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ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF ANTIBLOAT PRODUCTS

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Endorsement:
Date:

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF ANTIBLOAT PRODUCTS

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 an antibloat product, or to vary the conditions on a registered antibloat 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.

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

The standard provides specifications for:

- general efficacy requirements;
- field studies.

1.2 Definitions and abbreviations

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 and use patterns used in studies must be identical to those 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 ANTIBLOAT PRODUCTS

The following are mandatory clinical study and reporting requirements (with guidelines) for evaluating antibloat products. They are additional to the general efficacy requirements above.

It is recognised that products utilised to treat and prevent bloat may be used in either pasture based or feedlot type situations. These standards relate specifically to the generation of data in support of products claiming efficacy in pasture fed cattle.

Currently, the only technique that will fully assess the biological effectiveness of proposed antibloat compounds is a field study. Measurements of both detergency and anti-foaming ability can be produced by laboratory methods, but these are useful only for screening potential compounds for use in field studies. Data from these studies are explanatory and supportive only, and unsuitable for registration purposes.

3.1 General

3.1.1 Study animals must be of a similar genotype to the commercial genotype commonly used in New Zealand. Extrapolation within breed type may be justified in some cases, e.g. lactating dairy cattle to lactating beef cattle, but not vice versa.

It is preferred that studies involve genotypes that form the majority of the national dairy herd.

3.1.2 New Zealand bloat studies must contain Holstein-Friesian, Holstein-Friesian/Jersey or Jersey animals as the principal breed employed in the study.

3.1.3 All animals used in the studies must be free of any clinical disease that could affect the outcome of the study.

3.1.4 Efficacy field studies must be undertaken in similar environmental and management conditions to the proposed end use.

Animals should be managed on a daily basis following normal New Zealand practice. Water and feed should be supplied as per normal New Zealand farming conditions.

3.1.5 Staff must be appropriately trained for monitoring bloat scoring and treatment of bloated animals during field studies.

3.1.6 All ethics requirements must be strictly adhered to. These may vary from site to site and must be specifically outlined in the study protocol.

Information that should be outlined includes, for example, the bloat score at which animals must be removed from challenge pasture, the number of staff required at each scoring session etc.

3.2 Field studies

3.2.1 Experimental design

3.2.1.1 The study must include a negative (untreated) control group. The minimum study treatment group size is ten animals, if no prior bloat history is known.

3.2.1.2 Animals must be balanced for bloat score breeding value.

High susceptibility bloat herds should be used.

Treatment group numbers are preferably balanced numerically, but in some cases statistical methods may allow for some discrepancy in group numbers if total animal numbers are limited. Each group must, however, contain at least ten animals.

Study groups should be balanced for weight, gender, age and calving date.

3.2.1.3 All study treatment groups must be run as one herd throughout the duration of the study.

3.2.1.4 Non-lactating animals must not be used to generate bloat efficacy data if the product will be used on lactating animals.

If the applicant intends to register the trade name product for use in any bloat period where animals are lactating, it is required that lactating animals are used during the study. The appetite drive in lactating animals is much greater than in dry cows. This provides for potentially much greater bloat challenge. Protection against bloat in the dry period cannot be extrapolated to indicate protection from bloat in full lactation.

3.2.1.5 For novel actives, two field bloat efficacy studies must be submitted. One study must be conducted in New Zealand. The second study may be conducted overseas, but must be conducted under management systems very similar to New Zealand.

Novel active compounds must be trialled in New Zealand. Supporting overseas data from studies conducted in countries with pasture based management systems will be accepted as supporting data. At least one overseas bloat efficacy study conducted under a pasture based bloat challenge environment will be required if two local bloat efficacy studies are not conducted.

3.2.1.6 For variations (e.g. formulation developments) on previously assessed and New Zealand registered actives, one bloat efficacy field study, preferably conducted in New Zealand, is required. Overseas bloat efficacy field studies will be considered providing the study design aligns closely with New Zealand conditions and animals.

3.2.1.7 Study animals will need to be challenged for several days prior to beginning the bloat scoring to allow rumen microflora time to adapt to the offered pasture.

3.2.1.8 A score of 1.5 using the scoring method mentioned in section 3.2.2.2 is considered to be the stage at which an animal is at risk of death from bloat.

3.2.2 Reporting

3.2.2.1 Breed and pasture type used in the study must be described.

3.2.2.2 The bloat scoring method used must be described.

The bloat scoring method described in:
Johns, A.T. 1954: Bloat in cattle on red clover. I.
NZ Journal Science Technology 36A: 289-320.
is acceptable for bloat assessment. The addition of 0.5 scores, giving an eleven point assessment, is preferred as described in:
Lippke, H.; Reaves, J.L.; Jacobson; N.L. 1972: Rumen pressures associated with the scores of a bloat severity scale. *Journal of Animal Science 34*: 171-175.

3.2.2.3 The treatment technique and type must be described.

3.2.2.4 Ethics management must be described. This must detail how animals reaching a stage of rumen distension that places them at risk of death if left untreated are managed.

3.2.2.5 All mortality and cause of death must be recorded.

3.2.2.6 Measurements recorded must include:

- **number of cows at risk of death from bloat;**
- **average individual and group bloat scores on a daily basis;**
- **individual animal daily bloat scores; and**
- **number of bloat scoring days during the study.**

3.2.3 Statistical reporting

3.2.3.1 Bloat scores must be analysed using an animal-model repeated-record analysis of individual bloat scores using restricted maximum likelihood procedures. It is essential that the technique takes account of individual cow-to-cow differences and does not analyse 90 records (30 cows x 3 days) as if these arose from 90 different cows.

Repeated-record analysis of individual bloat scores should be carried out using appropriate statistical software.

3.2.3.2 For efficacy to be claimed there must be a significant ($P \leq 0.05$) reduction in the number of animals at risk of death from bloat between the animals treated with the test substance and the negative (untreated) control group.

3.2.3.3 Power calculations in statistical analysis are only of use where the applicant is investigating differences in bloat efficacy of two formulations against each other and a negative (untreated) control.

APPENDIX A

CONTENT OF AN EFFICACY DATA PACKAGE SUMMARY

1 Identity

1.1 Applicant

1.2 Trade name of product

1.3 Active ingredient(s) and concentration

1.4 Chemistry

Provide references to the section(s) in the chemistry data package that describe the properties of relevance to the assessment of efficacy.

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2 Proposed use pattern

2.1 Use situation

2.2 Condition(s) being treated

2.3 Administration method

2.4 Dosage

2.5 Number and timing of treatments

Provide the normal, minimum and maximum (where applicable) treatment intervals and number of treatments.

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3 Studies

Provide a concise summary of all efficacy studies provided and their conclusions, including the level of efficacy proven and the statistical methods used.

APPENDIX B

CONTENT OF A RISK ASSESSOR'S REPORT FOR EFFICACY DATA

CONCLUSIONS

1 Identity

1.1 Applicant

1.2 Trade name of product

1.3 Active ingredient(s) and concentration

1.4 Chemistry

Comment on the key properties of the active ingredient(s) that impact on the efficacy of the trade name product.

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2 Proposed use pattern

2.1 Use situation

2.2 Condition(s) being treated

2.3 Administration method

2.4 Dosage

Comment on the appropriateness of the dosages proposed in terms of efficacy of the product.

2.5 Number and timing of treatments

Comment on the number and timing of treatments and outline the circumstances of use that will result in the lowest level of efficacy.

2.6 Changes to practice

Include comments on any specific aspects of proposed use that are novel or at variance with similar compounds or common practices.

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3 Supporting data

3.1 Provide a concise statement on the quantity, quality, validity and completeness of the supporting data. Identify the level of efficacy proven.

3.2 Comment on the suitability of the method(s) of statistical analysis used.

3.3 If both New Zealand and overseas study data are submitted, indicate the level of consistency between them.

3.4 Advise whether the data are sufficient to assess efficacy of the trade name product.

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4 Conformance

State whether the supporting data conform to the *ACVM Registration Standard and Guideline for Efficacy of Antibloat Products*, the *ACVM Research Standard*, guidelines and information waivers. Where information waivers have been granted, comment on their impact.

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5 Risk statements

Provide a statement on the risk of the proposed use resulting in animal welfare thresholds being exceeded as a result of inefficacy.

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6 Further work or information

Identify any work that may reduce the level of uncertainty to an acceptable level, assist in the explanation or extrapolation of the data or provide a more complete database.

Assessor's name:
Signature:
Date:
