating agent. The test selected should be appropriate to the vaccine virus being used and should consist of at least 2 passages in cells, embryonated eggs or, where necessary in animals. The number of cell samples, eggs or animals should be sufficient to ensure appropriate sensitivity of the test. For cell cultures, at least 150 cm^2 of the cell culture monolayer should be inoculated with 1.0 ml of harvest. No evidence of the presence of any live virus or micro-organism should be observed.

2.5.10.6 A test for complete inactivation shall be performed on the bacterial harvest immediately after the inactivation procedure and, if applicable, the neutralisation or removal of the inactivating agent. The selected test should be appropriate to the vaccine bacteria being used and should consist of at least two passages in production media or in media prescribed in the relevant European Pharmacopoeia monograph. No evidence of any live micro-organism should be observed.

2.5.10.7 If not completely inactivated, the inactivation procedure must be repeated and re-tested on completion. The inactivation kinetics study must also be re-examined. An increased safety margin may be required for subsequent production runs.

2.5.10.8 A suitable test for the complete inactivation of vaccine organisms shall be carried out on the finished vaccine. The protocol for this test should normally be the same as the test carried out on the harvest material (refer 2.5.10.5 and 2.5.10.6). If the presence of adjuvant or other substances render this impractical, then the test should be performed prior to the addition of the adjuvant. Bulk antigen so sampled shall not be stored except in the vessel from which the sample was taken.

3. REQUIREMENTS - PRODUCTS

3.1 Master seed viruses (MSV)

3.1.1 A full and well documented history of the master seed must be available. The origin, date of isolation, passage history and cell lines and nutritive media used for the transport, storage and propagation of the master seed virus must be stated.

3.1.2 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 113.200; or as per European Pharmacopoeia - Vaccines for Veterinary Use (1997:0062)[2]; and

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

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

3.2 Master and Working Cell Seeds

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

3.2.2 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.

3.3.3 The country 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.

[2] 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.

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

3.3.4 If of ovine or caprine origin, 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

3.3.5 If of bovine origin, 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.

3.3.6 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).*

3.3.7 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 or as per 9CFR 113.52 for master and production (working) cell lines; and

d) extraneous pathogens as per European Pharmacopoeia - Vaccines for Veterinary Use (1997:0062 and 5.2.4) [4]; and

e) pathogens listed in Annex 1 and 3 of the Guidelines which are pathogenic to the species[5]
   -- from which the cell line was originally isolated
   -- of all nutritive factors of animal origin previously used on the cell line since its creation
   -- for which the vaccine is intended; and

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

3.3.8 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:

[4] 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.

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

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

3.4 Master seed bacteria

3.4.1 A full and well documented history of the master seed must be available. Purity and identity confirmation studies must be available. The species, origin, date of isolation, passage history and culture media used for transport, storage and propagation of the bacteria used in the vaccine must be provided.

3.4.2 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 113.26 and mycoplasmas as per 9CFR 113.28 is recommended)*; and

b) pathogens listed in Annex 1 which occur in the country of origin of and are pathogenic to the species[6]

-- from which the master seed bacteria was originally isolated; and
-- of all culture media ingredients of animal origin used since original isolation of the bacteria unless effectively sterilised (refer 2.3.3); and

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

3.5 Working and Production viral/bacterial seeds

3.5.1 All working and production viruses and 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.

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

3.6 Nutritive factors

3.6.1 Nutritive factors include 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. Nutritive factors are considered high risk products because they undergo only minimal processing/treatment prior to use. 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.

3.6.2 Additional pathogen testing may be required by AQIS depending on the country and species of origin and confidence in the certification.

3.6.3 The country of origin must be free of major exotic OIE List A pathogens relevant to the species of origin. Refer to Annex 1.

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

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

3.6.6 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.

3.6.7 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) other extraneous pathogens as per 9CFR 113.53 or Eu. Pharm (1997:0062)[7]; and

d) pathogens listed in Annexes 1 and 3 which are pathogenic to the species of origin of the nutritive factor[8]; and

e) bluetongue virus if of bovine or ovine origin (regardless of country of origin); and

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

[7] 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 vis versa.

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

3.7 Trypsin and other enzymes of animal origin

3.7.1 Trypsin is usually of porcine origin but occasionally, bovine origin trypsin is used in 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 should be provided.

3.7.2 The country of origin must be free of the major exotic OIE List A pathogens relevant to the species of origin (Refer to Annex 1). If of porcine origin, the product must not be sourced from 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, must not be from FMD or rinderpest affected countries.

3.7.3 If of bovine origin, the animal origin enzyme must not be from a BSE affected countries.

3.7.4 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) unless the country of origin is free of the disease, if of porcine origin:
- porcine parvovirus,
- porcine pestivirus (CSF)[9],
- porcine reproductive and respiratory syndrome (PRRS) virus,
- transmissible gastroenteritis (TGE) virus and
- Aujeszky's disease (pseudorabies) virus

Note: Testing will be necessary for all the above pathogens if government certification of origin is inadequate or the audit trail is inconclusive; and

e) unless the country of origin is free of the disease, if of bovine origin:
- bovine parvovirus,
- bovine pestivirus (BVD),
- vesicular stomatitis virus, and
- infectious rhinotracheitis virus.

Note: Testing will be necessary for all the above pathogens if government certification of origin is inadequate or the audit trail is inconclusive; and

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

[9] Although the country of origin must be free from classical swine fever (CSF), it is a high risk contaminant and the product must be tested if the audit trail is inconclusive.

Note: For d) or e), 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).

3.8 Fermentation broths and culture media

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

3.8.2 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

3.8.3 Unless effectively sterilised (refer 2.3.3) prior to use, meat extracts must not be sourced from countries 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.

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

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

3.8.6 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[10]; and.

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

3.9 Components of avian origin and embryonated eggs

3.9.1 Embryonated eggs and avian cell lines used for the growth and production of the inactivated vaccine should be derived from SPF flocks. The use of eggs from healthy non-SPF flocks free from the presence of certain agents and their antibodies will require additional assurances of safety and approval by AQIS[11].

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

[11] The country of origin must have an overall acceptable standard of avian health, veterinary services and diagnostic capabilities. SPF flocks must be tested as per Eu.Pharm (1997) Chapter 5.2.2.

SPF flocks must be under veterinary supervision and approved by the relevant government authority in the country of origin.

3.9.2 The principles, procedures and testing regime for SPF flocks must be as described in Eu.Pharm (1997) Chapter 5.2.2 (*Chicken flocks free from specified pathogens for the production and quality control of vaccines*).

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

3.9.4 SPF poultry flocks from which the embryonated eggs are derived must meet the requirements of and be tested for extraneous pathogens as per Eu.Pharm (1997) Chapter 5.2.2 and also tested for other avian pathogens as listed in Annex 3.

3.9.5 Avian cell lines and non-SPF derived embryonated eggs must be sampled and tested for extraneous pathogens listed in Eu.Pharm (1997) Chapter 5.2.2 and in Annex 3.

3.9.6 Other components/ingredients of avian origin must be derived from either:

a) a country free from clinical avian influenza and virulent Newcastle disease in their commercial poultry flocks provided the product is derived from such flocks; or

b) specific pathogen free (SPF) flocks; or

c) commercial poultry flock which vaccinates against avian influenza and Newcastle disease and there has been no outbreaks in the flock or within a 25 km radius for the preceding 3 months.

3.9.7 Other components of avian origin must be tested for extraneous avian pathogens as listed in Eu.Pharm (1997) Chapter 5.2.2 and Annex 3 unless effectively sterilised (Refer 2.3.3).

3.9.8 Avian cell lines and components of avian origin (unless effectively sterilised) must also be tested for bacteria, fungi, mycoplasma, salmonella and adventitious viruses as per 9CFR 113.26, 113.30, 113.31, 113.34[12].

3.9.9 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.

[12] 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.

3.10 Other material of animal origin

3.10.1 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.

3.10.2 Material of animal origin must not be sourced from countries affected by diseases listed in Annex 1 for the relevant species of origin unless effectively sterilised (refer 2.3.3).

3.10.3 Material of ovine or caprine origin must not be sourced from scrapie affected countries

3.10.4 Material of bovine origin must not be sourced from BSE affected countries

3.10.5 All other material of animal origin must be either effectively sterilised (refer 2.3.3) 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 of any fermentation/culture ingredients of animal origin[13]; and.

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

3.11 Final Product Testing - Viral Vaccines

3.11.1 Every batch of the inactivated final bulk (or final container) viral vaccine must be sampled and tested in general in accordance with either 9CFR 113.200 or Eu. Pharm 1997:0062.

3.11.2 Every batch of the inactivated final bulk (or final container) viral vaccine must be sampled and tested for bacterial and fungal sterility as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1

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

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

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

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

b) by any other method determined appropriate by AQIS.

3.11.5 In addition, every batch of the final bulk (or final container) 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

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

c) salmonella as per either 9CFR 113.30 or other method determined appropriate by AQIS.

3.11.6 The inactivation procedure must be confirmed as described in 2.5.10

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

3.12 Final Product Testing - Bacterial Vaccines

3.12.1 Every batch of the inactivated final bulk (or final container) bacterial vaccine must be sampled and tested in general in accordance with either 9CFR 113.100 or Eu. Pharm 1997:0062.

3.12.2 Every batch of the inactivated final bulk (or final container) bacterial vaccine must be sampled and tested for bacterial and fungal sterility as per 9CFR 113.26 or Eu. Pharm (1997) 2.6.1.

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

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

b) by any other method determined appropriate by AQIS.

3.12.4 The inactivation procedure must be confirmed as described in 2.5.10

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

3.13 Safety

3.13.1 Safety testing shall be carried out in accordance with any requirements specified by the NRA. In the absence of NRA specifications and subject to agreement with NRA, safety testing shall 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.

4. REFERENCES

1. *Guidelines for the Importation of Biological Material* (Australian Quarantine and Inspection Service (AQIS) 1994

2. *An Overview of Regulatory Aspects of Veterinary Immunobiologicals in Australia* (AQIS 1994)

3. (a). *Guidelines for the Production and Control of Inactivated Veterinary Vaccines in Australia* (AQIS 1994);
and
(b) *Guidelines for Submissions to Import Veterinary Vaccines* (AQIS 1994)

4. *Australian Code of Good Manufacturing Practice for Veterinary Preparations* (SCA Report No 41. CSIRO)

5. *The Requirements Manual for Veterinary Chemicals* National Registration Authority for Agricultural and Veterinary Chemicals, Commonwealth of Australia (1996)

6. *Therapeutic Goods Order No 11 - Standards for Sterile Therapeutic Goods* Therapeutic Goods Administration, Commonwealth of Australia

7. *Therapeutic Goods Order No 21 - General Standards for Live Avian Viral Vaccines*. Therapeutic Goods Administration, Commonwealth of Australia (1986)

8. *Therapeutic Goods Order No 30 - Standards Adopted from BP (Vet) 1977, BP (Vet) 1985 and the British Veterinary Codex 1965 Supplement 1970.*

9. *Code of Federal Regulations* (9CFR Part 113) Animal and Plant Health Inspection Service, USDA

10. *European Pharmacopoeia* (1997)

11. *Animal Health Yearbook - FAO Animal Production and Health Series No 29.* World Health Organisation (WHO) -International Office of Epizootics (OIE)

12. *The Rules governing Medicinal Products in the European Union Vol VII - Guidelines for the Testing of Veterinary Medicinal Products* European Commission 1994

APPENDIX 1 - A Guide to the Specific Tests Required for Master Seeds and Other Raw Materials of Biological Origin *

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) guaranteed 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)*

4. Assurances of freedom from pathogens listed in Annex 2 (ie prions) must include a guaranteed 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 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.

· * 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. Testing of mammalian vaccines produced on SPF eggs for avian pathogens may be waived. 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.

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 prions 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 Foot and mouth disease 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 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 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