



Anthelmintics Efficacy (Cattle, Sheep, Goats and Deer)

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Title

Guidance Document: Anthelmintics Efficacy (Cattle, Sheep, Goats and Deer)

About this document

This document explains the information needed to support an application to register an anthelmintic product under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997.

Related Requirements

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

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1 Purpose

This document explains the information needed to support an application to register an anthelmintic product under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997.

2 Background

The need for efficacy information arises from section 4 of the ACVM Act, which provides for prevention or management of risks associated with the use of agricultural compounds (including veterinary medicines):

- risks to trade in primary produce
- risks to animal welfare
- risks to agricultural security
- risks to public health.

Risks to animal welfare can arise if the use of a veterinary medicine, 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 requirements.

3 Definitions and abbreviations

aliquot size means a specified volume sample of gastrointestinal or other (lung etc) content collected to determine the number of parasites

claim means a statement of efficacy against a parasite species or genus (adult and/or larvae) which is sufficiently supported by data that conforms to the MPI requirement

controlled test means a comparative trial to investigate the efficacy of a drug using test animals allocated into a test group(s) and a negative control group. Trial animals in each group must have an adequate infection of parasites. At a specified time after treatment trial animals are necropsied and parasite species/genus are identified and counted. The efficacy of the test product(s) for a parasite species or life stage is calculated as follows:

$$\% \text{ Efficacy} = 100 \left[\frac{(\text{mean parasite count in control animals}) - (\text{mean parasite count in treated animals})}{(\text{mean parasite count in control animals})} \right]$$

Geometric mean counts are generally utilised to calculate % efficacy.

This test is most widely used and accepted when the group sizes are the same

dose confirmation study means a study performed to confirm the efficacy of a selected drug dose and formulation. It may be conducted in the laboratory or in the field

dose determination study means an *in-vivo* study conducted to determine the appropriate dose or dose range of a veterinary drug for efficacy

dose-limiting parasite means a susceptible parasite species/stage identified during dose determination studies, or from literature, that requires the greatest dose of active to achieve 90% efficacy. Administration of a lower dose of the anthelmintic will result in efficacy below 90% for this dose-limiting parasite even though it will adequately control other parasite species in the target animal

efficacy (of a veterinary medicine) means the degree to which the medicinal claims made by the applicant about the product have been justified and are likely to be attained under practical field conditions within New Zealand

field efficacy study means a large scale study to confirm the effectiveness and safety of a veterinary medicine under actual use conditions. It is conducted after dose determination and dose confirmation studies using faecal egg count (FEC) reduction as a measure of efficacy

field isolate means a helminth isolate that represents current parasitic field infections. Isolates must have been characterised by source, date, location, previous anthelmintic exposure and maintenance procedures

good clinical practice (GCP) means an international standard for designing, conducting, monitoring, auditing, recording, analysing, and reporting clinical studies that provides assurance that the data and reported results are complete, correct and accurate, and that the welfare of the study animals and the safety of the study personnel involved in the study are ensured, and the environment and the food chain are protected

laboratory strain means a sub-population of helminths isolated from the field, which has been characterised and segregated in the laboratory. Segregation is based on a particular property making it unique for areas of research such as resistance to certain anti-parasitic compounds

target species means the species of animal (that is, sheep, cattle, deer or goats) to which the test substance is administered

VICH means Veterinary International Co-operation on Harmonization

WAAVP means World Association for the Advancement of Veterinary Parasitology.

4 Information needed

- (1) The minimum information MPI considers necessary is presented in **bold** and numbered in each section, while any further guidance for a specific clause is in regular font. Extra guidance for a whole section is given (without numbers) under '**Additional guidance**'.

Guidelines reflect principles commonly recognised by the scientific community as appropriate and necessary for collecting scientific data. MPI recognises that there are acceptable methods, other than those described in this guideline, that are capable of achieving the principles of this document.

- (2) Applicants are responsible for providing all information required by MPI to make a decision on the application. Applications that do not contain the required information will not be assessed. If further advice is required, you are advised to contract the services of an appropriate consultant prior to submitting your application.

5 General requirements for efficacy studies

5.1 General clinical requirements

- (1) Conduct all studies in accordance with the ACVM Research Standard. The principles of good clinical practice (GCP) should be applied to all clinical trials.**
- (2) All trials must be conducted in accordance with an approval from a valid Animal Ethics Committee.**
- (3) The product formulation used in studies must be identical to that being proposed for registration.**
- (4) Report all studies conducted with the final formulation to investigate efficacy to MPI.**
- (5) If a dose range is stated on the label, undertake efficacy studies using the lowest dose rate.**
- (6) Investigate the efficacy of the product and its active ingredient(s) in each of the proposed target species.**

5.2 Documentation

- (1) Present all reports in accordance with Section 2.2 of the ACVM Research Standard. Include all trial design information, statistical methods and all raw data.**
- (2) Provide the Provisional Registration number and Animal Ethics Approval.**
- (3) Provide any papers, articles, documents or information referenced in the application documents. If the reference information is in a language other than English, provide the original document and an English translation.**
- (4) State the overseas licensing status of the veterinary medicine and supply approved product label(s).**
 - a) Discuss any differences in the overseas approval and what is proposed for registration in New Zealand.**
 - b) Give a reason if the veterinary medicine is not licensed for use in the country of origin.**

6 Requirements for efficacy of anthelmintics in cattle, sheep, goats and deer

- (1) **The following clinical study and reporting requirements for evaluating anthelmintics in cattle, sheep, goats and deer are additional to the general efficacy requirements above.**
- (2) **Efficacy data for ruminant anthelmintics, unless indicated in 6.1 and 6.2 below, should be generated in accordance with VICH and WAAVP guidelines, which are to be read in conjunction with this guideline.** VICH guidelines will take precedence if 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.

6.1 Specific requirements

6.1.1 Studies

- (1) **Investigate efficacy using dose determination and dose confirmation studies. Controlled tests are required for both study types.**
- (2) **Conduct dose determination studies according to VICH guidance.** These studies are generally not required for generic products if an optimum dose for effective control of dose limiting parasites in the target species has been established for the anthelmintic active using the proposed formulation type and route of administration.
- (3) **Submit at least two controlled dose confirmation studies with a minimum of one trial conducted in New Zealand. Include common, dose-limiting and clinically significant New Zealand parasites in the New Zealand study(ies) to enable a claim to be approved.**
- (4) Field efficacy studies using egg count reduction and larval differentiation may be required to support efficacy and safety under field conditions subsequent to dose determination and dose confirmation studies. **Field efficacy studies are required for 'New active ingredient' (A1) and 'Registered active ingredient with new risk profile' (A2) registrations. These studies are applicable in host species where a correlation between FECR and anthelmintic efficacy has been demonstrated.**

6.1.2 Efficacy claims

- (1) **Claims for each parasite species and life stage will be assigned if:**
 - a) **two dose confirmation studies are conducted with adequate numbers of adequately infected control and treated animals; and**
 - b) **the mean reduction of gastrointestinal helminths and lungworm parasite counts is $\geq 95\%$ and the mean reduction in liver fluke counts is $\geq 90\%$; and**
Geometric mean (GM) parasite counts will be used in the primary assessment of efficacy. However arithmetic mean (AM) parasite counts will be taken into consideration if there is a large difference between GM and AM total worm count reduction.
 - c) **the difference in mean parasite counts between treated and control animals is statistically significant ($p < 0.05$); and**
Parametric and Nonparametric procedures are acceptable. Data may be transformed if necessary to meet the assumptions of the statistical test conducted.
 - d) **the infection of the animals in each study is deemed adequate based on historical, parasitological and/or statistical criteria.**

Additional guidance

The efficacy thresholds for gastrointestinal helminths and lungworm have been amended from WAAVP recommendations and reflect the New Zealand farming requirement to minimise larval pasture contamination and subsequent larval challenge in target animals.

Efficacy claims for helminths and lungworm can be made only for the species and stage of infection for which $\geq 95\%$ reduction in mean worm count is achieved. If efficacy achieved is less than 95%, then an efficacy claim *may* be specified on the label in some circumstances, e.g. if there is no other effective treatment for the specific parasite or a lower efficacy may be justified based on the pathogenesis and significance of the parasite species. This will be assessed on a case by case basis. It is not intended to apply to anthelmintic resistant helminth strains.

Calculation of efficacy using geometric means is currently recommended by the VICH and has been adopted by MPI in efficacy assessments. However, the geometric mean may underestimate the biological significance of worms in the animals with the highest worm burdens. If the arithmetic mean total worm reduction shows marked variance from the geometric mean total worm reduction it will be taken into consideration during the efficacy assessment. Present both data in study reports. Arithmetic means will be used to calculate faecal egg count reduction.

During analysis, zero counts cannot be ignored.

For guidance on efficacy statements and mandatory label statements required for anthelmintic products refer to Labelling Veterinary Medicines: ACVM labelling requirements for veterinary medicines requiring registration.

6.1.3 Study design

- (1) **A minimum of 6 animals per group is required for dose determination, dose confirmation and persistent efficacy studies.** This number may need to be increased due to design or statistical considerations. Review sample size for each study.
- (2) **Target animals should be clinically healthy and representative of the age, sex, and class for which the anthelmintic is to be administered.** In general, the animals will be ruminating, and older than 3 months of age.
- (3) **Animals should be assigned randomly to each treatment group.** Blocking in replicates by weight, sex, age, and/or exposure to parasites may be appropriate to aid in reducing trial variance. This should be considered during trial design. Faecal egg/larval counts may also be useful to allocate the experimental animals.
- (4) **The level and distribution of helminth species and stage of infection among animals in the treatment and control groups must be adequate to permit the above standard of efficacy to be met with acceptable statistical and biological confidence. Multiple infections are acceptable, but each species must reach acceptable minimum levels of infection.**

Additional guidance

As a general guideline, the minimal mean number of nematodes considered to constitute an adequate infection is 100. However, much higher worm counts for many species are commonly observed, e.g. in cattle, adult *Cooperia spp.* worm counts of over 1000 are routinely seen.

For some parasites, e.g. large intestinal nematodes such as *Trichuris spp.* and *Oesophagostomum spp.*, and lung worms, e.g. *Dictyocaulus spp.*, lower minimal mean counts may be considered. Lower counts may also be considered for trematodes and cestodes, e.g. for *Fasciola spp.* minimal mean counts of 20 adults may be considered adequate.

If all animals in the control group are infected, one possible statistical method to confirm adequacy of infection advocated by the VICH involves calculating the lower 95% confidence limit of the control group geometric mean worm count. If this value is greater than 10% of the control group geometric mean, then the infection can be said to be adequate (see table below). This methodology is not appropriate if control animals have zero counts. Refer to the VICH guidelines for more advice.

Table: Example of adequacy of infection calculation when all control animals are infected			
<i>Trichuris spp</i> in negative control group			
Animal ID	Count	Log Count	Upper 95% CI = Antilog (logGM + (SE * t _{0.95})) Lower 95% CI = Antilog (logGM - (SE * t _{0.95})) t _{0.95} = t- value α= 0.05 (2 sided), n-1 d.f. SE = standard error
1	140	2.1	
2	30	1.48	
3	120	2.08	
4	110	2.04	
5	70	1.85	
6	100	2.00	
7	50	1.70	
8	100	2.00	
Mean	90	1.91	Interpretation of adequacy of infection All animals in the control group are infected. The mean count is less than 100 parasites. However, lower mean counts may be seen for this species. Using the statistical method described above, the lower 95% CI of the GM (52.8) is greater than 10% of GM (i.e. 8.15). Therefore this infection can be said to be adequate and further calculation of efficacy may proceed.
Standard deviation	37	0.22	
Standard error		0.08	
Geometric mean		81.5	
Lower 95% CI GM		52.8	
Upper 95%CI GM		125.6	

- (5) **Regardless of the statistical method employed, adequate infections are still required in a minimum of 6 control animals.**

6.1.4 Parasites

- (1) **Claims may be made only for parasites known to be in New Zealand.** For purposes of label harmonisation, species not found in New Zealand may be included on the product label but must be identified as “Not found in New Zealand”.
- (2) **Use current field isolates in all studies unless justified. Natural infections are preferred to assess efficacy against adult species and stages.** Superimposed infections may be used to assist in obtaining adequate infection. The decision to use natural or induced infections is determined by the species and stage of infection for which claims are proposed.
- (3) **For isolates used in induced infections, provide information regarding characterisation of each isolate, e.g. source, date, location of isolation, exposure to anthelmintics, resistance status (and maintenance procedures) as applicable.**
- (4) Studies to demonstrate treatment and control of larval stages generally require the use of induced infections. **Studies to investigate efficacy against hypobiotic larvae must use natural infections.**
- (5) **For all efficacy claims, specify species for each parasite. Claims against immature parasites must also be specified by life stage.** Claims against parasites by genus alone are not acceptable as there are known differences in susceptibility between species in some genera to some anthelmintics. The efficacy of some anthelmintics can also differ between life stages.

6.1.5 Sample analysis

- (1) **The aliquot examined for each organ must be reported and justified.**

Additional guidance

VICH guidelines stipulate a minimum of 2% aliquots be examined. Counts need to be interpreted carefully and the number of parasites counted must satisfy statistical requirements.

Generally a minimum of 10 parasites per species should be counted. A confidence interval may be requested for low counts using a small aliquot with interpretation made at the lower end of the confidence interval. If counts are very low, larger aliquots (5-10%) should be examined. For example, 100 nematodes is equivalent to only 2 parasites found in a 2% aliquot. In this instance a larger aliquot should be examined. 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.

If identification of species of nematode is made by examining male morphology, 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. If speciation identifies only a small number of minority species in a genus, a greater number of parasites may need to be examined.

Perform all faecal egg counts, larval culture and total worm counts using a validated method. Describe these methods in the study report.

6.1.6 Topical application

- (1) **For goats and sheep any claim for efficacy based on topical application of the anthelmintic must stipulate the breed type 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, which is stipulated on the product label.**
- (2) **For products applied topically, the impact of weather (e.g. rainfall, UV light etc) should be included in the evaluation of the effectiveness of the product.**
- (3) **Verify that anthelmintic efficacy is achieved due to percutaneous absorption of the formulation. Study design must account for animal behaviour, e.g. allolicking and heterolicking.**

6.1.7 Persistent efficacy

- (1) **Conduct a minimum of two negatively controlled slaughter studies per species claimed to support persistent efficacy. Conduct at least one of these studies in New Zealand.** The trial design should mimic natural reinfection as closely as possible to demonstrate ongoing protection. Persistent efficacy should be assessed at regular intervals throughout the trial period. Refer to VICH guidelines for additional advice.
- (2) **A persistent efficacy claim will be granted for the duration of time over which $\geq 95\%$ reduction in mean worm count is achieved at each test interval. Claims will be species specific.** Persistent efficacy claims for parasites will only be granted on a species-by-species basis, and should be made only for a species and not for particular life stages.

6.2 Special consideration for combination anthelmintic products

The registration of fixed dose combination anthelmintic products is currently not addressed in VICH guidelines. The following standards and guidelines are adopted from WAAVP (Geary *et. al.* 2012) recommendations, which are to be read in conjunction with this document.

- (1) **Provide a detailed justification for use of the specific combination of anthelmintic actives for each application** (for example, to achieve a wider spectrum of activity, or to overcome anthelmintic resistance of nematode species to individual anthelmintic actives).

6.2.1 Studies required

The following applies to all fixed dose combination anthelmintic products unless efficacy is achieved due to synergistic action of the actives. Products with synergistic activity will be assessed based on guidance for single active anthelmintics above.

Dose determination studies

- (1) **Dose determination studies are required if a novel anthelmintic active is included in the formulation.** If the anthelmintic actives are not novel, dose determination studies are likely to be required only if one or more of the actives have not been previously registered for administration in the target species using the proposed formulation type, route of administration and/or dose rates.

Pharmacokinetic non-interference studies

- (1) **Pharmacokinetic studies are required to investigate potential interference between constituent anthelmintic actives at the pharmacokinetic level.** Studies are to compare data from target animals administered the combination anthelmintic with data from positive control groups administered the individual constituent actives separately.
- (2) **The reference single active anthelmintic trade name products (TNP) used in these studies should be the innovator TNP if available.**
- (3) **The single active anthelmintic reference products are to be administered in the same dosage form using the same dose rate and route as proposed for the combination product unless prospectively justified.**

Dose confirmation studies

- (1) **Establish efficacy of combination anthelmintics in dose confirmation studies.** These studies are also required to confirm non-interference between active constituents as pharmacological antagonism between actives may occur against parasite species *in vivo*.
- (2) **The design of dose confirmation studies must reflect the rationale of the proposed use for the fixed combination anthelmintic.**
- (3) **Base study design, analysis and criteria for acceptance of efficacy claims on guidance provided in section 6.1.**
- (4) **Studies should include the dose-limiting parasite(s) for each anthelmintic active in the combination.**
- (5) **Confirm the efficacy of each individual anthelmintic active in the combination in the dose confirmation studies.**

Additional guidance

If the rationale for combination use is to manage existing resistance, conduct studies using parasite isolates demonstrated to be resistant to one or more of the individual anthelmintic ingredients. Resistance against the anthelmintic active(s) in question should be substantial, i.e. when treated with a dose that would historically be $\geq 95\%$ efficacious against the parasite species $\leq 80\%$ reduction in the mean worm count and /or FEC is observed. Studies should compare the efficacy of the combination anthelmintic administered in target animals with efficacy achieved in positive control groups administered the individual constituent actives separately. The reference products are to be administered in the same dosage form using the same dose rate and route as proposed for the combination product unless prospectively justified.

Studies conducted for combination products with a formulation that has greater than 2 anthelmintic actives with a similar spectrum of activity may also need to include innovator combination TNP containing 2 (or more) of the proposed active constituents as positive controls. For example, trials for a

triple combination broad-spectrum anthelmintic may require the inclusion of dual combination product(s) as positive controls.

The positive control products used in these studies should be the innovator TNP for which MPI holds efficacy data on file, if available.

Field efficacy studies

- (1) Field efficacy studies using egg count reduction and larval differentiation may be required to support efficacy and safety under field conditions subsequent to the controlled studies above. This is only applicable to host species if there is a correlation between FEC and anthelmintic efficacy. **Field efficacy studies are required for novel combinations.** (Refer to WAAVP (Geary *et. al.* 2012) guidelines for more information.)

7 References

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

ACVM Research Standard

Geary, T G., Hosking, B C., Skuce P J., von Samson-Himmelstjerna G, Maeder S, Holdsworth P, Pomroy W, Vercruysse J. (2012) World Association for the Advancement of Veterinary Parasitology (WAAVP) Guideline: Anthelmintic combination products targeting nematode infections of ruminants and horses. *Veterinary Parasitology* 190 306-316

Labelling Veterinary Medicines: ACVM labelling requirements for veterinary medicines requiring registration

VICH Efficacy of anthelmintics: General requirements*

VICH Efficacy of anthelmintics: Specific recommendation for bovines*

VICH Efficacy of anthelmintics: Specific recommendation for ovines*

VICH Efficacy of anthelmintics: Specific recommendation for caprines*

* The VICH documents are currently available on the VICH website at <http://www.vichsec.org>

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