



Efficacy of Veterinary Vaccines

ACVM Registration Standard and Guideline

25 March 2013

TITLE

Efficacy of Veterinary Vaccines, ACVM Registration Standards and Guideline

PURPOSE

This document specifies the minimum study and reporting requirements for efficacy studies submitted in support of an application to register a veterinary vaccine, or to vary the conditions on a registered veterinary vaccine.

COMMENCEMENT

This document comes into force on the 25th March 2013.

ISSUING AUTHORITY

This document is issued under sections 10 and 21 of the Agricultural Compounds and Veterinary Medicines Act 1997.

Dated at Wellington this day of 20xx

Xxxxx
Manager, xxx
Ministry for Primary Industries (MPI)
(Acting under delegated authority)

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Part 1: Introduction

1.1 Background

- (1) Before being imported, manufactured, sold or used in New Zealand, agricultural compounds (including veterinary medicines) must be authorised under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997. Authorisation is required:
 - (a) to manage risks to trade in primary produce, public health, animal welfare, and agricultural security
 - (b) to make sure that the use of ACVM products does not result in breaches of domestic food residue standards, and
 - (c) to ensure the provision of sufficient consumer information.
- (2) In most cases, authorisation for a veterinary vaccine takes the form of a registration under section 21 of the ACVM Act.
- (3) Applications for registration must include technical data and/or relevant scientific argument to support:
 - (a) the quality, purity and stability of the veterinary vaccine
 - (b) its effectiveness for all therapeutic claims indicated
 - (c) the choice of target animals
 - (d) any possible impact on trade resulting from use of the veterinary vaccine in food-producing animals
 - (e) compliance with domestic food residue standards.
- (4) The following documents provide information you will need to complete the registration application process:
 - (a) *ACVM Research Standard*
 - (b) *ACVM Registration Information Requirements for Veterinary Medicines in New Zealand*.

They are available on our website at <http://www.foodsafety.govt.nz/elibrary>

- (5) This document also incorporates guidelines, which are intended to provide more detailed information and guidance to applicants to assist them in complying with the requirements. Guidelines reflect principles commonly recognised by the scientific community as appropriate and necessary for collecting scientific data. MPI recognises that methods other than the guidelines provided here are capable of achieving the principles of this document. These guidelines are written in text boxes and do not form part of the requirements.

1.2 What and whom this standard applies to

- (1) This document specifies the minimum study and reporting requirements for efficacy studies submitted in support of an application to register a veterinary vaccine, or to vary the conditions on a registered veterinary vaccine, under the ACVM Act.
- (2) This document must be followed by:
 - (a) all persons applying to register a veterinary vaccine or to vary the conditions on a registered veterinary vaccine for which efficacy data are required
 - (b) all persons recognised under the ACVM Act to undertake a risk assessment of applications made to register a veterinary vaccine or to vary the conditions on a registered veterinary vaccine.

1.3 Consequences of not complying with this standard

- (1) Applicants are responsible for providing all information required by the Approvals and ACVM Group of MPI to make a decision on the registration application. Applications that do not contain the required information will not be assessed.
- (2) If further advice is required, applicants are advised to contract the services of an appropriate consultant prior to submitting the application.

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Part 2: General Requirements for Efficacy Studies

2.1 Clinical requirements

- (1) All studies must be conducted in accordance with the *ACVM Research Standard*.
- (2) The efficacy of the product and/or its active ingredients must be investigated in the target species.
- (3) Product formulation and use patterns used in studies must be identical to those being proposed for registration.
- (4) Experimental data must be confirmed by data obtained under practical field conditions.
- (5) Sample sizes must be adequate to detect differences among treatment groups with a statistical power of at least 80%.
- (6) Adequate statistical methods must be used and justified. A 5% or lesser probability level ($P \leq 0.05$) should be used in deciding whether to accept or reject the null hypothesis.
- (7) Where a dose range is stated on the label, efficacy studies must be undertaken using the lowest dose rate.

2.2 Documentation

- (1) Reports must be presented in accordance with the *ACVM Research Standard*.
- (2) The applicant must state the overseas licensing status of the veterinary medicine. A reason must be given if the veterinary medicine is not licensed for use in the country of origin.

Part 3: Specific Requirements for Efficacy of Vaccines

Guidance

- The following are minimum mandatory study and reporting requirements (with guidelines) for evaluating the efficacy of vaccine products. They are additional to the general efficacy requirements above.
- A number of the requirements listed below are also listed in the *ACVM Research Standard*. They are repeated here in order to expand on them for these particular products.

3.1 Overall

- (1) Efficacy must be demonstrated in each category of each target species that is recommended for vaccination, and by each recommended route of administration, using the proposed label schedule of vaccination. Study results may not be extrapolated from one species to another.

Guidance

- Studies should be conducted in animals of the youngest age for which the product is recommended.

- (2) The influence of passively acquired and maternally derived antibodies on efficacy must be addressed.

Guidance

- Study data should show efficacy in animals that have interfering levels of maternal antibody, or the label must state that the product is for use in susceptible animals of the minimum age used in the efficacy study and recommend revaccination at appropriate intervals until the animals reach an age at which interfering levels of maternal antibody will no longer be present.

- (3) Claims regarding onset and duration of protection must be supported by study data.

- (4) Multivalent or combined vaccines

- a) The efficacy of each component of multivalent or combined vaccines must be demonstrated. It must be shown that there is no interference between the components, i.e. that one component does not cause a significant decrease in the immunological response or viability of another component.

Guidance

- In a challenge study, where the final product is used, proven efficacy will demonstrate the lack of interference and no further test will be required.

- b) In a challenge study, where fractions have been studied separately, target species serological studies must be conducted to prove lack of interference. This is possible only where it has been proven that serology is correlated to efficacy (see section 3.3). If serology is not correlated to efficacy, fractions must not be studied separately.

Guidance

- If the product contains fractions that are contained in a registered product as well as previously unregistered fractions, or if it contains only previously registered fractions, lack of interference to the previously registered fractions can be demonstrated by target species serological studies, where serology is correlated to efficacy (see section 3.3).

- c) Lack of interference with viability of live fractions must be demonstrated when combining a live fraction with a killed or another live fraction. If final product challenge testing using the product as recommended is performed, this will show lack of interference with viability. In all other situations, data such as viable counts on the final product, residual formaldehyde level, viricidal activity etc must be presented.
- d) Some vaccine components can act as adjuvants, for example lipopolysaccharides of gram negative bacteria or *Bordetella bronchiseptica* fractions. If removal of such components from a registered product is requested, efficacy of the remaining antigens must be proven.

Guidance

- This may be by new target animal efficacy studies or serological studies (if serology is correlated to efficacy).

- (5) If the vaccine is recommended to be administered concurrently with another product, compatibility must be demonstrated.

Guidance

- This can be achieved by incorporating the other product in the efficacy study.

- (6) The type of efficacy study required for a product depends on the amount of information already known about the product. The following sets out the different types that may be required.
 - a) Efficacy studies to support an innovative registration must be controlled challenge studies (see 3.2) where validated immunogenicity test methods are not available (see below).

Guidance

- An innovative registration is defined as one that differs from products previously registered in New Zealand in terms of different master seed, master cell, route of administration, adjuvant type or concentration, or other significant changes to the product such as passage level. In some exceptional cases, a challenge model may not be available (as may be the case for a newly emerging disease). In these cases, field studies may be considered to be acceptable. Applicants should provide a case to be considered on its merits.

- (7) Where validated test methods are available, these may be used to demonstrate efficacy.

Guidance

- These may include immunogenicity tests in approved monographs or ACVM-approved validated test methods. Approved monographs are Code of Federal Regulations Title 9, British Pharmacopoeia, European Pharmacopoeia and United States Pharmacopoeia.
- Approval of other test methods should be obtained from the ACVM Group prior to an application for their use being made.
- One of the major principles employed to minimise the animal welfare implications associated with the use of animals in scientific procedures is reduction, refinement and replacement of test methods using live animals. The ACVM Group strongly supports this philosophy.

- (8) If alternatives to live animal techniques are employed, their validity must be proven and correlated to immunogenicity.

Guidance

- Where efficacy has been established for the fractions(s) and the proposed product constitutes a different antigenic combination to a registered product, a target species comparative serological study (see 3.3) may be sufficient to establish efficacy.

- (9) Study challenge organisms must be relevant to the major field strains found in New Zealand.
- (10) If the product has a label recommendation to be used as part of a vaccination program, the label claim must be supported by proving the contribution of each component and a lack of interference demonstrated.
- (11) Label statements must correspond to the degree of efficacy proven. Efficacy statements must be supported by the data and indicate expected efficacy.
- (12) A claim of 'prevention of infection' requires data to prove that the product prevents all colonisation or replication of the pathogen in vaccinated animals.
- (13) A claim that the product prevents disease caused by the pathogen requires data to prove that the product is at least 80% effective in the prevention of clinical disease in vaccinated animals.
- (14) Products that do not achieve this degree of efficacy, but do produce a significant effect, may make a claim of being 'an aid in the prevention of', or 'an aid in the reduction of disease caused by (the pathogen)'.
- (15) If the product is effective only in certain situations, e.g. in the absence of maternal antibody, the label statement must be qualified by specifying that the product is for the immunisation of 'susceptible' animals.
- (16) If the pathogen is associated with more than one disease form, the label claim must specify for which form of disease the product has had efficacy proven.

Guidance

- The immune mechanism used to target the organism in natural infections should be discussed and compared with the type of immune response stimulated by the vaccine under investigation.
- Where an adjuvant is used, the choice of adjuvant should be discussed and the mechanism of action, if known, should be described.
- During the efficacy study, the method of testing potency of the product should be validated.
- Acclimatisation to the study environment is appropriate.
- Study animals should be healthy.

3.2 Challenge studies

3.2.1 Experimental design

- (1) Studies must be conducted with final product vaccine from a batch manufactured according to the method specified in the manufacturing information supplied to the ACVM Group.
- (2) If the product contains multiple antigens, and the study is to establish efficacy for each fraction by vaccinating study animals with each fraction separately, then target species serological studies must also be conducted to demonstrate lack of interference between the fractions. This is possible only if the serology has been correlated to efficacy (see section 3.3). If serology is not correlated to efficacy, the product must be tested in its final marketed form.

3.2.2 Reporting

- (1) The method of randomly assigning study animals to treatment groups must be described. This must include the basis of any stratification used in the design.
- (2) The management of the groups must be described including the time points that the treatment groups were in contact or separated.
- (3) All scoring systems used must be described in detail.

Guidance

- Disparate parameters should not be combined into a single score. If they are combined, numerical values assigned to the scores should reflect the relative importance of the clinical signs in characterising the disease condition.
- The preventable fraction should be calculated and reported:
- Preventable fraction = $(\% \text{ of controls with clinical signs of disease} - \% \text{ of vaccinates with clinical signs of disease}) / \% \text{ of controls with clinical signs of disease}$
- Generally, an effective vaccine should have a preventable fraction of at least 80%. However, this may vary according to the disease in question and other such factors.

- (4) The method of statistical analysis must be described and justified. The method of analysis must be appropriate to the experimental design including the method of randomisation and the type of outcome variables measured.
- (5) Any computer software used must be identified.

3.3 Comparative serological studies

Guidance

- These studies are sufficient for previously registered fractions of multivalent mammalian vaccines. They apply to mammalian vaccines only – not to avian products. They apply to products that do not differ significantly from previously registered products in terms of master seed, master cell, route of administration, adjuvant type or correlation, or other significant changes to the previously registered product such as passage level.

3.3.1 Experimental design

- (1) Study animals must be seronegative. Blood samples must be taken on the day of the first vaccination to confirm this status.

- (2) Antibody response must not be significantly lower than the study vaccine ($p < 0.05$).

Guidance

- There should be at least 10 animals in each group.

3.3.2 Reporting

- (1) The management of the groups must be described including the time points that the treatment groups were in contact or separated if live vaccines are used.
- (2) The method of statistical analysis must be described and justified.
- (3) Any computer software used must be identified.

EXAMPLE ONLY