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**ACVM
REGISTRATION STANDARD
AND GUIDELINE FOR
EFFICACY OF
VACCINES**

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF VACCINES

1 INTRODUCTION

This document specifies the minimum study and reporting requirements, i.e. the standard, for efficacy studies submitted in support of an application to register a vaccine, or to vary the conditions on a registered vaccine. It also incorporates guidelines, which are intended to provide more detailed information and guidance to applicants to assist them in complying with the standard.

The requirements that form the standard are shown in this document in **bold font**, while the guidelines are in regular font.

Guidelines reflect principles commonly recognised by the scientific community as appropriate and necessary for collecting scientific data. It is recognised that there are acceptable methods, other than those described in these guidelines, that are capable of achieving the principles of this document.

The standard is compulsory in all cases where efficacy data are required to be provided for registration of vaccines, unless a waiver has been granted by NZFSA.

Waivers may be granted to reduce the number of studies or type of data that an applicant must submit (e.g. by permitting cross-referencing to existing data held by NZFSA). *These waivers must be granted by NZFSA prior to the applicant submitting an application.* This standard will be reviewed periodically, and waivers incorporated if appropriate.

Applicants should note that they are responsible for providing all information required by the ACVM Group of NZFSA to make a decision on the application. Applications that do not contain the required information will not be assessed. If further advice is required, applicants are advised to contract the services of an appropriate consultant prior to submitting the application.

1.1 Scope

This standard specifies the minimum clinical study and reporting requirements for efficacy data to be provided by applicants for registration of veterinary vaccines under the Agricultural Compounds and Veterinary Medicines Act 1997.

The standard must be followed by:

- all persons applying to register a veterinary vaccine or to vary the conditions on a registered veterinary vaccine for which efficacy data are required;
- all persons accredited under the Agricultural Compounds and Veterinary Medicines Act 1997 to undertake a risk assessment of applications made to register a veterinary vaccine or to vary the conditions on a registered veterinary vaccine.

1.2 Definition

Target species

The species of animal for which the test substance is intended for final use.

1.3 References

ACVM Research Standard

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

2 GENERAL REQUIREMENTS FOR EFFICACY STUDIES

2.1 Clinical requirements

- 2.1.1 All studies must be conducted in accordance with the *ACVM Research Standard*.**
- 2.1.2 The efficacy of the product and/or its active ingredients must be investigated in the target species.**
- 2.1.3 Product formulation used in studies must be identical to that being proposed for registration.**
- 2.1.4 Experimental data must be confirmed by data obtained under practical field conditions.**
- 2.1.5 Sample sizes must be adequate to detect differences among treatment groups with a statistical power of at least 80%.**
- 2.1.6 Adequate statistical methods must be used and justified. A 5% or lower probability level ($P \leq 0.05$) should be used in deciding whether to accept or reject the null hypothesis.**
- 2.1.7 Where a dose range is stated on the label, efficacy studies must be undertaken using the lowest dose rate.**
- 2.1.8 Expression of confidence intervals is generally appropriate, and they should be reported.**

2.2 Documentation

- 2.2.1 Reports must be presented in accordance with the *ACVM Research Standard*.**
- 2.2.2 The applicant must state the overseas licensing status of the remedy. A reason must be given where the remedy is not licensed for use in the country of origin.**

3 SPECIFIC REQUIREMENTS FOR EFFICACY OF VACCINES

The following are mandatory clinical study and reporting requirements for evaluating efficacy of vaccines. 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 General

3.1.1 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.

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

3.1.2 The influence of passively acquired and maternally derived antibodies on efficacy must be addressed.

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.

3.1.3 Claims regarding onset and duration of protection must be supported by study data.

3.1.4 Multivalent or combined vaccines

3.1.4.1 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.

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.

3.1.4.2 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.

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).

3.1.4.3 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.

3.1.4.4 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.

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

3.1.5 If the vaccine is recommended to be administered concurrently with another product, compatibility must be demonstrated.

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

3.1.6 Types of efficacy studies

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.

3.1.6.1 Efficacy studies to support an innovative registration must be controlled challenge studies (see 3.2) where validated immunogenicity test methods are not available (see 3.1.6.2).

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.

3.1.6.2 Where validated test methods are available, these may be used to demonstrate efficacy.

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. **If alternatives to live animal techniques are employed, their validity must be proven and correlated to immunogenicity.**

3.1.6.3 Where efficacy has been established for the fraction(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.

3.1.7 Study challenge organisms must be relevant to the major field strains found in New Zealand.

3.1.8 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.

3.1.9 Label statements must correspond to the degree of efficacy proven. Efficacy statements must be supported by the data and indicate expected efficacy.

A claim of ‘prevention of infection’ requires data to prove that the product prevents all colonisation or replication of the pathogen in vaccinated animals.

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.

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)’.

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.

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.

- 3.1.10 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.
- 3.1.11 Where an adjuvant is used, the choice of adjuvant should be discussed and the mechanism of action, if known, should be described.
- 3.1.12 During the efficacy study, the method of testing potency of the product should be validated.
- 3.1.13 Acclimatisation to the study environment is appropriate.
- 3.1.14 Study animals should be healthy.

3.2 Challenge studies

3.2.1 Experimental design

3.2.1.1 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.

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.

The study must use the diluent recommended for use with the product (if applicable).

3.2.1.2 The dose administered must be the dose recommended for use and must contain the minimum titre or potency in the final product specifications. The titre or potency of the test product must be stated. The test product must be produced at the highest specified passage level from master seed.

3.2.1.3 Clinical outcomes measured must be indicative of the disease being studied.

3.2.1.4 Challenge studies should be performed using seronegative animals under controlled conditions.

3.2.1.5 Animal numbers should be balanced by ethical considerations. A minimum of 20 vaccinates and 10 control animals are required in most situations in challenge studies.

3.2.1.6 The study environment should be as uniform as possible for all experimental groups in the study. If the product is not a live vaccine, the groups should be housed together.

3.2.1.7 The study should be blinded.

3.2.2 Reporting

3.2.2.1 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.

3.2.2.2 The management of the groups must be described including the time points that the treatment groups were in contact or separated.

3.2.2.3 All scoring systems used must be described in detail.

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.

3.2.2.4 The preventable fraction should be calculated and reported:

$$\text{Preventable fraction} = \frac{(\% \text{ of controls with clinical signs of disease} - \% \text{ of vaccinates with clinical signs of disease})}{\% \text{ of controls with clinical signs of disease}}$$

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.

3.2.2.5 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.

Any computer software used must be identified.

3.3 Comparative serological studies

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

3.3.1.1 Study animals must be seronegative. Blood samples must be taken on the day of the first vaccination to confirm this status.

3.3.1.2 Antibody response must not be significantly lower than the study vaccine ($p \leq 0.05$).

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

3.3.2 Reporting

3.3.2.1 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.

3.3.2.2 The method of statistical analysis must be described and justified.

Any computer software used must be identified.