ISBN 0-478-07781-5

26 ACVM 12/03

New Zealand Food Safety Authority
Post Office Box 2835
Wellington, New Zealand

ACVM REGISTRATION STANDARD AND GUIDELINE FOR TARGET ANIMAL SAFETY

This document may be altered at any time. It was current as at the date in the footer of each page of the document. It is recommended that anyone intending to use this document should contact the ACVM Group of NZFSA or check its website (http://www.nzfsa.govt.nz/acvm/) to confirm that it is the current version.

Endorsement:
Date:

CONTENTS

ACVM REGISTRATION
STANDARD AND GUIDELINE FOR
TARGET ANIMAL SAFETY

1 INTRODUCTION

While some pain or distress to the animal is inevitable at times from administration of a product, the intensity and duration must be no more than is necessary to prevent or treat the condition concerned. Some recognition is therefore required of the extent of suffering that may arise from the use of alternative products and the suffering that may arise from not administering the product.

This document specifies the minimum requirements for target animal safety studies submitted in support of an application to register a trade name product, or to vary the conditions on a registered trade name 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.

This standard is compulsory in all cases where safety data are required to be provided for registration of a trade name product, unless a waiver has been granted by the New Zealand Food Safety Authority (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 Agricultural Compounds and Veterinary Medicines (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 trade name product or to vary the conditions on a registered trade name product where safety data are required;**

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

The standard provides specifications for:

- ***in vivo* and *in vitro* techniques**
- **application devices**
- **pharmacology**
- **safety study requirements**
- **monitoring.**

1.2 Definitions and abbreviations

Alopecia
Deficiency of the hair or wool coat.

Ataxia
Failure of muscular coordination.

Bolus
Solid preparation of compressed medicine, designed for slow release of the medicine, usually by the oral route.

Capsules
Solid preparations with hard or soft shells of one or more parts, intended for oral administration. The active ingredient may be inside or be contained in the shell material. In the case of modified release capsules, the contents of the capsule and/or its shell are designed to modify the rate or the place in the tract at which the active ingredients are released.

Ear preparations
Preparations intended for installation, spraying, insufflation or application to the auditory meatus.

Erythema
Redness of the skin caused by congestion of the capillaries in the lower layers of the skin.

Eschar
Deep cutaneous slough, such as that produced by a thermal burn, a corrosive action, a decubitus ulcer or a saddle gall.

Eye preparations
Preparations intended for application or administration to the eyeball and/or the conjunctiva, or for insertion into the conjunctival sac.

Implant
A preparation that is inserted or grafted into the body.

Infusion
A preparation that enters the body by flow of gravity.

Injection
A preparation that is forced into the body by needle or other means.

Insufflation
A preparation that is blown into the site of administration.

Intramammary infusions (Intramammary injections)
Preparations intended for introduction into the mammary gland via the teat canal. They can be for administration to lactating animals (e.g. lactating cow preparations), or to animals at the end of lactation or non-lactating animals (e.g. dry cow preparations).

Oedema
An abnormal accumulation of fluid in the cavities and intercellular spaces of the body.

Oral preparations
Preparations administered into the gastrointestinal tract via the oral cavity, sometimes after dilution in the feed or drinking water.

Paralysis
Loss or impairment of motor function in a part due to a lesion of the neural or muscular mechanism.

Parenteral preparations
Preparations intended for administration by injection, infusion or implantation.

Paresis
Slight or incomplete paralysis.

Pharmacodynamics
Studies conducted to establish the pharmacodynamic effects (including both desired therapeutic effects and secondary pharmacological effects) and the mode of action.

Pruritis
Itching.

Repeated dose safety studies
The toxic phenomena (both functional and morphological) and their occurrence related to time, dose level, and route of administration which may result from repeated administration of the product by its recommended administration route (active ingredient and, where necessary, metabolites thereof), considering the maximum duration of treatment in the target species.

Single dose safety studies
The toxic phenomena (both functional and morphological) and their occurrence related to time, dose level, and route of administration which may result from a single administration of the product by its recommended administration route, including the likely effects of acute overdosage in the target animal.

Target animal
The animal (including all its life stages) purposefully treated with the trade name product and, in the case of a pregnant animal, includes a foetus in the second half of gestation.

Teratogenicity
The capacity to cause physical defects in the developing embryo.

Topical preparations
Preparations for application to skin, hair, coat, teats, udders, claws, hoofs or external mucous membranes. They may be intended for local or systemic action.

Unanticipated event
Any abnormal response associated with the use of a test substance, whether or not considered to be product related, which may impact on the results of a study.

Unnecessary pain or distress
Adverse effects arising from the use of a veterinary medicine, including chronic pain or distress, immediate pain or distress, delayed development of symptoms, and abnormalities in the animal, that are unnecessary (while accepting that some pain or distress may be necessary to achieve benefit).

Applicants should note that reduced productivity (e.g. reduced milk production, infertility) is not deemed to be an animal welfare concern.

1.3 References

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

ACVM Registration Information Requirements for Plant Compounds in New Zealand

ACVM Research Standard

2 GENERAL INFORMATION REQUIREMENTS

In some sections of this document, requirements that apply only to specific product categories are listed. Only products that fall into the category noted must comply with that section. Where a product falls into several categories, compliance with each category must be shown.

2.1 Use of *in vivo* and *in vitro* techniques

Registrants should note that the testing methods must be shown to be accurate. Validation studies will be necessary when an unapproved testing method is used.

Information can be generated about the impact of a trade name product on the health of animals using a range of techniques, particularly:

- *in vivo* experiments, where behavioural responses, physiological factors and/or pharmacological properties are monitored in conscious or anaesthetised animals;
- *in vitro* experiments, where animal tissues are isolated prior to experimentation and/or monitoring;
- chemical techniques, where no animals or animal tissues are utilised;
- a selection of a variety of the above techniques.

One of the major principles employed to minimise the animal welfare implications associated with the use of animals in scientific procedures is that of replacement, where use of alternatives to live animal techniques is encouraged. The ACVM Group strongly supports this philosophy.

If *in vitro* work will yield information that adequately satisfies the safety registration requirements of a product, it may suffice without proceeding with *in vivo* studies. However, it must be proven that the *in vitro* results can be extrapolated accurately to the *in vivo* situation in New Zealand. In cases of doubt, small pilot projects involving a few animals to confirm findings and to validate the extrapolate should be considered.

Similar considerations should be made where an applicant is conducting research to replace use of live animals in quality assurance techniques, e.g. to confirm potency of a vaccine. The development of *in vitro* techniques to replace routine *in vivo* safety and potency tests is to be encouraged.

If alternatives to whole animal experiments are employed, their validity must be proven.

Applicants should remember that eggs, foetuses and embryos, where development of an integrated nervous system is evident, must be treated in a humane manner. Development of an integrated nervous system must be assumed for all foetuses in the second half of gestation.

2.2 Application devices

2.2.1 Implants, capsules, boluses and other application devices (e.g. controlled release inserts or transdermal patches) that are attached on or inserted into the animal must be shaped appropriately for the administration site and have no sharp, obstructive or irritating edges.

2.2.2 Application devices must be easily applied or inserted without causing unnecessary stress, injury, sensitisation or pain, including after repeat administrations.

2.2.3 Application devices must remain firmly attached to or within the animal during their use life.

2.2.4 Application devices must not interfere with the usual behaviour and husbandry of the animal.

2.3 Pharmacology

2.3.1 Products must not cause undue irritation or sensitisation (either locally, systemically or to neighbouring tissues) when used according to proposed conditions.

2.3.2 Products must not cause any unacceptable adverse effects or symptoms of overdosing or toxicity when used according to proposed conditions.

The data on absorption, distribution, biotransformation, excretion, and the occurrence of metabolites in animals and, where available, in humans (pharmacokinetics) should be considered, including necessary extrapolations from laboratory animals to target animals.

3 SAFETY STUDY REQUIREMENTS

3.1 General requirements

3.1.1 All studies must be conducted in accordance with the *ACVM Research Standard.*

3.1.2 Product formulation and use patterns used in studies must be identical to those being proposed for registration. This includes age, rumen status, liveweight and breed where significant differences in response are anticipated. It also includes:

- **manufacturer and site of manufacture**
- **manufacturing method and standards**
- **packaging**
- **applicator and/administration device**
- **route(s) of administration or application**
- **site(s) of administration or application**
- **method of administration or application**
- **management of the product prior to and during treatment, and in accordance with that expected to be applied in New Zealand.**
- **management and condition of target animals prior to and during treatment, and in accordance with those expected to be applied under New Zealand conditions. This includes factors relating to summer and winter conditions, and wet and dry conditions where this is relevant.**
- **the target animal(s), including age, sex, breed, species, stage of lactation etc, particularly where it is anticipated that differences may occur.**

The medicine should be applied at the same time each day, where this is relevant to the use patterns.

The trade name product should be within its stated shelf life for the duration of the studies.

3.1.3 Safety studies must be undertaken in similar environmental and management conditions to the proposed end use.

3.1.4 All relevant classes of target animal (considering age, sex, breed, species, stages of lactation etc.) must be included in the selection of study animals.

3.1.5 Study animals must be healthy, i.e. not suffering from the condition for which the trade name product will be used, or from any unrelated condition that could impact on the absorption, metabolism or excretion of the product or its metabolites.

3.1.6 At least ten animals from each target animal group must be used for each different use pattern being proposed. It is recommended that at least five untreated control animals are required as comparison for each treated group of animals. If controls are not included, deviations from normal will be regarded as a product effect.

The results obtained from a pilot study should be used by the applicant to provide an indication of the number of study animals that should be used in the full safety study, in discussion with a biometrician and other scientific experts. The results obtained from the pilot study alone may be sufficient to support registration in some instances.

Where the application device, delivery route or active ingredient is novel (i.e. not registered in New Zealand previously for that product type), significantly greater numbers of animals will usually be required. Advice should be obtained from biometricians and other scientific professionals as to an appropriate number of animals. Consideration should be given to the likely extent of use of the product and the degree of control over its use that will ultimately be in place.

3.1.7 For investigation of local tolerance of intramammary preparations, treatment of individual quarters is acceptable.

3.1.8 Dosing regimen

- **Studies must be undertaken using the maximum recommended dose rate, the minimum recommended repeat dosing interval, and following the longest recommended treatment period on the label. Maximum dose volume per site must be as indicated on the product label.**

- **For new active ingredients or delivery devices, a safety study using multiples of the maximum recommended doses for at least the maximum duration of use and at the maximum administration rate is required.**

  In most cases, the combination of 1x, 3x and 5x the maximum recommended dose is appropriate. However, when it is expected that 5x dosing would result in adverse effects, the combination of 1x, 2x and 3x is acceptable. Alternatively, when it is unlikely that adverse effects may result from the 5x dose, the applicant may choose to increase the dosing.

  Where the product might adversely affect the immune response of the vaccinate or of its progeny, suitable tests on the immunological shall be carried out. In particular, evaluation should consider whether single and repeated dosing elicits sensitisation or allergic reactions at low concentrations of the active ingredient.

- **If the active ingredient and delivery device are not novel, studies need be carried out only at the maximum recommended dose rate, using the minimum recommended repeat dosing interval, and following the longest recommended treatment period on the label, providing that the formulation is also shown to be bioequivalent to a registered product with the same administration routes, use rates, target species etc.**

Administration of the product should continue for at least the maximum recommended treatment duration. In the case of continuous treatments for poultry, the studies should be carried out for the time periods stipulated:

- for broiler chickens, for 7 weeks or to market weight starting at one day of age;
- for replacement chickens, for 16 weeks starting at one day of age;
- for laying and breeding turkeys and chickens (including broiler breeders), for 4 months of egg production;
- for meat turkeys, for 5 months or to market weight.

3.1.9 A complete gross and histopathological examination must be carried out on all animals that die during, or as a result of, the study.

3.1.10 Observations must be recorded, where relevant, for at least one week pre-treatment; throughout the maximum treatment period; and, where relevant, for at least two weeks post-treatment.

A sufficient time must elapse between administration of treatments similar to those used in the study and commencement of the study. A minimum of two weeks is required to ensure that previous treatments will have no effect. Note the pre-treatment observations are to be recorded and reported for the week prior to commencement of the study.

3.1.11 Reports must be presented in accordance with the *ACVM Research Standard* and must include the following:

- **Full details of each observed reaction must be reported on an individual animal basis.**
- **Study results must be reported as a comparison between untreated and treated animals.**
- **Observation and examination criteria must be reported.**

3.1.12 Irrespective of the results obtained during safety studies, any unanticipated reactions occurring during any other studies, or known or suspected by reports from users, either in New Zealand or overseas, must be reported at the time of application.

The onset and duration of toxic effects and unanticipated events arising from administration of a trade name product, the dose-relationship of these, and their reversibility or irreversibility, and all species-, breed-, age- or sex-related differences should be considered, in particular:

- toxic signs
- causes of death, clinical-chemical, haematological, pathological and other clinical observations.

3.2 Monitoring

The extent of monitoring undertaken in field studies must be adequate to address a range of safety factors in the target animal, including:

- **effects associated with the pharmacology of the product; and**
- **effects associated with the route of administration.**

Where long-term or repeat administration is expected to result in a higher risk of adverse effects, drug accumulation or sensitisation, or where the product is likely to be used in breeding animals and could result in teratogenic effects, by knowledge of its formulation or properties, the study period should be extended for an appropriate length of time.

3.2.1 Effects of pharmacology

The following observations and examinations are required for all trade name products:

- **gastrointestinal system: appetite and faecal changes**
- **cardiovascular system: heart rate and rhythm, and colour of mucous membranes**
- **respiratory system: respiratory rate**
- **body weight and condition**
- **body temperature**
- **production changes**
- **behavioural changes**
- **neuromuscular effects**
- **morbidity**
- **mortality**
- **lack of interactions with other medicines if recommended for concurrent use**
- **clinical chemistry (haematology, biochemistry, urinalysis), according to the pharmacological properties of the formulation.**

Where not provided, applicants are expected to provide justification for the omission.

3.2.2 Effects of route of administration (for both local and systemic effects)

3.2.2.1 Topical products applied to the skin

Data must address the incidence and severity of, and the risks arising from:

- **pruritis**
- **erythema**
- **oedema**
- **alopecia**
- **oral ingestion, e.g. via grooming or suckling.**

3.2.2.2 Topical products applied to the ear

Data must address the incidence and severity of, and the risks arising from, the product exerting pressure or otherwise causing damage to the tympanic membrane.

3.2.2.3 Topical products applied to the eye

Data must address the incidence and severity of, and the risks arising from changes to the:

- **eyelid**
- **conjunctiva**
- **cornea**
- **uvea**
- **lens**
- **retina.**

3.2.2.4 Parenteral products

Data must address the incidence, severity, persistence and risks arising from the following reactions at the site of injection, implantation or insertion:

- **pain**
- **swelling**
- **inflammation**
- **necrosis**
- **evidence of infection or parasite infestation**
- **blood pressure (intravenous routes only).**

Where the site of injection is not indicated on the label, the ACVM Group's preferred injection site for food producing animals (the anterior half of the neck) must be used during field studies. Where a specific site of injection is recommended, it must be used.

3.2.2.5 Oral products

Data must address the incidence, severity and risks of:

- **exacerbated toxicity**
- **irritation of the gastrointestinal tract**
- **oral cavity and mucous membrane changes**
- **abdominal pain**
- **faecal changes**
- **vomiting.**

3.2.2.6 Cardiovascular products

Data for products that affect the cardiovascular system must address the incidence, severity, persistence and risks arising from changes to blood pressure.

3.2.2.7 Respiratory products

Data for products that are administered by nasal or oral respiratory routes must address the incidence, severity, persistence and risks arising from changes to respiratory sounds and nasal discharge.

3.2.2.8 Additional data required for fish

Data for products administered to fish must be generated at water temperatures between 17º and 22ºC for warm water fish, and 12º and 17ºC for cold water fish.

Therapeutic compounds are administered to fish in three ways:

- by addition to water;
- by incorporation in the feed; or
- by parenteral injection.

Temperature is a very important external factor that should be considered for fish as they are poikilothermic; therefore, temperature changes affect their metabolism and elimination of drugs. In the case of oral and injectable medicines, studies should therefore be conducted at no fewer than two different water temperatures which reflect the practical range of commercial culture conditions (e.g. 17º and 22ºC for warm water fish and 12º and 17ºC for cold water fish).

In the case of water treatments, products must be evaluated under an appropriate range of no fewer than two different levels of various water quality conditions likely to affect product efficacy and/or animal safety (e.g. temperature, pH, total hardness, total alkalinity and/or organic matter loading). Specific conditions selected for testing will depend upon the known physicochemical behaviour of the product in water.

4 GUIDELINES FOR OBSERVATIONS AND EXAMINATIONS OF STUDY ANIMALS

4.1 Physical examinations

An examination should be conducted for the purpose of detecting any abnormalities that may be drug-related or related to its administration.

4.1.1 Neuromuscular effects

Levels and locations of ataxia, paresis and paralysis.

4.1.2 Faecal changes

- blood or other signs of haemorrhage
- excessive cellular debris
- quantity, colour, consistency
- propulsive diarrhoea.

4.1.3 Behavioural changes (mental attitude)

- hyperactivity
- depression
- recumbence
- other changes.

4.2 Reproductive observations

Observations required for pregnant animals include:

4.2.1 Fertility

- number of abortions, stage of gestation and cause
- number of premature births, stage of gestation and cause.

4.2.2 Parturition

- teratogenicity
- embryo toxicity.

4.2.3 Newborn performance

- age and cause of death of any neonate.

4.3 Histopathology

Histological requirements will depend upon what is known about the product being studied. Generally, the following tissues should be considered for examination:

- pituitary gland
- thyroid glands
- parathyroid glands
- adrenal glands
- pancreas
- ovaries
- uterus
- testes
- prostate gland
- thymus
- lymph nodes (cervical, mediastinal, mesenteric)
- brain (cerebrum, cerebellum, mid-brain, brain stem)
- spinal cord (cervical, thoracic, lumbar)
- eyes
- lung
- muscle tissue at intramuscular injection site
- mammary gland
- liver
- gall bladder
- kidneys
- urinary bladder
- heart
- bone and marrow
- marrow smear
- spleen
- stomach
- duodenum
- jejunum
- ileum
- colon
- caecum.

4.4 Clinical pathology

Clinical pathology will depend on the product being studied. Generally, the following parameters should be considered, and appropriate tests conducted:

4.4.1 Haematology

- white blood cell (WBC) count
- red blood cell (RBC) count
- white blood cell differential
- packed cell volume (PCV)
- mean corpuscular volume (MCV)
- haemoglobin
- platelet count.

4.4.2 Blood and serum chemistry

- total protein
- albumin
- globulin
- liver enzymes
- biliary function
- muscle enzymes
- electrolytes
- blood urea nitrogen (BUN)
- sorbital dehydrogenase (SDN)
- glutamate dehydrogenase (GLDH)
- gamma glutamyl transferase (GGT)
- serum alkaline phosphatase (SAP).

4.4.3 Urinalysis

- visual observations - colour, consistency, quantity
- specific gravity
- pH
- protein
- glucose
- ketones
- bilirubin
- urobilinogen
- microscopic examination.

4.5 Assessment scales

4.5.1 Pain or distress

1 No or virtually no stress, irritation or pain
2 Stress, irritation or pain of a minor intensity for a short duration
3 Stress, irritation or pain of a minor intensity for a long duration, or of a moderate intensity for a short duration
4 Stress, irritation or pain of a moderate intensity for a long duration, or of a severe intensity for a short duration
5 Stress, irritation or pain of a severe intensity for a long duration

4.5.2 Erythema

0 No erythema
1 Very slight erythema (barely noticed)
2 Well defined erythema
3 Moderate to severe erythema
4 Severe erythema (beet redness to slight eschar formation)
5 Severe eschar and/or corrosion

4.5.3 Oedema

0 No oedema
1 Very slight oedema (barely noticed)
2 Slight oedema (well defined by definite raising)
3 Moderate oedema (raised approximately 1mm)
4 Severe oedema (raised more than 1mm and extending beyond the area of exposure)