

Guideline 47

Data requirements and guidelines for registration of new veterinary immunobiological products

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1. INTRODUCTION

These requirements and guidelines describe the data requirements of an application to register a new immunobiological product, and the format in which dossiers should be presented in support of the application.

These requirements and guidelines should be read in conjunction with other guidelines on the APVMA website, <LINK> guidelines provided by overseas regulatory authorities and international pharmacopoeia. Those documents provide specific guidance on the conduct of various types of tests or trials that may be required to support an application for registration of a new immunobiological product.

The APVMA generally accepts data generated by tests which have been conducted according to monographs in the most recent editions of the European Pharmacopoeia, British Pharmacopoeia, US Pharmacopoeia and US Code of Federal Regulations (9CFR).

1.1. Definition of immunobiological products

Immunobiological products are products which, when administered to the host, provide, induce or change an immune response to a target chemical or biological entity.

Immunobiological products include vaccines, antisera and other immunobiologicals (eg antibodies and cytokines).

New immunobiological veterinary products are generally exempt from requirements for toxicological and OHS assessments except in the case of new adjuvants or other excipients of OHS concern. Aerosolised vaccines may require toxicological and OHS assessment.

Vaccines containing genetically modified organisms require evaluation by the Office of the Gene Technology Regulator (OGTR) and environmental assessment.

1.2. Autogenous vaccines

Autogenous vaccines are not covered by these requirements and guidelines because they are normally not registered and require issues of a permit for their manufacture, supply and use. Applicants for a permit to manufacture and supply autogenous vaccines should contact the APVMA for information on data requirements and guidelines for the manufacture of autogenous immunobiological products.

1.3. Imported biological constituents and the role of AQIS

Applicants must obtain an import permit from the Australian Quarantine and Inspection Service (AQIS) before the APVMA will register an imported immunobiological product or a product containing imported biological material. Applicants may apply simultaneously to AQIS for an import permit and to the APVMA for registration.

Issue of an AQIS permit for import of an immunobiological product or constituent does not automatically lead to APVMA registration of the product.

1.4. Expert reports

Applicants may provide expert reports if they consider that such reports may assist in interpretation of data and evaluation of the application. A brief resumé for each expert must be provided and their professional relationship to the applicant must be stated.

Applicants should refer to MORAG Volume 1 <LINK>for further information on how to submit an application.

2. DATA REQUIREMENTS AND GUIDELINES

This section sets out the data requirements and guidelines for data Parts 1 to 10.

Note that the information provided in this chapter is more specific to applications to register immunobiological products, than the information contained in MORAG Volume 3, '*Data requirements and guidelines*'.

Data must be provided for each of the elements described below. The APVMA may accept valid scientific argument that data need not be submitted for one or more of the data elements.

PART I APPLICATION FORM AND OVERVIEW

Application form

Part 1 of a veterinary chemical product application comprises the combined Application Form and Overview.

New immunobiological products will be evaluated under:

- Category 2 if the APVMA has not previously approved the active constituent
- Category 10 if the APVMA has previously approved the active constituent.

The application form can be accessed from the relevant category chapter in MORAG.

The APVMA will not accept applications for registration of immunobiological products under Categories 5, 6, 7 or 8 (the image categories) because immunobiological products cannot be considered to be similar to a reference product.

Overview

The purpose of the Overview section of the combined Application Form and Overview is to provide a brief outline of the application. The Overview is intended to lead reviewers through an application. The Overview may contain other general information on the product, and a summary of all data in the application.

Some parts of the Overview may not apply for new products based on existing approved active constituents. If an applicant considers that certain data are not required, a statement to that effect must be provided under the appropriate heading, together with scientific argument for not including the data.

The Executive Summary within the Overview must include the reasons for the application. For a new product this should include whether the product contains a new active constituent and scientific argument for registration of the product. The argument should outline the importance, prevalence and (if applicable) the regional distribution of the disease/pest/problem the product is intended to control, plus the economic and/or technical advantages of the product.

A summary of the detailed information on the product characteristics must also be provided. The information must include the immunobiological properties and the clinical particulars of the product.

Immunological properties

These are the diseases and/or conditions that the product is designed to treat, prevent or detect and the type of immune response and correlation with protection.

If the type of response has not been determined, a general summary of what is known about the infectious agent and the type of responses that are likely to be effective in conferring protection must be provided. Information on efficacy claims and the duration of immunity must also be provided.

Clinical particulars

These are target species, indications for use, contra-indications, undesirable effects (with reference to frequency and seriousness), precautions for use, dosage and method of administration, overdose, special warnings for each target species, major and minor incompatibilities (if appropriate), withholding periods, special precautions for the user/administrator of the product, first aid and safety directions.

Registration status overseas

Details of any known current or previous applications or approvals in other countries for products containing the same formulation must be provided in Part 1 of the application. If the product has previously been evaluated, full details of the outcome must be provided.

In all cases the details of any current or previous application or approvals for this formulation overseas must be provided. Full details of the overseas-approved use pattern (host species, claims, directions for use and withholding periods) must be provided, including any use restrictions.

Where available, overseas evaluation reports should be provided in the relevant Parts of the application.

A list of other relevant approvals and description of their relationship to the current application, eg approvals for other formulations containing the same active constituents, should be provided where they relate to the current application.

PART 2 CHEMISTRY AND MANUFACTURE

GMP status of the manufacturing facility

Applicants must provide evidence that the product is manufactured to a standard comparable with the Australian Code of Good Manufacturing Practice for Veterinary Preparations. For Australian manufacturers, compliance is by provision of an appropriate APVMA Manufacturer's Licence. For products manufactured overseas, applicants must supply evidence of compliance with good manufacturing practice (GMP):

- if manufacture takes place in a country with which Australia has a Mutual Recognition Agreement on Conformity Assessment with respect to veterinary chemical products, the evidence required is a current and acceptable certificate of GMP compliance issued by the competent authority (see http://www.apvma.gov.au/qa/EU_MRA_contacts.pdf).
- if manufacture takes place in another country whose GMP program is recognised by the APVMA, such as the USA, NZ and Canada, the evidence required is a current and acceptable certificate of GMP compliance, a licence and/or an audit report from a recognised authority.
 - in some instances, the APVMA will also recognise audit reports from competent authorities that are members of the Pharmaceutical Inspection Convention/Cooperation Scheme.
- if manufacture takes place in a country with which Australia does not have a Mutual Recognition Agreement, or whose regulatory program is not recognised by the APVMA, the acceptable evidence of GMP compliance might include:
 - a current and acceptable certificate of GMP from a regulatory authority recognised by the APVMA, which is based on a satisfactory audit by that authority
 - a satisfactory audit report by an auditor from a regulatory authority recognised by the APVMA, confirming that the premises comply with a GMP Code recognised by the APVMA as comparable to the relevant Australian GMP Code
 - a satisfactory audit report by an Australian APVMA-authorized GMP auditor, confirming that the premises comply with the Australian Code of GMP. All fees incurred for such an audit must be met by the registrant or the overseas manufacturer.

The preceding information on the APVMA Manufacturers' Licensing Scheme should be read in conjunction with the information available on the APVMA website at <http://www.apvma.gov.au/qa/mls.shtml>.

Formulation/composition of product

This information is best presented in a table:

- active constituent(s): maximum and minimum release titres and end of shelf-life titre must be provided
- adjuvant(s)
- excipients: including diluent, preservatives, stabilisers, emulsifiers, colouring matter, markers
- reference to standards where applicable
- function of each constituent
- quantity of each constituent in the formulation: this must be expressed in appropriate units (eg TCID₅₀, mL, mg etc).

Containers

The specifications for the immediate container and stoppers/closures (including acceptable tolerances) must be supplied.

The material used for the immediate container must be shown to be compatible with the type of product. The choice of material should take into consideration the potential for toxicity, because some materials are known to have the potential to leach and/or react with the product and produce substances which can be toxic to the target species.

The method of closure and opening must be specified.

Manufacturing process of the final product

A flow chart of the manufacturing process must be provided, showing each step from production of the active constituent to formulation of the final product in final containers, including any critical in-process control testing steps.

Applicants should also present a detailed description of each process step in the flow chart, eg amplification/culture, harvesting, purification, inactivation procedures, blending, adjuvanting, bulk antigen storage, filling, lyophilization, as relevant.

Production, control and testing of starting materials

Starting materials means all components used in the production of the veterinary immunobiological product. The EP, BP, USP or 9CFR requirements, where appropriate monographs exist, must apply to all substances in the product. References to other compendial standards will be considered on their merits.

Documentation from suppliers, such as certificates of analysis and/or raw material specifications, must be provided in an annex to this part of the application dossier.

Raw materials

Specifications and functions of all raw materials must be provided. If biological raw materials of animal origin are imported, the provision of an AQIS import permit and the manufacturer's specification will suffice.

Where appropriate, the applicant should indicate the methods used to determine that starting materials of biological origin are free from contaminants.

Materials from defined and reliable sources should be used. The specification should note the manufacturer(s) and origin of the raw material.

Starting materials listed in a pharmacopoeia

Applicants must provide:

- the name and code identifying the starting material
- title of monograph, year of publication, preferably together with a copy of the monograph
- certificate(s) of analysis.

Starting materials of non-biological origin, not listed in a pharmacopoeia

Applicants must provide:

- the name of each starting material (trade name, scientific synonyms)
- description and function
- material specification (identification and purity)
- controls and tests performed on the starting material and/or certificates of analysis.

Starting materials of biological origin not listed in a pharmacopoeia

Applicants must provide:

- the name(s) of the starting material (trade name, scientific synonyms)
- description and function of the starting material
- material specifications (identification and purity)
- controls and tests performed on the starting material and/or certificate(s) of analysis.

Evidence that imported biological materials of animal origin used in the manufacture of the master seed are free from agents which cause transmissible spongiform encephalopathies (TSEs) must be provided where applicable. Provision of a current AQIS import permit will suffice.

Genetically modified starting materials

Genetically modified organisms (GMOs) require a licence issued by the Office of the Gene Technology Regulator (OGTR; see <http://www.ogtr.gov.au/>) before the APVMA can consider the application.

For products based on biotechnology where genetic engineering occurred in Australia, applicants are advised to contact the OGTR before submitting an application to the APVMA. The following information is also required on all genetically engineered starting materials:

Source materials

- gene of interest, name, origin, isolation, sequence analysis

Construction of expression vector

- name, origin, replicon function, regulator elements
- genes for and method of selection
- mode of introduction into producer strain
- constitutive or controlled expression
- cloning and fusion (if relevant)

Description of producer strain or cell line

- name, origin, identification
- potential microbial and/or viral contaminants

Genetic stability

- construct stability
- stability up to and beyond the maximum passage level used for full-scale production
- occurrence of the vector inside the cell (extrachromosomal or integrated)
- copy number.

Master seed organism

Whenever possible, immunobiological production should be based on a seed lot system and on established cell banks. Each master seed lot must be assigned a specific code description for identification purposes.

For production of antisera and immunobiologicals where production is carried out in animals, the origin, general health and immune status of the producing animals must be verified. Defined pools of source materials must be used.

A record of the origin, date of isolation, storage conditions and passage history of all seed materials (eg cell, virus, bacteria, fungi, protozoa and rickettsias), including purification and characterisation procedures and substrates used, must be provided.

Characterisation of the micro-organism must include as a minimum:

- the genus and species
- strain/serotype.

Information on the biological characteristics of the master seed must include information on growth characteristics and environmental distribution.

Studies and tests carried out to demonstrate purity, identity, target animal safety/pathogenicity, and target animal immunogenicity of the master seed lot must be provided. A brief description should be provided of the methods of identifying each strain by biochemical, serological and morphological characteristics and distinguishing it as far as possible from related strains. The method of determining the purity of the strain must be described.

Applicants must also demonstrate that the master seed is free from extraneous agents. Tests to demonstrate that the master seed lot is pure and free from extraneous agents must be performed as per EP, BP, USP or 9CFR, where monographs exist. For live attenuated immunobiological products, proof of the genetic and phenotypic stability of the attenuation characteristics of the seed must be provided.

The minimum and maximum number of passage levels from master seed to production level must be specified and should not exceed five unless justified by data. The methods, substrates used, testing and storage of seed lots and seed passages must be specified and appropriately documented.

The applicant must demonstrate that the characteristics of the seed material (eg dissociation or antigenicity) are not changed by these subcultures. The conditions under which each seed lot is stored must be documented.

A release specification of the master seed organism must be provided.

Working seed organism

The method of preparation and description of the working seed lot must be provided. Description must include the range of passage levels to be used for production, controls applied, tests carried out on working seed lot and storage conditions.

A release specification for the working seed organism must be provided.

Cell substrate/production medium

There are essentially three classes of cell substrate/production medium:

- live animal culture, eg specific pathogen-free (SPF) eggs, chickens, cattle
- tissue culture (continuous cell lines or primary cells)
- microbiological media.

If cell substrate/production medium consists of SPF eggs, primary SPF chicken cells or SPF chickens, compliance with EP/BP/9CFR must be demonstrated. The following information must also be provided:

- the source of SPF eggs or chickens or other animals
- SPF status of source flock/herd
- history
- test monitoring procedures and specification
- Disease prevention protocols, eg isolation, vaccination.
- Disease/agent monitoring procedures and testing specification

If cell substrate/production medium consists of tissue culture substrates (continuous cell lines), the following information must be provided:

- source of the master cell seed
- treatment of the master cell seed since origin
- seed lot system
- designation/identification of master cell seed
- master cell seed testing method and results to demonstrate sterility, freedom from extraneous agents and freedom from specific adventitious virus contamination including Type C in particular
 - agents covered by the tests applied must be specified. Particular attention must be given to the potential for contamination with bluetongue, pestivirus, porcine parvovirus, rabies virus, and prion agents of transmissible spongiform encephalopathies
- AQIS import permit where appropriate
- proof of freedom from Mycoplasma (where applicable)
- evidence that master cell seed tests comply with EP, BP USP or 9CFR (where applicable).

If the cell substrate/production medium consists of microbiological media the following information must be provided:

- name of the medium and composition
- raw material specifications including any tests required for freedom from specific agents such as pestivirus, prion agents of transmissible spongiform encephalopathies
- AQIS import permits where appropriate
- method of preparation and sterilisation should be described under the heading Media Preparation.

Other types of products for which guidelines are yet to be developed include products produced in animals or plants by chemical synthesis (chemical conjugates) and those produced by other methods (eg nematodes). In all cases full details of the cell substrate/production medium must be provided.

Media preparation

The methods of preparation and sterilisation of all media used in such a way that they become ingredients of the product must be provided in detail, including the controls applied, the testing carried out and the certificates of analysis of ready-to-use media.

In-process control tests during production

All critical analytical test procedures must be described in sufficient detail to enable the procedures to be assessed. Procedures must be validated where appropriate and the results of validation studies on all key procedures as identified by the manufacturer must be provided.

Where applicable, current pharmacopoeial monographs must be used. Copies of the pharmacopoeial monographs, specifications and certificates should be given in an annexe to this part of the application dossier.

With a view to verifying the consistency of the production process and the final product, a flowchart of the production process showing the stages at which critical in-process control tests are carried out should be provided. This may be cross-referenced to the section headed 'Manufacturing process of the final product' on page 6, if the flowchart is provided there.

Applicants must provide information on critical tests performed for each control stage, as follows:

- title and company test code
- timing and frequency
- function of test
- a brief description of the test (a more detailed description should be given as an annexe to Part 2 with details and results of the validation studies as appropriate). The detailed description should contain sufficient information to enable the APVMA to assess the adequacy of the test method and (if applicable) whether it is consistent with the cited monograph. A copy of the test procedure document may be provided as the detailed description, but this is not compulsory.

Only details of tests which are considered critical to allow the manufacturing process to continue to the next stage should be provided. The APVMA reserves the right to request additional information.

The assay methodology for detoxified or inactivated immunobiological products must be provided in detail and the limit of detection specified. This may be cross-referenced to the section headed 'Manufacturing process of the final product on page 6' if the assay methodology is provided there.

Each pilot production batch must be shown to have been appropriately detoxified or inactivated using relevant test standards wherever available. Kinetics of inactivation or detoxification must be provided.

Control tests on the final product

Detailed information on final product tests performed on each batch, including the batch release specification, must be provided. This should include as appropriate:

- identification assay for active ingredients
- identification assay for adjuvants
- sterility
- moisture (as required)
- safety when required
- extraneous agents including Mycoplasmas.

For each test, applicants must provide information on:

- title and company test code (specify monographs where appropriate)
- timing and frequency
- function of the test
- brief description of the test. (A detailed description should be given as an annexe to Part 2 with details and results of the validation studies where appropriate. The detailed description should contain sufficient information to enable the APVMA to assess the adequacy of the test method and (if applicable) whether it is consistent with the cited monograph. A copy of the test procedure document may be provided as the detailed description, but this is not compulsory)
- The fate of material that has failed the test (eg any re-test provisions)

The batch release specification must indicate the following:

- provision for identification of the batch undergoing test and the test date
- the name of each test
- the company test code
- limits of acceptance of results.

Summary of test results from two consecutive pre-registration batches

A summary of results of tests on at least two preferably consecutive batches of finished product must be provided to support the application for registration of the product. These batches may be pilot or production batches. If they are pilot batches, they must be representative of production batches.

Stability of the finished product

The storage shelf-lives of conventional vaccine products may vary from days to several years, therefore it is difficult to provide uniform guidelines regarding the stability study duration and testing frequency that would apply to all types of conventional vaccine products. However, with only a few exceptions, the shelf-lives for existing products and potential future products will be within the range of six months to five years. Therefore, this guidance is based upon expected shelf-lives in that range.

When shelf-lives of less than one year are expected, real-time/real-temperature stability studies should be conducted approximately monthly during the first three months and at three-month intervals thereafter, so as to generate multiple measurements (a minimum of five tests three months apart) for the purpose of assessment.

For products with expected shelf-lives of greater than one year, the studies should be conducted every three to four months during the first year of storage, every six months during the second year, and annually thereafter.

While the testing intervals described above are appropriate in the pre-registration stage, reduced testing may be appropriate after approval or licensing/registration where data are available that suggest adequate stability.

While not mandatory, stability testing (at least potency/titre) should be conducted to three months past the claimed shelf-life.

A summary of the proposed shelf-life, storage conditions and justification for the proposed shelf-life must be provided. Real-time studies must be carried out on the final finished product in the marketed container. If there are insufficient real-time stability data to support the proposed shelf-life of the product, a stability testing protocol and timetable for testing the product must be provided with the application dossier.

Applicants may refer to the VICH Guidelines for Stability Testing of Biotechnological/Biological Veterinary Medicinal Products on the APVMA website at <http://www.apvma.gov.au/guidelines/vich59.shtml>.

Information must be supplied for at least three batches as follows:

- a description of the product packaging during testing
- a description of storage conditions (eg temperature ranges)
- a brief description of each test (a detailed description to be given as an annexe to Part 2, if this information has not been provided earlier). The tests should include (as appropriate) physical, chemical, biological and microbiological aspects of the product, and should indicate those tests claimed to be critical stability indicating measures
- for multi-dose, not-for-immediate-use formulations, preservative efficacy testing must be conducted to validate inclusion of the preservative chosen. The tests should be consistent with those indicated on the batch release specification. A test for sterility and safety (where included on the batch release specification) must be conducted at the final time-point of the stability test protocol
- a table of results with batch number, date of manufacture, dates of testing and storage conditions.

The results of the stability testing must be consistent with and confirm the minimum release titre and end-of-shelf-life specifications for the product.

For inactivated multi-dose, not-for-immediate-use products which may or may not require reconstitution or dilution before use, stability data will be required to support the recommended storage time and conditions after broaching, if not used within 12 hours (clostridial immunobiologicals may be used within 36 hours).

For live multi-dose, not-for-immediate-use products which may or may not require reconstitution or dilution before use, stability data will be required to support the recommended storage time and conditions after broaching.

The APVMA may request additional data for products containing one or more ingredients which are recognised to be inherently unstable. Where reference is made to BP, EP, USP or 9CFR for a shelf-life exceeding 12 hours, provision of adequate data or argument may be acceptable.

Information must be provided on the effect of external influences, such as sunlight and heat, on the stability of the product when in use.

Each antigen or active ingredient in a combination immunobiological must be tested. Stability data for a multivalent formulation may be extrapolated to formulations of lower valency provided that the quantity of each antigen, adjuvant and excipients of each combination immunobiological under consideration are approximately identical, and providing that the market packaging and recommended storage conditions are also identical. Variation in any of these parameters will require the generation of separate stability data for each formulation.

Single-dose/single-application products requiring reconstitution or dilution will require data to support the proposed shelf-life for the reconstituted product, if not used within 30 minutes of reconstitution.

PART 3 TOXICOLOGY

Toxicity data are not normally required for veterinary immunobiological products but may be required where a novel active constituent, novel adjuvants and or excipients are used.

Data will be required for assessment by the Office of Chemical Safety if Poisons Schedule classification is necessary.

PART 4 METABOLISM AND KINETICS

See Part 5A.

PART 5 RESIDUES AND TRADE

Part 5A: Residues

Residues data are not normally required for veterinary immunobiological products, but may be required in some circumstances where novel adjuvants and/or excipients are used in vaccines administered to food-producing animals.

Applicants must consider the possibility of any residues remaining in food. Precise identification of the substance or product concerned must be provided. This includes:

- International Non-proprietary Name (INN)
- International Union of Pure and Applied Chemistry (IUPAC) name
- Chemical Abstract Service (CAS) name and number
- classification (therapeutic, pharmacological)
- synonyms
- material safety data sheet
- other relevant information.

For most immunobiological products, the establishment of a withholding period is relevant only with respect to a product which contains live zoonotic organisms, novel adjuvants, and preservatives. Justification for a nil withholding period must be provided.

In consideration of implications for trade and where a persistent local tissue reaction may occur following injection, the APVMA may also require that a withholding period or carcase disposal statement be included on the label.

Part 5B: Trade

If the immunobiological product is used in food-producing animals, the applicant must comment on the potential of the product to affect trade. Trade issues relating to the use of genetically modified organisms must also be addressed.

The potential for an immunobiological product to mask or interfere with diagnosis or monitoring of outbreaks of the disease against which it is directed must also be addressed, as should any implications of its use in maintenance of Australia's specific disease-free status.

Immunobiological products containing antigenic components for diseases which are not known to occur in Australia not only have the potential to mask or interfere with diagnosis in the case of an outbreak of that disease, but may also severely compromise Australia's disease-free status. Therefore, this type of product will not usually be granted registration.

PART 6 OCCUPATIONAL HEALTH AND SAFETY

Potential occupational health and safety risks associated with the manufacture and use of the product must be addressed in the application. This may include any or all of:

- safety instructions
- use of personal protective equipment
- first aid instructions
- information for medical practitioners.

PART 7 ENVIRONMENT

Information must be provided on the extent of exposure of the product, its active constituents or relevant metabolites to the environment, and proposed disposal methods for unused or waste product.

PART 8 EFFICACY AND TARGET ANIMAL SAFETY

Introduction

Efficacy of a vaccine means induction of immunity to provide protection against a specified disease. The nature, degree, onset and duration of immunity are the main parameters of the protection. The APVMA requires all claims for the efficacy of vaccines, including the duration of protection and the administration schedules to be fully supported by data from specific laboratory trials and field studies.

In the first instance, the efficacy and safety of veterinary vaccines will normally be demonstrated by experiments under laboratory conditions. All laboratory/pen and field trials must be precisely described. Unless otherwise justified, the results from laboratory/pen trials should be supplemented with data from field/clinical trials measuring clinical end points. Under some circumstances, such as where an acceptable laboratory challenge model is not available, field efficacy trials alone may be acceptable.

Efficacy data generated in Australia are required for the registration of all immunobiological products intended for use in food-producing animal species, unless the applicant can provide strong scientific argument that overseas data are applicable to Australia's climatic conditions, genetic stocks and farm management practices.

The acceptance of such argument will be at the discretion of the APVMA.

Australian efficacy data may also be required for non-food-producing animals where it is necessary to confirm efficacy because of any potential for differences in the strain types and virulence of disease-causing micro-organisms.

There are two main reasons for conducting field trials on veterinary vaccines:

- (i) confirmation that the efficacy and safety of a product demonstrated in laboratory studies is reflected in field conditions and on a large scale
- (ii) investigation of aspects of efficacy that cannot be studied sufficiently well in the target animals under laboratory conditions. Examples of this are:
 - diseases where a suitable experimental infection model does not exist
 - diseases with more than one causal agent
 - cases where special husbandry facilities are involved (eg drinking water vaccines for poultry, water qualities and temperatures for fish vaccines)
 - diseases where environmental factors play a major role in the aetiology.

Requirements for efficacy and safety data

The number of animals and/or groups used in a trial must be sufficient to enable the trial results to be evaluated for statistical significance.

In general the animals to be used must be susceptible to the disease(s) against which the vaccine is being evaluated. Where available, and if appropriate to the study, SPF animals should be used.

The effect of factors such as age, bodyweight, gender and maternal antibodies must be addressed in the trial design and analysis of results.

The product used in the trial must have a titre which is the end-of-shelf-life titre or lower, under the recommended conditions of use.

For immunobiological products which contain GMOs, applicants should consult the OGTR before the trial begins, irrespective of whether the trial would be conducted under contained conditions or in the field.

Clinical trials/field trials must be conducted in a manner consistent with the principles of good clinical practice (GCP). Advice on trial protocols may be sought from the APVMA by lodging an application under [Category 25](#) for evaluation of a trial protocol.

If Australian data are to be generated through field trials, such trials must be conducted under a research permit issued under [Category 23](#) or the APVMA small trial permit PER 7250 which may be seen on the APVMA website at <http://permits.apvma.gov.au/PER7250.PDF>

The following trials are normally required to generate data in support of efficacy and safety claims:

1. Pen/laboratory trials

Efficacy trials

- establishment of minimum protective dose and vaccination schedule
- confirmation of protection against challenge in each target species and representatives of each class of target animal.
- influence of passively acquired and/or maternally derived antibodies on efficacy, if appropriate.
- onset of immunity
- duration of protection
- timing of, and response to, booster vaccination
- compatibility with other treatments (vaccines) administered within seven days of administering the product under evaluation.

Safety studies

- single dose studies
- repeat single dose studies (where applicable)
- overdose studies (10× for live vaccines, 2× for inactivated vaccines)
- immunological effects
- reproductive effects (where appropriate)
- compatibility with other known products administered within seven days of administering the product under evaluation.

For live vaccines also include:

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

It would be preferable to undertake the above studies under controlled laboratory conditions. However, where a suitable laboratory challenge model or marker of protection is not available, or for other justifiable reasons, reliance may need to be placed on large scale well planned field trials for some or all of these studies. Field trials will usually supplement the data generated from laboratory studies.

2. Clinical/ field trials

Field trials can serve two purposes.

- i) they can be used to demonstrate safety and efficacy of commercially-produced batches of vaccine where safety and efficacy have been determined by pen studies (using product at the end-of-shelf-life titre or lower under the recommended conditions of use)
- ii) they can be used as a method of determining safety and/or efficacy of a product where it is not possible or practical to undertake appropriate pen studies. In this case field efficacy studies should be undertaken using product at the end-of-shelf-life titre or lower under the recommended conditions of use. Field safety studies should be undertaken using product at the maximum release titre.

Efficacy and safety trials

The trials must:

- use the recommended dose and vaccination schedule as per proposed label instructions, using product which is at, or close to, the proposed end of shelf-life titre
- use representative batches manufactured using procedures outlined in the dossier
- replicate the proposed major uses of the product (route, method, administration schedule, target species including the most sensitive class or members of the target species)
- for animals kept under extensive or pastoral conditions, use a minimum of three sites, encompassing different husbandry practices and environments
- for intensively-reared animals, a minimum of two sites will suffice.

The dossier must document any adverse reactions.

These studies must be well-planned, controlled, monitored, and carried out under conditions where endemic disease is known to occur and challenge rates would be expected to mimic those seen commonly in the field.

All techniques involved should be fully described and validated where necessary. All results, whether favourable or not must be reported and statistical analysis, if appropriate to a particular study, must also be presented.

Discussion and conclusions

Detailed discussion and conclusions must be provided, based on the results of the pen/laboratory studies and clinical/field trials.

Animal welfare

Special care should be taken with the trial protocol in order to respect the welfare of animals used in the trials.

The applicant must obtain the approval of a properly constituted animal ethics committee prior to the commencement of any trial conducted in Australia. If the applicant has not yet received such approval, the applicant must state in the APVMA application when approval is expected. The approval must be submitted to the APVMA before the trial begins. More information on research permits is available in MORAG under [Category 23](#) and APVMA PER 7250.

Guidelines for trials to generate efficacy and safety data

Parameters of efficacy trials

The parameters to be measured in efficacy trials must be clearly defined in the study protocol and justified in relation to the indications and specific claims for the vaccine. Conversely, justification should be given for not measuring parameters that are usually related to the disease concerned.

Three types of parameters exist:

- i) clinical parameters (eg mortality, morbidity, lesions, weight gain, epizootiological impact)
- ii) indicators of immune response to vaccination (eg serological response). For an indicator to be acceptable as a correlate of vaccine efficacy, it should be shown that a sufficient qualitative and quantitative correlation exists between the indicator measured and the claimed protection in the target species. Where claims are made for a specific age, breed, category or class of animal, supporting data must be provided
- iii) indicators of infection (eg viraemia, organism shedding) or transmission (eg serological response).

For an indicator to be acceptable as a correlate of vaccine efficacy, it should be shown that a sufficient qualitative and/or quantitative correlation exists between the indicator measured and the claimed protection in the target species. Where claims are made for a specific age, breed, category or class of animal, supporting data must be provided.

If they are relevant and available, test methods should be used that can differentiate naturally infected from vaccinated animals.

Controls and trial design

Unless otherwise justified, the efficacy trial should compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo-vaccinated controls.

In some circumstances, unvaccinated or placebo-vaccinated groups cannot be used, for management, animal welfare or other reasons. In such circumstances, the reasons should be explained and comparison with animals vaccinated with a reference product may be used if available.

For modified live vaccines whose vaccine agent(s) may potentially spread, it may be necessary to separate vaccinates from controls. In such cases, separate housing of the two groups would be justified.

The selection and utilisation of the controls must be justified. It is necessary to define in the study protocol what purpose the control group serves. This may include:

- evidence that exposure to infection took place (unvaccinated controls)
- evidence of the test product's efficacy in comparison with a registered reference product with the same indications for use (reference product as control)
 - provide evidence that exposure to infection took place

- historical comparison (where whole herd or whole flock vaccination is required and comparisons are with historic data on the same site)
 - provide evidence that exposure to infection took place.

For such comparisons to be valid:

- with the exception of historical comparisons, the controls and vaccinated animals should be of a similar age, sex and weight, and preferably be investigated at the same time
- the experimental animals should be allocated at random to their groups. Where whole herds or flocks are to be compared, they should be matched as closely as possible according to a set of characters defined in the trial protocol
- the environment in which the two groups of animals are housed or otherwise managed should be as equivalent as possible (ie same farm/barn/batch) or at least as similar as possible (eg same farm/different barn/same batch).

The challenge infection or exposure should be as similar as possible in the two groups of animals. This will not be the case if cohorts consist exclusively of vaccinated animals or controls. In this case, replicates of the trials under the same or matched conditions may be necessary, using randomised groups or a number of different sites. The implications for the incidence of infection (infection rate) of running vaccinated and unvaccinated controls together should be considered when designing a trial.

The use of historical data for control purposes may be acceptable but where such data are used, they should have been shown to be well documented and consistent over a representative length of time. Use of historical data usually requires trials to be undertaken on a number of sites.

When investigating a combined vaccine, the control group may comprise animals vaccinated with a product formulated to contain all the components of the vaccine except the component under study. Data must be submitted to support efficacy of each component in the multivalent/combined vaccines for which registration is sought. The data must be generated using the formulation or particular combination for which registration is sought.

Ideally, the trials should be double blind, placebo-controlled, but this is often difficult to achieve in practice.

The need for placebo controls depends on the study plan. If the parameter to be measured is a subjective one (eg coughing), the trial should be conducted in a blind manner and either placebo controls should be included, or the person who measures this parameter should have no information on the details of the vaccination.

Establishment of the minimum protective dose and vaccination schedule

This can be undertaken as a dose-response study or as a study to confirm that the chosen dose and vaccination schedule is efficacious in the target species. From this study the end of shelf-life titre may be established. Allowance may need to be given for assay variation in setting the end of shelf-life from the minimum protective dose.

The method for determining the minimum protective dose must be justified, particularly if a suitable laboratory challenge model or serological (or other) marker of protection is not available. It may be appropriate to use a pharmacopoeial ‘standard’ recommendation where that ‘standard’ has a long history of satisfactory use.

Efficacy of each component of a combination vaccine must be demonstrated following inoculation of the combination vaccine rather than from an evaluation of each component as a monovalent product. The potential for interference between the components must be evaluated, unless valid scientific argument is presented.

Field efficacy trials

Field trials must follow a study plan (trial protocol) which has been prepared before commencement of the trials. Any variations to the study plan must be documented and justified.

Field trials should include statistically significant numbers of animals to enable the results to be appropriately analysed. Wherever possible, field trials should be carried out on a number of sites to ensure the evaluation covers representative animal houses/husbandry practices and environmental (geographical) differences.

Field trials must at least cover the proposed major uses of the vaccine. The vaccine must be administered by the route, method and vaccination schedule which will be recommended on the product label, and in the most relevant category of target species (age, weight, sex etc.).

The vaccine dose used must be at antigen levels equivalent to, or lower than those expected at the end of the product’s shelf-life. The vaccine used in the trial must be taken from a batch or batches manufactured according to procedures described in the application for registration. The formulation of the product submitted for registration approval must be identical to that used in the efficacy trials.

Applicants should note that the data generated from a field efficacy trial should support the proposed expiry or end-of-shelf-life titre and may form the basis for establishing the expiry titre or potency for the product in the absence of relevant laboratory data.

The antigen component of the product may be diluted to achieve an ‘expiry titre or potency’ for the study. A complete description of the dilution process should be provided. The titre or potency of the batches used for the trials must be clearly specified. All adjuvants and excipients should be present in the same concentrations as in the proposed formulation

Whenever possible, the field trial should include the challenge of animals which have been vaccinated using the vaccine under investigation, by exposure to natural infection. However, it is recognised that a natural infection can neither be predicted nor standardised. It may not appear at the appropriate time and may be too weak or too low

in incidence; in the case of multivalent vaccine testing, not all natural challenges may occur in the study timeframe.

In a field trial where productivity data are required to establish safety or efficacy (but not necessarily to make a claim for productivity gains) it may be necessary to include large numbers of animals to obtain significant differences in some of the productivity parameters. In some intensive industries, whole sheds of animals may need to be replicated to obtain significant differences.

Reference product

The reference product and the vaccine under study must have the same efficacy claims. The level of efficacy of the reference product should be established by using a product currently registered in Australia.

When the vaccine under study is being compared with a reference product, a group of controls should be included whenever possible to establish exposure to infection. Even if this is not possible, sufficient evidence should be presented that both products have a demonstrable beneficial effect rather than just comparing the results of the two groups of animals.

Exposure to infection

The trial results should supply clear evidence that the vaccinated animals and control animals have been exposed to the pathogen of interest. In principle, the level and timing of exposure should be the same in both groups of animals, but this may be difficult to achieve under field conditions.

Observations of signs of disease are rarely sufficient by themselves and wherever possible, clinical records should be supported by laboratory tests. In principle, the agent itself should be detected and identified.

In the case of live vaccines, whenever possible the isolated field strains should be differentiated from the vaccine strains. Depending on the agent and disease concerned, serology performed on a statistically significant number of animals may indicate exposure to infection. The serological method used must be validated and in general, be the same as used in the laboratory trials.

The cause of any deaths or unexpected signs of disease related to the parameters being measured must be determined, unless otherwise justified. With poultry vaccines, standard poultry company procedures for diagnosis may be used to determine the cause of death.

If field challenge does not occur, there may be justification for challenging some of the vaccinated animals and controls under laboratory conditions to determine the level of protection achieved by field vaccination.

Intercurrent infections

The potential for infection with intercurrent agents other than those under study should be considered in the trial design. Such infections may influence the parameters being measured and thus affect the outcome of the trial. In some circumstances their impact on the interpretation of trial results may be reduced considerably if vaccinated and control animals can be investigated at the same time and allocation of both groups of animals has been made at random.

Pre-existing antibodies

Pre-existing antibodies against the vaccine agents may be maternally derived, or be due to infection or vaccination.

If the indication or specific claims for the vaccine are related to efficacy in the presence of maternal antibodies, the trial protocol must include vaccination of animals with maternal antibody titres at the age of vaccination that normally occurs in the field.

Where pre-existing antibodies due to previous exposure to the agent being studied or a related agent are present, the trial may be acceptable if the immunological status of the vaccinated animals and controls at the time of vaccination is known, and a justification for their use is given. Unless justification can be provided, field trials must not be carried out in animals that have been previously vaccinated with products containing the same active substances as the vaccine under study.

Interactions with other products

If a product is recommended for administration in combination with or at the same time as another veterinary chemical product including a vaccine, compatibility, efficacy and safety must be demonstrated. Any known interactions with other products must be declared.

Analysis and interpretation of field trial data

All relevant field trial data must be included in the dossier. Only data of valid field trials may support an application. All relevant details should be given of any incomplete or abandoned test or trial.

Reports of relevant individual field trials (including incomplete or abandoned trials) or trials at different geographic locations should be provided as individual study reports. Large, combined reports are more complex to navigate during the evaluation process. Also, individual reports make it easier for the reviewer to identify data not relied upon (eg incomplete trials) for data protection.

The analysis of field efficacy trial data must be related to the indication and specific claims made for the vaccine and the parameters measured. The analysis of field safety trial data must be related to the recommendations for the administration of the vaccine, ie the vaccine must be shown to be safe under the recommended pattern of use.

Careful consideration should especially be given to:

- the study plan
- the plan for analysis
- evaluation of the data
- the method of statistical evaluation
- randomisation of the various groups of animals
- the use of blinding in the study method
- the number of animals required, including eventual losses during the trial.

In the case of efficacy as judged by serology, the titres achieved in vaccinated animals used in field trials should not be significantly lower than those achieved in the laboratory trials.

In the case of a marker vaccine, special attention should be paid to properties of the marker.

Duration of protection

The duration of protection is the longest interval between the administration of a vaccine to target animals and loss of protection against challenge. The level of protection against challenge should be consistent with the label claim for the entire nominated duration of protection or revaccination interval.

The studies required to generate these data should be conducted under well-controlled conditions. If the necessary studies are very difficult to conduct under laboratory conditions, field trials only may be carried out. Since the duration of protection given by vaccination is being measured in the studies, the vaccinated target animals should not be exposed to intercurrent field infection which could boost natural immunity. For this reason it is usually necessary to maintain unvaccinated target animals in contact to act as sentinels in laboratory or field studies.

The results from vaccination-challenge trials conducted under laboratory conditions may be supplemented with data from well-controlled field studies. In field studies, target animals may be vaccinated in the field and undergo a natural challenge in the field or an experimental challenge under laboratory conditions.

The duration of protection achieved by vaccines is influenced by a number of factors such as:

- the characteristics of the causal agents of the disease
- the epizootiology of the infection
- the immunogenicity of the vaccines' active substances
- the nature of the target animals' immune response.

The duration of protection may be different for each category of vaccine and for the products within a category of vaccines, as a consequence of the particular properties of the products concerned.

In addition, the apparent duration of protection achieved under field conditions may not be consistent and may vary from that achievable under laboratory conditions because of a number of factors, such as episodic or occasional exposure to the infectious agent(s) and health condition and immunological status of the animals to be vaccinated.

In order to reduce the frequency of vaccination, it is recommended that wherever possible, studies demonstrate the actual duration of protection provided (ie end point studies). The duration of immunity to each antigen in a multivalent vaccine should be determined.

In some cases, one administration of a vaccine will provide protection for the natural or economical life of the vaccinated animals. In other cases a primary vaccination course (usually two administrations) is required with a follow-up or booster vaccination.

Where the primary vaccination course involves more than one administration and/or a follow-up or booster vaccination is required, the level of protection afforded between administrations should be assessed.

Where there is no recommendation for more than one administration of a vaccine or for only a primary vaccination course, this implies life-long protection. As the natural or economic life span of animals differs between species, and between categories of animals within a species, the claimed duration of protection should be specified and supported by adequate data.

In cases of seasonal diseases, it may be sufficient to demonstrate the duration of protection in the year after vaccination until the end of the natural occurrence of the disease, provided that the vaccination is undertaken at the appropriate time in respect of anticipated disease occurrence. Persistence of protection in subsequent years, with or without revaccination, should be addressed.

It is not possible to generalise about the minimum period for which a vaccine should be expected to provide protection. However, in all cases the duration of protection must be relevant to the length of time during which an animal is likely to be at risk.

Duration of protection from the primary vaccination schedule

Active immunity

The duration of protection provided by the primary vaccination schedule should usually be demonstrated by a challenge of vaccinated animals just before the recommended time for the start of re-vaccination. In some circumstances (eg animal welfare grounds, scientific justification) where there is a strong correlation between a marker (such as serological response) and protection, evidence of protection from the marker alone may be acceptable.

Passive immunity in progeny

Data must be presented to support the duration of passive protection that is claimed for progeny from vaccinated parents. The duration of immunity should usually be demonstrated by challenging the progeny at the end of their claimed period of protection. In some circumstances (eg animal welfare, scientific justification), where there is a strong correlation between a marker such as antibody level and protection, evidence of protection from the marker alone may be acceptable.

Duration of protection from the re-vaccination schedule

The response to revaccination is best demonstrated by challenge trials at suitable times between the end of the schedule and the end of the claimed period of protection. In some circumstances (eg animal welfare grounds, scientific justification) where there is a strong correlation between a marker (such as antibody levels) and protection, evidence of protection from the marker alone may be acceptable.

For an indicator to be acceptable, evidence must be provided to show that the indicator plays a substantial role in the protection of the target species and that there is a sufficient qualitative and quantitative relationship between the indicator and the target species' protection against the disease concerned.

Applicants must demonstrate via serological studies or other markers of protection that the level of response before revaccination or at the end of the protection period is consistent with the efficacy claims made for the product.

The data generated for a multivalent vaccine may be used to support the protection claimed for a vaccine containing fewer active constituents, provided the latter vaccine is manufactured according to the same process, has the same composition (with the exception of the deleted antigens) and there is no evidence of a negative or positive interference from the other active ingredients present in the multivalent vaccine.

Immunobiological product safety trials

Safety trials must be conducted in the most sensitive class or members of the target species with the dosage that is recommended for use and preferably with the maximal titre or potency for which the application is made.

For live vaccines, the vaccine agents should be at the lowest attenuated passage level that will be present in the vaccine to be registered. Applicants should note that the titre or potency of the batches used for safety testing, particularly the overdose studies, will form the basis for establishing the maximum release titre or potency for batch release.

The vaccine used for testing should be taken from a batch or batches produced according to the manufacturing process as described in the dossier. Once the maximum release titre has been established, the APVMA will not accept release of product batches with a higher titre or potency, unless results of additional safety testing at the higher titre or potency are provided.

Potential risks versus potential benefits from the use of the product must be stated. If the product contains live organisms, especially organisms which could be shed by vaccinated animals, the potential risks to unvaccinated animals, whether the same species or any other potentially exposed species, should be evaluated. Reference should be made to BP, EP or 9CFR/USP monographs where they exist.

Laboratory tests

For each test, applicants must specify the title of the test with reference number, names of collaborators in the study, introduction and objective of the test or study, reference to the relevant EP, BP or 9CFR/USP monographs, dates of start and end of the study (at least 14 days observation or as specified in the monograph) and a summary of study materials and methods, results, assessment criteria (eg systemic and local reactions, rectal temperature, growth performance), discussion and conclusions.

Tests should be repeated using each recommended route of administration. The titre or potency of the batches used for testing must be clearly specified.

The trial should normally compare a group of vaccinated animals with an equivalent group of unvaccinated or placebo controls. The choice of the controls must be justified. The control group must comprise animals against which the vaccinated animals can validly be compared.

Any adverse systemic and/or local reactions must be described in detail. Observation records for each animal should be provided as an annexe to the study report.

Field/single dose effect

Each animal species and category, including animals of the minimum age at which the product is to be used, must be tested with a single dose taken from either a pilot or production batch. Unless for use in a single geographical region only, testing should be carried out on two significantly different geographical sites if geography may impact on product safety.

Adverse systemic and/or local reactions must be documented. Where appropriate, macroscopic and microscopic examination of the injection site should be carried out to determine if a recorded abscess is aseptic or secondary to a skin or product contaminant.

The safety studies should in the first instance verify the safety of the vaccine under field conditions after one administration of one dose of vaccine as well as after repeated administrations, depending on usage recommendations.

The single dose should also be used to investigate the possible systemic side-effects of vaccination with the product. Examples of systemic effects include allergic reactions, mortality, anorexia, pyrexia, changes in behaviour, weight gain, feed conversion, carcass quality, milk/wool/fur production, egg production and hatchability of breeding eggs, and male and female fertility.

In the case of live vaccines, the behaviour of the vaccine agents in animal populations should be documented. In terms of local reactions, the size, duration and nature of any lesions appearing at the sites of injection must be monitored and recorded.

Repeat administration of a single dose

This may be required to reveal any adverse events induced by repeated administration. The timing of repeat administration of a single dose should be determined by the applicant but the interval between repeated administrations must not be longer than that recommended for field use. This test would not be required where the product is administered only once in a lifetime.

Overdose effects

Overdose safety assessment of inactivated and non-pathogenic live vaccines will not normally be required. Unless otherwise advised by the APVMA, overdose testing is required for live vaccines shown to retain residual pathogenicity (as defined in the glossary). Using the recommended dose based upon the maximum release titre, an overdose is usually 2× for inactivated vaccines or 10× for live vaccines, unless otherwise specified in the EP, BP or 9CFR/USP.

Both overdose and repeat administration studies should be carried out using the most sensitive classes or categories of the target species. Testing may be carried out as follows:

- rectal temperature monitoring for one to two days before vaccination, four hours after vaccination and thereafter twice daily through to four days (96 hours). If there is no evidence of rising temperatures, monitoring may then be discontinued. Body temperature measurement is not required for birds
- monitoring for signs of systemic or local site reaction through to 14 days unless otherwise stated in the EP, BP or 9CFR/USP monographs for specific immunobiologicals. Performance monitoring, including appetite and general disposition, should be carried out daily
- examination of injection sites at regular intervals during the 24 to 96 hours after administration (time intervals should be justified by the nature of the product under investigation). If significant lesions are still present at the end of 96 hours, observation should continue daily until lesions have subsided to an insignificant level
- careful examination of the administration site for signs of inflammation by inspection and palpation. The dimensions of palpable lesions should be recorded. The injection site should be checked on the final day of clinical observation and again at the time of slaughter, as appropriate.

Abnormalities detected in the above tests should (where possible) be thoroughly investigated to assess the likely incidence, aetiology or sequelae.

Reproductive performance

Examination of reproductive performance of breeding animals must be considered when data or scientific argument suggest that the starting material from which the vaccine is derived may be a risk factor. Laboratory safety studies are required unless an exclusion statement is included on the label. eg use in pregnant females/breeding males is not recommended or safety in pregnant females/breeding males has not been determined. These studies should involve at least one dose per test animal of a representative pilot or production batch, at least eight test animals and last for at least 14 days. The observation period will depend on the nature of the vaccine under test and may have to extend to beyond parturition.

In assessing the need for testing in future breeding animals, the potential effects of the vaccine on progeny, the potential for teratogenic and abortifacient effects, and the potential effects on reproductive performance of both sexes must be considered. If recommended for use in active breeding males semen quality should be monitored, together with the potential for shedding of vaccine organisms into semen. If shedding is found, semen quality should be monitored. Pregnant animals must be tested in each of the specific periods of gestation recommended for use on the label. An exclusion statement will be required for those gestation periods not tested.

If the vaccine is recommended for use in future breeding poultry the study design should evaluate parameters relevant to the future use of the target birds.

Laboratory and/or field safety studies are required to support use of the vaccine in breeding animals. If reproductive performance studies are not considered necessary, the reasons must be clearly stated.

Examination of immunological functions

Where the vaccine is known to affect, or could be expected to adversely affect the immune response (eg by immunosuppression, autoimmunity, or hypersensitivity) of the vaccinee or of its progeny, suitable tests on their immunological function must be carried out. Alternatively, a rationale for no detrimental effect on immune response should be provided.

Special data requirements for live virus vaccines

Data must be provided on spread of the vaccine strain to non-vaccinated and non-target animal species unless acceptable argument can be provided to show this cannot happen. Data must also be provided on dissemination in the vaccinated animal, including tests for the presence of virus in excretions and secretions, including eggs, milk, urine and faeces, where relevant.

Other information required is:

- the possibility of reversion to virulence in the case of attenuated strains
- the possibility of recombination or genomic reassortment.

Interactions with other products

Claims that the vaccine can be administered simultaneously or in combination with other products must be substantiated. Any known interactions with other products must be declared.

PART 9 NON-FOOD TRADE

This data Part is not relevant to immunobiological products.

PART 10 SPECIAL DATA: GENETICALLY MODIFIED ORGANISMS

Products which contain genetically modified organisms (GMOs) require a licence issued by the Office of the Gene Technology Regulator (OGTR) before the application can be considered by the APVMA. An OGTR application and an APVMA trial permit application may be submitted at the same time.

A copy of the OTGR licence for field release must be submitted to the APVMA before the APVMA trial permit can be issued. Where APVMA trial requirements are met, a trial permit will be issued on receipt of a copy of the OTGR licence.

3. REFERENCES

Supplementary guidelines

Code of Federal Regulations 9, Animal and Animal Products (Parts 113 and 114)

Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products (EMEA/CVMP/074/95)

Environmental Risk Assessment for Immunobiological Veterinary Medicinal Products (EMEA/CVMP/074/95)

General Requirements for the Production and Control of Inactivated Mammalian Bacterial and Viral Immunobiologicals for Veterinary Use (CVMP/III/3181/91)

General Requirements for the Production and Control of Live Mammalian Bacterial and Viral Immunobiologicals for Veterinary Use (CVMP/III/3182/91)

In-use Stability Testing of Veterinary Medicinal Products (EMEA/CVMP/127/95)

Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMEA/CVMP/145/97)

Guidelines for testing veterinary products from The Rules Governing Medicinal Products in the European Union

Evaluation of the Safety of Veterinary Medicinal Products for the Target Animals

Good Clinical Practice for the Conduct of Clinical Trials on Veterinary Medicinal Products in the European Union

Inclusion of Antimicrobial Preservatives in Immunobiological Medicinal Products

OECD Principles of Good Laboratory Practice

Specific Requirements for the Production and Control of Avian Live and Inactivated Viral and Bacterial Immunobiologicals

Specific Requirements for the Production and Control of Bovine Live and Inactivated Viral and Bacterial Immunobiologicals

Specific Requirements for the Production and Control of Equine Live and Inactivated Viral and Bacterial Immunobiologicals

Specific Requirements for the Production and Control of Ovine Live and Inactivated Viral and Bacterial Immunobiologicals

Specific Requirements for the Production and Control of Pig Live and Inactivated Viral and Bacterial Immunobiologicals

Other APVMA or agency documents

AQIS Import Permit for Biological Products

<http://www.daff.gov.au/content/output.cfm?ObjectID=0E7B0A1F-C014-410F-A2396D3DD5F119DF>

The Australian Code of Good Manufacturing Practice for Veterinary Preparations

MORAG Volume 5: Vet Labelling Code

OGTR Guidelines (website <http://www.health.gov.au/tga/gene/gmac/gmac.htm>)

Recognition of Overseas Manufacturers of Veterinary Chemical Products. APVMA
GMP Technote Series, No. 99/01

4. GLOSSARY

Adjuvant

A substance which given in combination with an antigen augments the immune response to that antigen.

Autogenous immunobiological

An immunobiological product prepared from a micro-organism or micro-organisms isolated from sick or dead animals in the herd or flock of origin, which is believed to be the causative agent(s) of the disease affecting the animals.

Batch (final lot)

A collection of closed, final containers or other final dosage units that are expected to be homogenous and equivalent with respect to risk of contamination during filling or preparation of the final product. Preparation is from the same final bulk lot of the immunobiological product, freeze-dried together (if applicable) and closed in one continuous working session.

Field trial or study

A scientific investigation to assess efficacy and/or safety of a product under field conditions in target animals and using the product in accordance with the label.

Finished product

The formulated product, in its final dosage form and held in the final, sealed container. and packaging, in a form that is intended to be released for supply.

Manufacturer

Any person involved in any stage of the manufacturing process, including any person involved in packaging and labelling, sterilising and testing, up to and including release for supply.

Master seed lot (MSL)

A homogenous suspension of the original cells or organisms on which production is based and aliquoted into individual containers for storage.

For genetically modified products, the cells in the MSL are normally already transformed by the expression vector containing the desired gene. In some cases, the MSL for the expression vector and MSL for host cells may be distinct. (See also working seed lot (WSL).)

Overdose

Usually 2× the maximum concentration but may be as high as 10x in the case of live immunobiologicals. Refer to relevant pharmacopoeia monographs where and applicable.

Primary vaccination schedule

One or more administrations of a vaccine with the second and any recommended subsequent doses given a short time after the first dose. This is the vaccination schedule which is necessary to obtain and maintain the level of protection claimed by the applicant.

Reference product

A product that has been registered by the APVMA with similar indications for use and recommendations for use.

Re-vaccination schedule

One or more administrations of a vaccine used to maintain the initial protective effects induced by the basic vaccination schedule. The first (or only) dose of the re-vaccination is given a relatively long time (eg three months or more, depending on the species and the disease) after the basic vaccination schedule.

Residual pathogenicity:

The potential of viruses or bacteria which have been attenuated for specific target animal species and for specific routes of administration to retain different levels of pathogenicity (eg induction of clinical signs or lesions of disease or persistence/latency of the micro-organism in the body of vaccinated animals) under certain conditions of use (eg in animals of a certain age or class) as demonstrated in the passage test described in VICH GL41.

Vaccination schedule

The basic vaccination schedule and revaccination schedule combined.

Withholding periods

The time between the last administration of the product to food-producing animals and the collection and/or processing of foodstuffs from such animals.

Working seed lot (WSL)

A homogenous suspension of cells or organisms derived from the MSL under defined conditions and aliquoted into individual containers for storage. The WSL is used at a defined passage level for routine production. Containers of MSL and WSL, once removed from storage, must not be returned to the seed lot stock.

Revision history

Revision date	Description of revision
January 2000	First edition
May 2006	Second edition <ul style="list-style-type: none">• complete revision of the content