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**ACVM
REGISTRATION STANDARD
AND GUIDELINE FOR
EFFICACY OF
INTRAMAMMARY
ANTIMICROBIALS**

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Endorsement:

Date:

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF INTRAMAMMARY ANTIMICROBIALS

1 INTRODUCTION

Efficacy of a veterinary medicine is understood to be the degree to which the medicinal claims made by the applicant have been justified and are likely to be attained under practical field conditions within New Zealand. The need for an efficacy standard arises from section 4 of the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997, which provides for prevention or management of risks associated with the use of agricultural compounds:

- risks to trade in primary produce; and
- risks to animal welfare; and
- risks to agricultural security.

Risks to animal welfare can arise if the use of a compound, or its failure to achieve product claims, could result in unnecessary pain or distress in the target animal. Efficacy data is the verification that the trade name product will prevent or treat diseases characterised by unnecessary pain or distress. Any claim for these diseases must be soundly supported by scientific evidence consistent with these standards.

This document specifies the minimum study and reporting requirements, i.e. the standard, for efficacy studies submitted in support of an application to register an intramammary antimicrobial or to vary the conditions on a registered intramammary antimicrobial. 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 is required to be provided for registration of an intramammary antimicrobial, unless a waiver has been granted by the New Zealand Food Safety Authority (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

The standard must be followed by:

- all persons applying to register an intramammary antimicrobial or to vary the conditions on a registered intramammary antimicrobial;
- all persons conducting a data assessment on applications made to register an intramammary antimicrobial or to vary the conditions on an intramammary antimicrobial.

The standard provides specifications for:

- general efficacy requirements;
- target animal field studies; and
- interpretation of results.

The issue of monitoring antibiotic resistance will be addressed separately to this standard.

1.2 Definitions and abbreviations

Good Research Practice (GRP)

A standard for the design, conduct, recording and reporting of studies that provides assurance that the data and reported results are complete, correct and accurate.

MIC

Minimum inhibitory concentration.

Target species

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

1.3 References

ACVM Research Standard

Current version of VICH Harmonised Guidance for Good Clinical Practice

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 In the case of fixed combination products, it must be demonstrated that all active ingredients produce their expected effect(s).**
- 2.1.6 Sample sizes must be adequate to detect differences among treatment groups with a statistical power of at least 80%.**
- 2.1.7 Adequate statistical methods must be used and justified. A 5% or lesser probability level ($P < 0.05$) should be used in deciding whether to accept or reject the null hypothesis.**
- 2.1.8 Where a dose range is stated on the label, efficacy studies must be undertaken using the lowest dose rate.**

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 veterinary medicine. A reason must be given where the veterinary medicine is not licensed for use in the country of origin.**

3 SPECIFIC REQUIREMENTS FOR EFFICACY OF INTRAMAMMARY ANTIMICROBIALS

The following are minimum study and reporting requirements (with guidelines) for evaluating the efficacy of intramammary antimicrobials. They are additional to the general efficacy requirements above.

3.1 General

3.1.1 Cow numbers required will depend on magnitude of effect, but at least six animals will be required.

Cows with clinical mastitis, subclinical mastitis and healthy dry cows should be treated separately.

A negative control group cannot be justified if the trial is examining the effects of drugs on clinical mastitis because unnecessary suffering is likely to result from not treating the cows. A negative control group is justified in subclinical mastitis cases or for prophylactic use in dry cows.

3.1.2 The inoculum infused into the quarters must be of specified species relevant to New Zealand and recent field isolates for which the MICs of common drugs (and the test product) have been established.

In vitro information should be available on the efficacy of the active ingredient.

Information should be presented on the activity of the active ingredient *in vitro*. Its minimum inhibitory concentration in milk against a range of pathogens likely to be found in New Zealand should be specified, along with the method of measuring MIC.

3.1.3 The end points to be measured will depend on the claims for the product but must include:

- **clinical cure;**
- **cell counts;**
- **bacterial counts (at least three); and**
- **MICs, yields and drug pharmacokinetics in the milk.**

3.1.4 Cows must be otherwise fit and healthy; any cows with teat lesions or that have received antibiotics in the last month should be excluded. The criteria for selection of cows, e.g. clinical signs, Delvotest screening for inhibitory substances, must be stated.

3.1.5 The following data are required for each cow:

- **identification number**
- **breed**
- **number of lactations**
- **date of calving**
- **previous cell counts**
- **yield**
- **mastitis history**
- **appearance of milk**
- **general condition**
- **condition of udder.**

A record for each cow is required in the final report.

3.1.6 Adverse effects must be noted and any animals that die must have a postmortem examination, including udder histopathology, carried out and reported.

3.1.7 An explanation must be provided for removal of any animal from the trial.

3.2 Field studies

3.2.1 At least two field trials in commercial herds are required.

3.2.2 Milk samples must be cultured from all cows before treatment and resistance profiles of all relevant bacteria obtained. The resistance profiles of any bacteria cultured after treatment must also be assessed.

3.2.3 There must be adequate control groups, both positive (a similar registered veterinary medicine) and negative (saline or vehicle) as appropriate.

3.2.4 All treatments must be administered using suitable aseptic precautions.

3.2.5 All bacterial cultures, cell counts and examinations must be reported.

3.2.6 Subclinical mastitis

- **Positive and negative control groups are required.**
- **The experimental unit is the quarter.**
- **Milk samples must be examined for cell counts and general appearance, and cultured for bacteria at appropriate intervals after treatment. The cow must also be clinically examined at these times.**

Appropriate intervals for milk sampling for cell counts, general appearance and bacterial culture are 7, 14 and 21 days after treatment.

3.2.7 Clinical mastitis

- **A positive control group is required.**
- **The experimental unit is the quarter.**
- **Milk samples must be examined for general appearance and cultured for bacteria at appropriate intervals after treatment.**
- **The cow must also be clinically examined at appropriate intervals after treatment and the condition of the udder reported.**
- **Cows that fail to respond to treatment and are considered to be in pain must be withdrawn from the trial and treated as necessary. This must be noted in the final report.**

Appropriate intervals for milk sampling for general appearance and bacterial culture are 7, 14 and 21 days after treatment. Appropriate intervals for clinical examination are at 3, 7 and 14 days after treatment.

3.2.8 Dry cow treatment

- **Positive and negative control groups are required.**
- **The experimental unit is the cow.**
- **Milk samples should be taken for bacterial culture at the first milking after calving and at 10 days after calving. A milk sample for cell counts should also be taken at 10 days after calving.**

Milk yields at drying off and the method of drying off should be reported.

3.3 Interpretation of results

3.3.1 The definitive test of efficacy is elimination of bacteria from milk. Other claims for efficacy, e.g. reduced cell counts, must be justified.

3.3.2 Three successive negative bacterial cultures indicate a bacteriological cure.

3.3.3 Return of udder condition and appearance of milk to normal indicate a clinical cure.