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**ACVM
REGISTRATION STANDARD
AND GUIDELINE FOR
EFFICACY OF
ANTHELMINTICS IN CATTLE,
SHEEP, GOATS AND DEER**

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Endorsement:

Date:

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR EFFICACY OF ANTHELMINTICS IN CATTLE, SHEEP, GOATS AND DEER

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 anthelmintic for cattle, sheep, goats or deer or to vary the conditions on a registered anthelmintic for cattle, sheep, goats or deer. 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 anthelmintics for cattle, sheep, goats or deer, 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 anthelmintic for cattle, sheep, goats or deer or to vary the conditions on a registered anthelmintic for cattle, sheep, goats or deer;
- all persons conducting a data assessment on applications made to register an anthelmintic for cattle, sheep, goats or deer or to vary the conditions on a registered anthelmintic for cattle, sheep, goats or deer.

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

1.2 Definitions and abbreviations

Target species

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

VICH

Veterinary International Co-operation on Harmonization.

WAAVP

World Association for the Advancement of Veterinary Parasitology.

1.3 References

ACVM Research Standard

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

Wood, I.B., Amaral, N.K., Bairden, K., Duncan, J.L., Kassai, T., Malone, J.B., Pankavich, J.A., Reinecke, R.K., Slocombe, O., Taylor, S.M., Vercruysse, J. (1995): World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) second edition of guidelines for evaluating the efficacy of anthelmintics in ruminants (bovine, ovine, caprine). *Veterinary Parasitology* 58: 181-213.

*VICH Harmonization of Veterinary Anthelmintic Guidelines**

*VICH Harmonization of Veterinary Anthelmintic. Specific recommendations for bovines**

*VICH Harmonization of Veterinary Anthelmintic. Specific recommendations for ovines**

*VICH Harmonization of Veterinary Anthelmintic. Specific recommendations for caprines**

* The VICH documents are currently available on the EMEA website at
<http://www.eudra.org/vetdocs/vets/vich.htm>

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 ANTHELMINTICS IN CATTLE, SHEEP, GOATS AND DEER

The following are mandatory clinical study and reporting requirements for evaluating anthelmintics in cattle, sheep, goats and deer. They are additional to the general efficacy requirements above.

Conduct of trials, unless indicated in 3.1 below, should be in accordance with VICH and WAAVP guidelines. VICH guidelines will take precedence where two separate views on an issue exist, unless indicated below. Reference is made to WAAVP guidelines as they provide more detail on trial design and conduct. For deer, the recommendations for cattle should be adopted.

3.1 Additional requirements

- 3.1.1 Claims may be made only for parasites known to be in New Zealand.**
- 3.1.2 There must be at least two controlled dose confirmation studies with at least one of these conducted in New Zealand. Any claim against a common parasite in New Zealand should be included in the New Zealand study(ies).**
- 3.1.3 Claims made for a genus, rather than a species, in a dose confirmation trial are not acceptable as there are known differences between species in some genera with some anthelmintics.**
- 3.1.4 Each of six animals in each respective treatment group should be infected with each stage and species of parasite for which a claim is to be made. If this cannot be established antemortem, it will be assumed for the treatment group if all control animals are infected.**
- 3.1.5 Efficacy claims must be in line with WAAVP recommendations that such claims should be expressed as a percentage against each separate genus/species as:**
 - **highly effective (>98%);**
 - **effective (90-98%);**
 - **moderately effective (80-89%); or**
 - **insufficiently active or inactive (<80%).**

Such claims can be made only for the species and stage of infection for which this reduction is achieved.

3.16 VICH guidelines state that geometric means are preferable to calculate efficacy but that there may be conditions where arithmetic means may be used. Data must be presented in full so that arithmetic means may be calculated if required.

3.1.7 Pooling of data across trials is not acceptable.

3.1.8 If efficacy is claimed against a strain resistant to the same action group as the active, this resistance must be demonstrated by including appropriate treatment groups. This is also applicable to claims made against resistant strains in other action groups if there is evidence that resistance to the action group confers resistance to the active.

Resistance should be substantial, i.e. less than 80% reduction in mean worm burden against the anthelmintic in question.

3.1.9 The aliquot examined for each organ must be reported and justified.

VICH guidelines stipulate a minimum of 2% aliquots be examined and that there be at least 100 worms present for each species. This needs to be interpreted carefully at the lower end as this could result in only two parasites found in a 2% aliquot. A reasonable number of parasites needs to be counted to satisfy statistical requirements. A confidence interval for counts may be requested for low counts using a small aliquot with interpretation made at the lower end of this. If counts are low it may be necessary to count larger aliquots (5-10%). For some parasites, total counts may be required, e.g. large intestinal parasites. Appropriate samples should be taken at necropsy to allow for these situations.

3.1.10 For goats and sheep, any claim for efficacy based on topical application of the anthelmintic must stipulate the type/breed and length of wool/hair, and these must be used in the relevant trials. Similarly for cattle and deer, trials must include both winter and summer hair coats unless the product is to be used only in a particular season.

3.1.11 Persistent efficacy claims

Details of these are poorly described in both VICH and WAAVP guidelines. VICH has indicated that, for the sake of conformity internationally, one standard protocol should be adopted.

VICH guidelines state that a minimum for a persistence claim (for each duration and parasite claim) should include two trials, each with a non-treated and a treated group. As described for dose confirmation studies, at least one of the studies must be conducted in New Zealand.

Following challenge, animals should be housed for an appropriate period to allow immature larvae to mature. In general, claims should be made only for a species and not for particular stages.

- 3.1.12 If identification of species of nematode is made by examining male morphology, it is necessary to examine at least 50 male nematodes from one genus with allocation of all members of this genus based on the resulting ratio of members of each species found.
- 3.1.13 An acceptable means of preserving gastrointestinal tracts for later examination is to immediately freeze them at -20°C. This precludes saline digests for recovery of immature larval stages but pepsin digests may be conducted. Immediate washing of small intestines may not recover all members of the genus *Trichostrongylus* and there should be either a delay between slaughter and washing of the intestine or it should be subjected to pepsin digest.