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

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**Endorsement:**

**Date:**

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# ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF CORTICOSTEROIDS

## 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 corticosteroid or to vary the conditions on a registered corticosteroid. 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 a corticosteroid, 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

The standard must be followed by:

- all persons applying to register a corticosteroid or to vary the conditions on a registered corticosteroid;
- all persons accredited under the Agricultural Compounds and Veterinary Medicines Act 1997 to undertake a risk assessment of applications made to register a corticosteroid or to vary the conditions on a registered corticosteroid.

The standard provides specifications for:

- general efficacy requirements;
- pharmacokinetic and pharmacodynamic requirements;
- laboratory studies;
- target animal clinical studies; and
- target animal field studies.

## 1.2 Definitions

### **Target species**

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

### **Use pattern**

The parameters of use of a product, i.e. target species, target disease/condition, dose rate, dose route, dose frequency, and treatment duration.

## 1.3 References

*ACVM Research Standard*

*ACVM Registration Information Requirements for Veterinary Medicines in New Zealand*

*ACVM Registration Standard and Guideline for Therapeutic Equivalence of Trade Name Products*

## **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 lesser 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.**

### **2.2 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 CORTICOSTEROIDS

The following are minimum study and reporting requirements (with guidelines) for evaluating the efficacy of corticosteroids. 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 Proposed label claims must be substantiated by well-designed and executed clinical studies. *In vitro* and *in vivo* studies in non-target species will be regarded as support data and must be provided.**

If data provided does not adequately support registration, additional data will be requested.

**3.1.2 Application for products containing novel active ingredient(s) must be supported by properly designed and conducted laboratory and clinical studies (see table 1).**

**3.1.3 Applications for products containing ACVM-approved active ingredient(s) must be supported by properly designed and conducted laboratory and clinical studies, or must be supported by bioequivalence studies and appropriate scientific argument (see table 1).**

For bioequivalence studies, refer to the *ACVM Registration Standard and Guideline for Therapeutic Equivalence of Trade Name Products*.

**3.1.4 Overseas data may be acceptable if it is adequately argued or demonstrated that it applies to New Zealand conditions. In some cases, New Zealand conducted studies may be necessary.**

#### 3.1.5 Combination products

**3.1.5.1 Where product combinations are instigated on pharmacological grounds, the pharmacodynamic and/or pharmacokinetic studies shall demonstrate those interactions that make the combination itself of value in clinical use.**

**3.1.5.2 Where product combinations are instigated by clinical indications and scientific justification is sought through clinical experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and if any side effects occur.**

**3.1.5.3 It must be demonstrated that all active ingredients in a combination product produce their expected effect(s).**

**Table 1: Matrix for determining information requirements**

Application type	P'kinetics/ P'dynamics	Lab animal <i>in vitro</i>	Target spp clinical studies	Target spp field studies	Bioequivalence
Novel active <sup>1</sup>	✓	✓	✓	✓	-
Known active <sup>2</sup> Change in use pattern <sup>3</sup>	✓	✓	✓	✓	-
Known active, similar <sup>4</sup> formulation	-	-	-	-	✓
Known active, dissimilar formulation, same use pattern	Provide scientific argument & literature	-	✓	✓	✓
Known active, similar formulation, novel disease or condition	-	-	✓	✓	-

**Notes**

- 1 Active ingredient(s) not currently or previously registered in any trade name product in New Zealand.
- 2 Active ingredient(s) already registered by the ACVM Group.
- 3 Novel route of administration, change in dose rate (both increased and decreased), change in frequency of administration, change in dosage form, change in treatment duration, novel species, novel physiological status that may impact on efficacy (e.g. lactating vs non-lactating).
- 4 Similar formulation means:
  - same active ingredient
  - same formulation type
  - same dose regime on an active ingredient basis
  - same use patterns.

## **3.2 Pre-clinical studies**

**All pre-clinical studies must be reported.**

### **3.2.1 Pharmacokinetic studies**

**Pharmacokinetic data is required to:**

#### **3.2.1.1 Evaluate basic parameters such as:**

- **body clearance;**
- **volume(s) of distribution;**
- **area under the curve;**
- **any other pharmacokinetic parameter(s) that are necessary to assess safety and efficacy.**

#### **3.2.1.2 Establish dosage regimes (route, site of administration, dose, dosing interval, number of administrations), and to adopt dosage regimes according to certain population variables, e.g. age, disease.**

#### **3.2.1.3 Investigate relationships between dosage regime, plasma and tissue concentration and pharmacological and therapeutic effects.**

#### **3.2.1.4 In the cases of ACVM-approved active ingredients, pharmacokinetic studies are not required if it can be justified that the administration of the proposed formulation does not change the pharmacokinetic properties of that active ingredient(s).**

### **3.2.2 Pharmacodynamic requirements**

#### **3.2.2.1 The mechanism of action and pharmacological effects on which the recommended application in practice is based must be adequately described.**

#### **3.2.2.2 The results must be expressed in quantitative terms e.g. dose-effect curves, time-effect curves, etc.**

#### **3.2.2.3 Where greater efficacy than a reference product is being claimed, the difference to the reference product must be demonstrated and shown to be statistically significant.**



### 3.3 Laboratory studies

Laboratory studies on non-target animals and *in vitro* testing may be required to demonstrate that the active ingredient(s) produces a desirable pharmacological effect, which can then be tested in the target species.

**Laboratory *in vivo* models used must provide adequate challenge/pathology to demonstrate efficacy of the active ingredient(s).**

The following tests are suggested for the evaluation of the stated activity.

**Table 2: Laboratory *in vivo* tests**

Test	Species used	Test demonstrates
Liver glycogen	Rat	Glucocorticoid activity
Cotton pellet	Rat	Inhibition connective tissue (anti-inflammatory)
Granuloma pouch	Rat	Anti-exudative properties (anti-inflammatory)
Induced oedema of the paw	Rat	Anti-oedematous action (anti-inflammatory)
Thymus weight/involution	Rat	Thymolytic effects
Sodium/potassium excretion	Rat	Mineralocorticoid activity
Pituitary inhibition	Rat	Effect on adrenocortical-pituitary axis
Induction of hepatic enzyme TAT	Rat	Effect on hepatic enzyme

## 3.4 Target animal clinical studies

### 3.4.1 Types of clinical studies required

**3.4.1.1 Proposed label claims must be substantiated by well-designed and executed clinical studies.**

**3.4.1.2 Clinical studies must include control animals.**

Negative control animals should be given no treatment or a placebo, e.g. formulation excipients or 0.9% saline. Positive control animals should be given a registered product of known efficacy for the disease or condition treated.

**3.4.1.3 Where positive control animals are used, the full details of the product given to them must be reported, i.e.:**

- trade name;
- registrant;
- dose rate and route;
- dose frequency; and
- duration of treatment.

**3.4.1.4 Where animals serve as their own controls (a crossover study), a washout period based on appropriate pharmacokinetic data must be used.**

The duration of the washout time should be approximately seven times the half life to provide for more than 99% of the administered dose to be eliminated from the body. If more highly complex kinetic models are anticipated, or for drugs with the potential for physiological carryover effects, the washout time should be adjusted accordingly.

**3.4.1.5 In the case of combination topical/otic preparations, study design must be such that group comparisons to verify that each component is contributing to the combined efficacy of the proposed product can be made (see example below).**

**Table 3: Combination antifungal/antibacterial/corticosteroid preparation**

Group	Control (e.g. vehicle)	Antifungal	Antibacterial	Corticosteroid
Group 1	appropriate	-	-	-
Group 2	-	-	optimal	optimal
Group 3	-	optimal	-	optimal
Group 4	-	optimal	optimal	-
Group 5	-	optimal	optimal	optimal

### 3.4.2 Parameters to be measured

Parameters to be measured depend upon the proposed use of the product (see table 4).

**Table 4: Suggested parameters to be measured for each proposed use**

Proposed use	Clinical signs	Haematology	Blood chemistry	Histopathology/ cytology
<b>Anti-inflammatory</b>				
Musculoskeletal	✓	✓	✓	✓
Topical (skin, eyes, ears)	✓	✓	✓	✓
Immunosuppression	✓	✓	✓	✓
Anti-allergic	✓	✓	✓	✓
<b>Gluconeogenic</b>	✓	✓	✓	-
<b>Shock</b>	✓	✓	✓	-
<b>Induction of parturition</b>	✓	✓	✓	✓

#### 3.4.2.1 Clinical signs may include:

- bodyweight changes;
- feed and water consumption;
- milk production;
- rectal temperature;
- heart and respiratory rates;
- degree of pain (scored according to conventional criteria);
- degree of inflammation (manually detected heat around lesion, infrared measurements);
- degree of lameness (scored according to conventional criteria);
- degree of joint flexion;
- joint circumference;
- size of lesion (area, depth, volume);
- any adverse events, e.g. injection site lesions, systemic reactions, etc.).

#### 3.4.2.2 Haematology parameters may include:

- complete blood count (RBC, WBC);
- differential blood counts (lymphocytes, monocytes, neutrophils, eosinophils);
- abnormal cell types noted.

3.4.2.3 Blood chemistry parameters may include:

- total protein;
- plasma albumin and globulin;
- liver enzymes (analysis that is appropriate for target species);
- BUN/creatinine;
- CPK;
- bilirubin;
- blood glucose;
- serum electrolytes (sodium, potassium, chloride, phosphorus);
- levels of relevant endogenous hormones;
- blood levels of active ingredient(s) (+/- metabolites).

3.4.2.4 Histopathology/cytology may include:

- histopathology of pertinent tissues and lesions;
- analysis of body fluids.

**3.4.3 Reporting of clinical studies must be in accordance with the *ACVM Research Standard*, with the following points to be noted.**

**3.4.3.1 Reporting of the test management system must include feeding, stating feed composition and presence/quantity of any feed additives.**

**3.4.3.2 Reporting of methods of the study must include description of the period of observation.**

**3.4.3.3 The significance of any variations in the results of studies must be explained.**

## **3.5 Target animal confirmatory field studies**

The purpose of field studies is to confirm data obtained under controlled clinical conditions under practical field conditions.

**3.5.1 Studies must reflect typical veterinary use conditions and must be undertaken in enough different locations to allow for variance.**

**3.5.2 Pertinent parameters must be measured and, where possible, conventional clinical criteria must be used.**

**3.5.3 Reporting of field studies is as for clinical studies in 3.4.3 above.**

## 4 FURTHER READING

Animal Techniques for Evaluating Adrenocortical Drugs in: *Animal and Clinical Pharmacological Techniques in Drug Evaluation*. Silber & Arcese

FDA Guideline 16

FDA Guideline 38: Guideline for Effectiveness Evaluation of Topical and Otic Drugs