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ACVM REGISTRATION STANDARD AND GUIDELINE FOR THERAPEUTIC EQUIVALENCE OF TRADE NAME PRODUCTS

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Date:

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ACVM REGISTRATION STANDARD AND GUIDELINE FOR THERAPEUTIC EQUIVALENCE OF TRADE NAME PRODUCTS

1 INTRODUCTION

For certain new products, a comparable registered product exists. An applicant may wish to apply for registration of a new product based on data already held by the ACVM Group in support of a currently or previously registered product.

In order for such an application to be considered, the applicant must provide scientific information to prove the relevance of the data held by the ACVM Group to their new product. This can be done by proving therapeutic equivalence of the new product if the applicant proposes that the new product is similar to a previously or currently registered product.

Product types for which the demonstration of pharmacological equivalence alone cannot be used to obtain registration of a trade name product are ectoparasiticides (e.g. pour-ons), intramammary formulations and teat dips. Therapeutic equivalence cannot be used to obtain registration for vaccines and other immunobiologicals.

For registration purposes, the demonstration of therapeutic equivalence can be used to support claims that the new product has the same target species efficacy granted to the reference product. That is, efficacy claims cannot be made that are not already present on the reference product labelling.

Residue and safety data must be addressed separately because demonstration of therapeutic equivalence does not infer a similar residue outcome or similar safety profile to that of the reference product. For example, in the case of intramuscular/ subcutaneous injections, differences at injection sites may lead to altered tissue depletion or local tolerance. Registrants are advised to consult the *ACVM Registration Standard and Guideline for Target Animal Safety* and *ACVM Standard and Guideline for the Determination of a Maximum Residue Limit and Withholding Period for Veterinary Medicines* for specific information requirements.

The demonstration of therapeutic equivalence by the mechanisms outlined below are not compulsory, and applicants may wish to perform clinical studies to provide data on the efficacy of their trade name product.

Therapeutic equivalence may be demonstrated by one or more of the following mechanisms (dependent upon product and formulation type):

A. Demonstration of Bioequivalence by bioequivalence studies performed to any of the following internationally recognised standards:

1. *Bioequivalence Guidance*, October 10, 2000. Centre for Veterinary Medicine, FDA;
2. *Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products* effective from 11 July 2001. Committee for Veterinary Medicinal Products, EMEA.

Two trade name products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be demonstrated to be essentially ‘the same’, as specified in the guidelines above. These studies may investigate blood levels, and/or pharmacological endpoints, and/or clinical endpoints.

B. Demonstration of Pharmaceutical Equivalence

Two trade name products are considered to be therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to efficacy are essentially the same, as determined from appropriate *in vivo* or *in vitro* studies and/or peer reviewed literature. The supporting data should demonstrate that the bioavailability of the similar and reference products can be expected to be essentially the same.

C. Demonstration of Chemical Equivalence

This can be demonstrated by registrants submitting appropriate chemistry and manufacturing data, which identifies their trade name product as being identical to the registered reference product. Registrants are advised to consult the *ACVM Registration Requirements for Veterinary Medicines in New Zealand*, regarding Type B1 applications for further information.

This document specifies the minimum requirements, i.e. the standard, for the demonstration of therapeutic equivalence. It also incorporates guidelines that 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 therapeutic equivalence is attempting to be proven unless a waiver has been granted by the 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 the ACVM Group). *These waivers must be granted by the NZFSA prior to the applicant submitting an application.* These standards 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 the 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 demonstrate therapeutic equivalence of two or more veterinary medicines;
- all persons accredited under the Agricultural Compounds and Veterinary Medicines Act 1997 to undertake a risk assessment of therapeutic equivalence data.

The standard provides specifications for:

- general requirements for therapeutic equivalence;
- requirements for bioequivalence studies;
- requirements for demonstration of therapeutic equivalence via pharmaceutical equivalence.

1.2 Definitions

Bioavailability

The rate and extent of absorption into the systemic circulation of active ingredient(s) of a trade name product.

Bioequivalence

Two trade name products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be demonstrated to be essentially the same, using bioequivalence studies performed to any of the following internationally recognized standards:

1. *Bioequivalence Guidance*, October 10, 2000. Centre for Veterinary Medicine, FDA;
2. *Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products*, effective from 11 July 2001. Committee for Veterinary Medicinal Products, EMEA.

Chemical equivalence

Trade name products are chemically equivalent if they contain the same quantity and quality of formulation ingredients, are from the same sources, formulated at the same manufacturing plant by the same manufacturing procedures, equipment and quality controls, and packaged in the same container material(s). See ‘identical products’ below.

Good Laboratory Practice (GLP)

An international quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

‘Identical’ product

A trade name product is considered to be identical to a reference product if the formulation ingredients are the same, are from the same sources, formulated at the same manufacturing plant by the same manufacturing procedures, equipment and quality controls, and packaged in the same container material(s). That is, the only difference is the trade name. This is defined as a B1 application in the *ACVM Registration Requirements for Veterinary Medicines in New Zealand*.

Pharmaceutical equivalence

Trade name products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form, if they meet the same or comparable compendial standards, and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence because differences in the excipients and/or the manufacturing process can lead to differences in product performance.

Reference product

The product with which the ‘similar’ product is compared.

‘Similar’ product

The product for which therapeutic equivalence is sought to be proven, in the formulation in which it will be sold.

Simple aqueous solutions

A solution that contains the active ingredient(s), water and buffers, preservatives, colouring or flavouring agents, and no other types of constituents. A simple aqueous solution can be further defined as a homogenous mix in which the solute is in molecular dimensions. Simple aqueous solutions do not include emulsions or suspensions.

Therapeutic equivalence

Two trade name products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

1.3 References

ACVM Research Standard

ACVM Registration Information Requirements for Veterinary Medicines in New Zealand

2 PRODUCT SELECTION

2.1 Selection of similar product

Therapeutic equivalence cannot be used as a method of fulfilling efficacy data requirements for trade name product applications where the trade name product is a vaccine, immunobiological, intramammary preparation, ectoparasiticide or teat dip.

2.2 Selection of reference product

2.2.1 Demonstration of therapeutic equivalence must be conducted against the reference product approved for the same indications as intended for the ‘similar’ product. The reference product selected should be the ‘pioneer’ product.

The reference and ‘similar’ products must have the:

- same active ingredient(s);
- same formulation type;
- same dose regime on an active ingredient basis; and
- same use patterns.

The reference product must be the product for which the data being cross-referenced is held. It cannot be a product that already cross-references that data from another product.

2.2.2 The applicant must clearly identify the reference product in the final study report, including the batch number and expiry date of the batch.

The reference material should be taken from a current batch of the reference product.

2.2.3 The reference product must be, or have previously been, registered in New Zealand.

3 REQUIREMENTS FOR BIOEQUIVALENCE STUDIES

3.1 General

3.1.1 Studies must be conducted and reported in accordance with the *ACVM Research Standard*, the *Bioequivalence Guidance*, October 10, 2000, Centre for Veterinary Medicine, FDA; or the *Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products*, effective from 11 July 2001, Committee for Veterinary Medicinal Products, EMEA.

3.1.2 All analytical laboratory studies must be conducted by a GLP compliant laboratory.

3.1.3 Bioequivalence studies must be conducted using the most appropriate method available for the specific use of the product. The applicant must provide justification for choosing either a pharmacological or clinical end-point study in preference to a blood level (or other biological fluids or tissues) study.

The preferred hierarchy of bioequivalence studies (in descending order of sensitivity) is:

- the blood level study;
- the pharmacological end-point study; and
- the clinical end-point study.

When absorption of the drug is sufficient to measure the drug concentration *directly* in the blood (or other appropriate biological fluids or tissues) and the blood level is correlated to the drug action, then a blood (or other biological fluid or tissue) level bioequivalence study should be conducted.

When the measurement of the rate and extent of absorption of the drug in biological fluids can not be achieved or is unrelated to the drug action, a pharmacological end-point (i.e. drug induced physiologic change that is related to the approved indications for use) study should be conducted.

If drug concentrations in blood (or fluids or tissues) are not measurable or are inappropriate, and there are no appropriate pharmacological effects that can be monitored, then a clinical end-point study should be conducted.

3.1.4 Bioequivalence must be proven for all active ingredients in the ‘similar’ product.

3.1.5 The sample size selected must be large enough to detect at least a $\pm 20\%$ difference at the 5% level of significance with 80% power.

3.1.6 Bioequivalence studies should be conducted for each major species for which the reference product is approved.

Relevant scientific argument and/or peer reviewed literature may be used appropriately to argue bioequivalence in a second (and/or third) species, where that species can be shown to have a similar rate and extent of absorption of the active ingredient(s). This may occur where the reference trade name product has registered use patterns in ruminant and monogastric species. Demonstration of bioequivalence in cattle using appropriate studies may support the assumption of bioequivalence in sheep. In monogastrics, demonstration of bioequivalence in dogs may support the assumption of bioequivalence in cats.

3.1.7 Bioequivalence studies must be conducted with the highest dose rate approved for the reference product. The same dose rate must be used for both ‘similar’ and reference products.

3.1.8 Ninety per cent confidence intervals must be used to interpret bioequivalence data.

For the area under the concentration/time curve (AUC) and the maximum concentration (C_{max}), the general rule is that the difference between reference and test product should not be more than 20% within 90% confidence limits.

For compounds with a large safety margin or a large efficacy window, differences exceeding 20% can be tolerated. However, tighter limits for permissible differences may be required for products that have:

- a narrow therapeutic index;
- serious dose-related toxicity;
- a steep dose-effect curve, or
- non-linear pharmacokinetics within the therapeutic dose range.

For T_{max} , an absolute interval of variation must be selected recognising that a $\pm 20\%$ variation for a T_{max} of 10 minutes does not have the same meaning as a $\pm 20\%$ variation for a T_{max} of 120 minutes.

4 REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE VIA PHARMACEUTICAL EQUIVALENCE

4.1 General

For certain dosage forms, an applicant may wish to address therapeutic equivalence by providing data demonstrating pharmaceutical equivalence of a product with the reference product. Registrants must note that pharmaceutical equivalence in itself does not infer therapeutic equivalence because differences in the excipients and/or the manufacturing process can lead to differences in product bioavailability and critical pharmacokinetic/pharmacodynamic parameters.

Supporting data must include:

- **nature of dosage form;**
- **solubility of active ingredient(s);**
- **relevant pharmaceutical characteristics, including particle size, crystal form, viscosity, water:oil miscibility, pH, and dissolution profile where applicable;**
- **rate limiting steps in absorption of the active ingredient(s), e.g. disintegration, dissolution, gut absorption where applicable or in access to the site of effect;**
- **relevant scientific argument justifying use of this mechanism for demonstrating therapeutic equivalence, i.e. justification that the registrant's data/argument can lead to the deduction of similar pharmacokinetics behaviour between the similar and reference products;**
- **relevant scientific argument regarding clinical consequences of therapeutic inequivalence.**

Products that may have therapeutic equivalence addressed in this manner include:

- simple aqueous solutions (and powders for reconstitution into simple aqueous solutions) with similar formulation as the reference product and that are intended to be given by the same route;
- solutions/suspensions for parenteral or oral administration, where the excipients can be shown not to affect the absorption of the active ingredient(s) significantly when compared to the reference product;
- solid oral dosage forms (e.g. tablets, capsules, caplets, intraruminal delivery devices).
- multiple strength oral dosage forms;
- trade name products that have been reformulated by the original manufacturer, and that are identical to the original registered trade name product except for colouring agents, flavourants or preservatives (which are recognised as having no significant effect upon bioavailability);
- inhalation volatile anaesthetic agents;
- solutions that do not contain pharmacologically active ingredients, e.g. lubricants, irrigation or cleaning solutions;
- oral dosage forms that are not intended to be absorbed systemically (e.g. antacid, radio-opaque media).

4.2 Simple aqueous solutions

The buffers, preservatives, colouring or flavouring agents in the formulation must not be novel and should be the same or comparable to those in similar approved products.

4.3 Solutions/ Suspensions for parenteral or oral administration

The active substance must be in the same effective concentration as the cross referenced product. The effect of the excipients on absorption and or gastrointestinal transit must be discussed. Excipients must not be novel and should be the same or comparable to those in similar approved products.

4.4 Solid oral dosage forms

In vitro comparability may be adequate to confirm the comparability of the similar product and reference product, where these products are to be administered orally. This applies particularly to immediate release oral dosage forms that are rapidly dissolving and contain active ingredient(s) that are both highly soluble and highly permeable.

Parameters selected must be justified with respect to the correlation with appropriate pharmacokinetic parameters.

It may be sufficient to discuss the relation between dissolution time and the absorption rate for the products compared, i.e. when the dissolution process is not the rate limiting step with respect to the rate and extent of absorption of the active ingredient(s).

In vitro equivalence could then be demonstrated by comparison of dissolution profiles after fitting to a mathematical model, or by comparison of parameters like 50% dissolution time and 90% dissolution time and total amount dissolved and AUC. Statistical analysis could be comparable to the analysis used in *in vivo* bioequivalence studies (section 3), or could be performed using suitable ANOVA techniques.

The methodology used to determine dissolution and disintegration profiles should be that described in the British Pharmacopoeia, European Pharmacopoeia or US Pharmacopoeia.

At least 20 dosage units (e.g. tablets, capsules) of each product are tested individually and mean and individual results reported. The percentage of nominal content released is measured at a number of suitably spaced time points providing a profile for each product, e.g. at 10, 20 and 30 minutes, or as appropriate to achieve virtually complete dissolution. The similar and reference products are to be tested using the same apparatus and if possible on the same day.

4.5 Multiple strength oral dosage forms

One *in vivo* bioequivalence study or one *in vitro* equivalence study with the highest strength product may suffice if the multiple strength products have the same ratio of active to inactive ingredients and are otherwise identical in formulation. In addition, *in vitro* dissolution testing must be conducted to compare each strength of the test product to the corresponding strength of the reference product.

The methodology used to determine a dissolution profile should be that described in the British Pharmacopoeia or US Pharmacopoeia. At least six dosage units (e.g. tablets, capsules) of each batch are tested individually and mean and individual results reported. The percentage of nominal content released is measured at a number of suitably spaced time points providing a profile for each batch, e.g. at 10, 20 and 30 minutes, or as appropriate to achieve virtually complete dissolution. The batches are tested using the same apparatus and if possible on the same day.

5 FURTHER READING

FDA Bioequivalence Guidance, October 2000

Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products
The Committee for Veterinary Medicinal Products, EMEA, July 2001

NRA Bioequivalence Guidelines for Veterinary Chemical Products

NRA Guideline for Category 37 Applications – Minor formulation changes for veterinary chemicals

APPENDIX A

CONTENT OF A BIOEQUIVALENCE 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 bioequivalence.

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.

3 Studies

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

APPENDIX B

DATA ASSESSMENT REPORT FOR THERAPEUTIC EQUIVALENCE

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 and pharmacodynamics of the active ingredient(s) that impact on the bioequivalence of the trade name product.

2 Proposed Use Pattern

2.1 Use situation

2.2 Condition(s) being treated

2.3 Administration method

2.4 Dosage

Compare the dosage regimes of the products under investigation.

3 Supporting Data

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

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

3.3 Comment on the relevance of the reference product selected.

3.4 If pharmaceutical equivalence data or pharmacological or clinical end point studies were submitted, comment on the justification of the method of proving therapeutic equivalence.

3.5 If a pharmacological or clinical end point study was conducted, comment on the parameters measured.

3.6 Advise whether the data are sufficient to confirm therapeutic equivalence of the trade name product.

4 Conformance

State whether the supporting data conforms to the *ACVM Registration Standard and Guideline for Therapeutic Equivalence of Trade Name Products*, the *ACVM Research Standard* and information waivers. Where information waivers have been granted, comment on their impact.

5 Risk Statements

5.1 Animal welfare

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

5.2 National productivity (*antimicrobials and anthelmintics only*)

A statement on the risk of the proposed use resulting in national productivity thresholds being exceeded as a result of inequivalence.

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:
