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**ACVM
REGISTRATION STANDARD
AND GUIDELINE FOR
EFFICACY OF
ORAL REHYDRATION
THERAPY**

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Endorsement:

Date:

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF ORAL REHYDRATION THERAPY

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 Veterinay 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.

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 oral rehydration therapy product, or to vary the conditions on such a registered product. It also incorporates guidelines, which are intended to provide more detailed information and guidance to applicants to assist them in complying with the standard. This document does not apply to products exempt from registration.

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 oral rehydration therapy products, unless a waiver has been granted by NZFSA.

It is expected that most applications for oral electrolyte replacers will use information waivers based on cross-references and published literature. Clinical trials with a high welfare impact on experimental animals will not be required in circumstances where an information waiver can be considered.

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 oral rehydration therapy product or to vary the conditions on a registered oral rehydration therapy product;
- all persons conducting a data assessment on applications made to register an oral rehydration therapy product or to vary the conditions on a registered oral rehydration therapy product.

The standard provides specifications for:

- general efficacy requirements;
- experimental studies; and
- field studies.

1.2 Definitions and abbreviations

ECF

Extracellular fluid.

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.

PCV

Packed cell volume.

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 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 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 ORAL REHYDRATION THERAPY PRODUCTS

The following are mandatory clinical study and reporting requirements for evaluating efficacy of oral rehydration therapy. They are additional to the general efficacy requirements above.

Efficacy must be demonstrated through a combination of:

- experimental studies
- field studies.

3.1 General

3.1.1 Studies must be conducted using the class of animal for which the product is intended.

Animals should be managed on a daily basis following normal New Zealand practice.

3.1.2 Any study animals that die must be necropsied and an aetiological diagnosis attempted and reported.

3.1.3 Pre-clinical studies in the target animal must be reported, including the rationale for the selection of the type of substance (kind and composition of active ingredients), concentration (osmolality of the substance and of its electrolyte components), dose level and dose intervals claimed to be optimally effective.

The amount of the test substance administered should be reported.

3.1.4 Feed and water must be made available as per label instructions of the test substance.

3.1.5 Animals that fail to respond to treatment and that are considered to be in pain must be withdrawn from the study and treated as necessary. This must be noted in the final study report.

3.1.6 In all studies, fluid loss, electrolyte imbalances and acid/base imbalances must be measured as accurately as possible under the circumstances and the correct dosage of the test substance used for each animal.

3.1.7 A positive control group (given a similar registered veterinary medicine with the same indications) must be used.

3.2 Experimental studies

3.2.1 The method of inducing dehydration must be reported, and must reflect the condition for which the test substance is intended.

Dehydration may be induced in several ways. Examples include:

- administration of an infectious agent causing diarrhoea;
- administration of a diuretic;
- administration of castor oil causing diarrhoea;
- strenuous exercise;
- deprivation of food and water.

3.2.2 All animals must be healthy at the start of the experiment.

Animals should be stressed as little as reasonably possible to avoid exacerbating the dehydration.

Acclimatisation to the study environment is appropriate.

3.2.3 The vaccination status of all the animals in the study must be the same.

3.2.4 Where neonates are used, experimental groups must be balanced for immunoglobulin concentration.

3.2.5 The observation period must cover a pre-treatment, treatment and post-treatment period of time suitable to control the induced condition and, if claimed, recovery.

A sanitation and biosecurity programme should be adopted to avoid the inadvertent occurrence of disease other than that intended in the experiment.

3.2.6 Treatment must begin on diagnosis of the condition induced. Criteria for diagnosis must be reported.

Clinical assessment of the animals should be made by the same person.

3.2.7 The following parameters must be reported:

- plasma and ECF volumes;
- PCV and total protein;
- serum Na⁺, K⁺ and Cl⁻;
- HCO₃⁻ and pH; and
- further parameters relevant to product claims, eg blood glucose.

Plasma and ECF volumes may be measured using the Evans Blue/sodium thiocyanate (NaSCN) method as described in:

Michell, A.R.; Brooks, H.W.; White, D.G.; Wagstaff, A.J. (1992): The Comparative Effectiveness of Three Commercial Oral Solutions in Correcting Fluid, Electrolyte and Acid-Base Disturbances Caused by Calf Diarrhoea. *Br Vet J.* 148, 507-521.

3.2.8 Clinical signs to be reported include:

- **demeanour;**
- **enophthalmus;**
- **mucous membrane moisture and colour;**
- **temperature of extremities;**
- **skin elasticity;**
- **body weight;**
- **urine colour and output.**

A scoring system must be predefined and reported.

An appropriate system for clinical assessment is:

- Demeanour
N = normal
D = dull, standing
R = recumbent
C = collapsed
- Mucous membranes
N = normal
D = dry
- Skin elasticity
N = rapid return to normal
S = slow
V = very slow
- Eyes
N = normal
S = sunken
- Extremity temperature
W = warm
C = cold
V = very cold

3.2.9 These parameters are to be measured at:

- **induction of dehydration;**
- **beginning of treatment;**
- **end of treatment.**

3.2.10 The interval from treatment to desired clinical and biochemical response must be reported.

3.2.11 Animals must be checked in the post-treatment period for clinical signs of relapse. Any animal showing such signs must have the appropriate physiological parameters measured and reported.

3.3 Field studies

Parameters to be measured at the beginning and end of treatment are:

- **PCV and total protein;**
- **serum Na⁺, K⁺ and Cl⁻;**
- **demeanour;**
- **enophthalmus;**
- **mucous membrane moisture and colour;**
- **temperature of extremities;**
- **skin elasticity;**
- **body weight;**
- **urine colour and output.**

Parameters may be measured as above.