MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

MRLS AND WITHDRAWAL PERIODS

This document has been prepared to serve as a recommendation to applicants wishing to submit residue depletion data to substantiate the recommended withdrawal periods for veterinary medicines used in food producing animals. It represents the Medicines Control Council™s current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of veterinary medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

REGISTRAR OF MEDICINES
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1. Introduction and General South African Overview of Requirements

Manufacturers of veterinary medicines all have a responsibility to ensure that human health is not placed at risk by the presence of hazardous residues in foodstuffs.

Residues of veterinary medicines in foodstuffs of animal origin are controlled in terms of the provisions of the Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act No 54 of 1972). One of the aims of this Act is to protect the consumer against foodstuffs, which may be harmful or injurious to human health.

> It does this by, amongst others, prohibiting the importation, manufacture or sale of a foodstuff, which contains or has been treated with a substance not present in any such foodstuff when it is in a normal, pure and sound condition [Section 2. (1)(c)]
>
> Section 15.(1)(d), however empowers the Minister of Health to make regulations "prescribing any foreign substance, that may be considered as unavoidably present in any foodstuff or cosmetic as a result of the process of its collection, manufacture or treatment, or the greatest measure in which any such substance or substances of such nature may be present in any foodstuff or cosmetic".

There may be no residues of veterinary medicines in foodstuffs of animal origin unless the Minister has, in the Government Gazette, published such permissible maximum residues, which may be present.

Regulations have been made in which maximum residue levels (MRLs) have been allotted to a number of active ingredients of veterinary medicines (GN. No R 1809 of 3 July 1992). Where MRLs have not yet been published, no residue of the active ingredient of such medicines, above the level of 0,05 mg/kg, which is considered to be equivalent to zero, is allowed in any foodstuff derived from animals.

In the light of the acceptance of international daily intake figures as published by the Joint FAO/WHO Food Standards Programme, Acceptable Daily Intakes (ADI's) and MRL's of a veterinary medicine with an active ingredient that has been accepted by the Codex Alimentarius or the European Communities, will also be accepted by the Department of Health.

Withdrawal periods are determined only from residue depletion data. Withdrawal periods are dependent on the formulation, dose, the route of administration, species and class of animals in a particular species. Each country has to establish a withdrawal period depending on the particular formulation and label, which are approved.

The overall objective of the assessment of the toxicological and related data is to determine the acceptable daily intake (ADI) of the active ingredient for humans. The ADI for humans is calculated using the lowest No-Observed-Adverse-Effect-Level (NOAEL) obtained in the most sensitive test and the most susceptible species, usually from the chronic toxicity studies and an appropriate safety factor (SF). This calculation is done by the Department of Health, Directorate: Food Control.

If the active ingredient has been evaluated by the Joint Expert Committee on Food Additives (JECFA) and accepted by Codex the ADI and Maximum Residue Limits (MRLs) will be accepted by the South African registration authorities.

Residue studies need only be done on food producing animals. Manufacturers are required to submit tissue residue and depletion rate data on all new veterinary medicines and animal health products, including a method of detection of residues. Residue studies are done in the target species at the recommended dosage with the particular formulation to be marketed. This is done on a non-radio active labelled product using a fully validated isolation technique. Methods of analysis for measuring residues in food commodities are in most cases available in published manuals or in chemical literature [Food and Drug Administration (FDA) General Guidelines and European Union (EU) Directives]. Appropriate sources of methods for many compounds are available in the Guide to Codex Recommendations Concerning Residues. Treated animals are slaughtered or specimens of edible products (e.g. milk or eggs) are collected at specific intervals after treatment and the residues in different tissues determined. Good husbandry practices are taken into account. Residue studies with formulations of veterinary medicines and animal health products done in other countries on the target food animals will be acceptable.

In order to protect all segments of the population, it is reasonable to use intake data at the upper limit of the range for individual edible tissues and animal products. The following daily intake values as determined by JECFA in their 34th report entitled "Evaluation of Certain Veterinary Drug Residues in Food" have been accepted by the Department of Health:

Meat (as muscle)	300 g
Liver	100 g
Kidney	50 g
Tissue fat	50 g
Egg	100 g
Milk	1.5 litres

The total amount of residues in this range for individual edible tissues and animal products is calculated and compared to the determined ADI of the active ingredient. The data will determine the withdrawal period between the last dosage application and the earliest date that the animal may be slaughtered or the product from animal origin may be collected for sale for consumption. This period would ensure that the residues would be below the MRL.

The New Zealand Registration Standard and Guideline for Determination of a Residue Withholding Period for Veterinary Medicines are currently acceptable and in the mean time can be used as an "official guideline". However, in the N.Z. documentation, one can see that all is under one Act (policy). At this stage in SA, if we do not have the Act 101 and Act 36 registrations under one Act, reference must be made to the guidelines within the Directorate: Food Control.

GUIDELINE FOR DETERMINATION OF A MAXIMUM RESIDUE LIMIT AND WITHHOLDING PERIOD FOR VETERINARY MEDICINES

1. INTRODUCTION

1.1 Purpose

This standard specifies the requirements for residue data for a veterinary medicine that must be supplied with an application for assessment and registration of certain trade name products under the Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965) .

One purpose of assessment under Act is to determine the disposition of certain residues in the edible tissues of treated animals or other specified primary produce obtained from a treated animal
The relevant risks that lie within the scope of this standard are:
(a) risks to trade and market access for primary produce containing any substance, mixture of substances, or biological compound that forms part of the trade name product;
(b) risks to domestic food residue standards.

1.2 Scope

This document only applies to trade name products registered under Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965) with active ingredients that have either:
an ADI and an MRL pursuant to the Food Act 1984;
a PDE issued under the Hazardous Substances and New Organisms (HSNO) Act and an MRL pursuant to the Food Act 1984 from the relevant competent New Zealand authority and for which the active therapeutic or zootechnical substance has been previously assessed by the ACVM Group of the NZFSA. These are referred to as A2, B1, B2, C4 and C8 applications. Certain electable options in this standard do not apply to A2 applications;
an MPL listed in the Meat Residue Regulations Notice 2000 and any amendments;
a residue threshold specified in the NZFSA Dairy Standard D107.
Those products for which an MRL is required prior to registration will be subject to a separate Residue Standard in respect of data requirements.
This standard is compulsory in all cases where:
residue data are required for registration of a trade name product; or
an application is made to vary any condition of a registered trade name product which changes, or is likely to change, the residue risk as specified above;
and a data waiver or application for a default WHP has not been granted.
This standard must be followed by:
all persons applying to register a trade name product or to vary the registration conditions on a registered trade name product where a WHP is required to be determined except where specific exemptions apply or waivers are granted;
all persons accredited to undertake a technical assessment of applications made to register a trade name product that requires a WHP or to vary the WHP conditions on a registered trade name product.
This standard shall not apply for exempted active ingredients (see Annex III) or restricted substances (Annex IV)

This standard shall not apply to applications for which the WHP is elected by the applicant and who then subsequently shows that product formulation lies within the specifications for a ‚standardised WHP™ (Annex V) for those active ingredients.

Waivers may be granted to reduce the number of studies or type of data that an application must submit. These waivers will be granted only in accordance with the prescribed ACVM standard and must accompany any application to which they apply.

Where the guidelines have not been followed and no explanation noted in the dossier or there is no information waiver, the ACVM Group may return the application as incomplete.
The ACVM Group reserves the right in such cases that are not returned as incomplete to interpret data that fall outside the traceability and veracity guidelines very conservatively.

Registrants may elect to apply for the default WHP wherein no residue data of any kind needs to be supplied (see also 1.2.5). Default WHP options for full registration are documented in the ACVM standard *Information Requirement*s.

Registrants may nominate a WHP that is supportable by a mix of trial data and public information.

In this option where all the required elements of the standard are not met and a waiver is approved, the ACVM Group will assess the proposed WHP supporting information conservatively (against a conformance standard higher than that specified for GLP audited trials).

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 may not be assessed or progressed. All data deficiencies and non-compliance with this standard will be documented by the data assessor and measures or risk management appropriate to the assessment will be assigned by the ACVM Group at the time of registration.

If further advice is required, applicants are advised to contract the services of an appropriate consultant prior to submitting the registration application to the ACVM Group. While much of the data specified in this document is also required for the determination of an MRL for a veterinary medicinal substance, the procedure to be followed and the specifications for supporting data for the elaboration of an MRL is specified in a separate ACVM standard, *ACVM Data Requirements for the Determination of an MRL (NZ Food Act) for a Veterinary Medicine and the Assessment of a WHP for that New Use.*
The standard documents a preferred method of data analysis for residues in edible animal produce. If applicants elect not to use this procedure then certain extra information as specified in the relevant section must be supplied.

This standard provides a recommended template for the:
data assessor™s report;
data package summary.

Definitions and abbreviations
Active ingredient (a.i.)
The substance or substances in a formulated product that is/are responsible for the biological or other effects that make the product an agricultural compound or veterinary medicine.

ADME
Adsorption, Disposition, Metabolism, Excretion data in tissues, blood or plasma.

ACVM
The Agricultural Compounds and Veterinary Medicines Group within the NZFSA, responsible for the implementation of the ACVM Act.

ANOVA
Analysis of variance.
g™
A factor for calculating a one-sided tolerance estimate of conformance with a given threshold with a given confidence level (see **Population conformanc**e). The factors listed are based on the assumption of a normal distribution of data at any one time point although, for the small sample sizes specified in this standard, this cannot usually be proven for any particular sample set. The factor can be seen to be a special case of SD for application across different residue trials.

GAP
Good Agricultural Practice. Currently accepted ‚best practice™ standard that is applied to the use of veterinary medicines and agricultural compounds in animal husbandry and production, and consistent with the required residue threshold.

Good Laboratory Practice (GLP)
The organisation, process and conditions under which studies are planned, monitored, recorded and reported. The requirements for GLP are provided in the following documents:
OECD GLP Guidelines:
Number 1 The OECD Principles of Good Laboratory Practice. Environment monograph No. 45, Paris (1992, as revised in 1997).
Number 6 GLP Consensus Document. The Application of the GLP Principles to Field Studies. Environment monograph No. 50, Paris (1992).
Code of Federal Regulations section 21 part 58, Sections A to K, USA.

Limit of Quantitation or Determination (LOQ)
The smallest measured content of an analyte in a given matrix using the specified analytical method above, which a determination of the analyte can be made with a specified degree of accuracy (usually ±20%).

Marker residue
That chemical compound or aggregation of compounds to which the MRL applies.

Marker tissue
The edible tissue (kidney, liver, fat [+skin], meat, honey, milk or eggs) of highest residues at the assessed WHP.

Maximum permissible level (MPL)
The maximum concentration of an agricultural compound marker residue (expressed as mg/kg or ppm) legally permitted in food products as specified in the Meat Residue Regulations Notice 2000 (or any Notice that supersedes Notice 2000) or the Dairy Standard D107.

Maximum residue limit (MRL)
The maximum concentration of an agricultural compound marker residue (expressed as mg/kg) that is legally permitted in food products or agricultural produce as specified in Regulations pursuant to the NZ Food Act, Mandatory Food Standard Table of MRLs of Maximum Permissible Proportions.
Note that for compliance purposes a different marker tissue (e.g. urine, blood etc.) may be used in lieu of one of the marker tissues noted above. In this instance the MRL applicable to the tissue shall not apply to this surrogate substrate and the applicable thresholds will be issued under regulations pursuant to the Animal products Act or Dairy Act.

New Zealand Mandatory Food Standard (NZMFS)
The table of MRLs (and exemptions) for the active substances for various primary agricultural products as cited according to the requirements under the New Zealand Food Act and subsequent regulations.

Plant compound
Any substance, mixture of substances, or biological compound used or intended for use in the direct management of a plant. It also includes compounds used in the post-harvest treatment of unprocessed agricultural commodities of plant origin.

Population conformance
At the proposed WHP the population characteristic is to be that at a specified (upper) confidence level (UCL) bound of 100(1-) % (with ¹ being the significance level) and 10*0p*%, where *p* is the fraction of the total population to be less than the MRL Œ estimated using g™. The factors ¹ and *p* take into account that the desired conformance outcome relates to the cohort of the animal population as a whole presented for slaughter on any one day and not just the trial (treated animals).

Pre-Natal Treatment Interval (PNTI)
The elapsed time between application of an intrammary preparation or a sustained release dosage device to a non lactating animal and when birth occurs and lactation commences within one season. The PNTI is the controlling interval to enable bobby calves to meet the required residue conformance and also to enable the residue conformance for milk to be met at the end of the current mandatory 8 milkings WHP.

QA
Quality assurance.

Residue
Any substance or mixture of substances in food for man or animals resulting from the use of an agricultural compound and includes any specified derivates, such as degradation and conversion products, metabolites, reaction products and impurities, which are considered to be of toxicological significance. They may be free or bound to cellular or sub-cellular components of tissue.

SD
Standard deviation of a statistically normal data set.

Significant residue components
Compounds other than the active ingredient(s) that are present in the trade name product and that may be toxicologically significant.

Supervised residue trials
Scientific studies conducted according to prescribed codes in which agricultural compounds are applied to target host species according to specified conditions that reflect the claimed use pattern and after which harvested crops or tissues of slaughtered animals are analysed for residues. Supervised means that a nominated person (of standing, experience and credibility), is responsible and accountable to the regulatory authority and sponsor for assurance that the trial protocols were followed.

Target species
Any organism that is subject to the intentional action of an agricultural compound or veterinary medicine or its residues.

Trade name product
An agricultural compound containing one or more active ingredient(s) normally mixed with non-active ingredients (such as surfactants, solvents, diluents, suspending agents), intended for application, with or without dilution prior to use, and which is labelled with directions for use.

UCL
The upper (confidence) level bounding the required population conformance statistic for compliance with the MRL.

Veterinary medicine
Any substance, mixture of substances, or biological compound used or intended for use in the direct management of an animal.

Withholding period (WHP)*
The WHP is a regulatory tool used by the ACVM Group as a condition of registration to manage compliance with the residue thresholds (section 1.21) as prescribed under the ACVM Act or at the direction of the Minister of Agriculture and Forestry.
WHP is that time for which a particular agricultural produce must be withheld before entering the food chain and is defined as the ihminimum permissible time between the last application of that agricultural compound to an animal and either:

its slaughter for human consumption
the taking of eggs from treated poultry, for human consumption
the taking of honey from treated hives, for human consumption
the taking of milk from a herd of cows where the milk is aggregated after each milkingle

For the purposes of assessment, the ACVM Group differentiates WHPs according to the manner by which they are determined:

Calculated WHP. The least amount of time calculated from the data set; or adjusted data set at which conformance with the MRL is met.

Proposed WHP. The WHP proposed by a prospective registrant according to their interpretation of the data.

Assessed WHP. The WHP determined by the ACVM Group after assessment of the trial data only according to the rules and guidelines specified within the ACVM Residue Standard and evaluation of the various residue risks identified.

Allocated WHP. The WHP determined by the ACVM Group to be appropriate to a reduced or non-existent data set but which takes into account other evidence supplied as part of a Waiver.

Default WHP. The set of predetermined WHPs that will be applied in the absence of any residue data (and a supportable residues information waiver).

Standardised WHP. A WHP assigned to a group of formulations with at least one active ingredient in common and with the same method(s) of administration. The standardised WHP will correspond to certain specifications attached. Future registrations of products within these specifications need supply no residue data (only) at all if the registrant elects to take the standardised WHP.

Notwithstanding any of the above, the product label will be annotated only with iiWHPlt irrespective of how it is derived.

In general ie calculated WHPll ¡ÜlHAssessed WHPls < iHallocated WHPll << i<default WHPlf
Milking Animals not in Lactation
For cows not in lactation the expression of residue controls on milk is comprised of two parts the PNTI (see definition) and the milk WHP after calving/lactation commences. The former is the variable subject to product specific regulatory control while the latter is currently fixed and currently mandated at 8 milkings irrespective of product.

References

This standard and guideline is based on those for residue data developed by the FAO (JMPR), Australia, (National Registration Authority), USA (Environmental Protection Agency and the Food and Drug Administration), but modified according to the principles and requirements in the ACVM Act.
OECD series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 1. The OECD

Principles of Good Laboratory Practice, Environmental Monograph No 45, Paris, 1992 (as revised in 1997).

Number 6 GLP Consensus Document. The Application of the GLP Principles to Field Studies, Environment monograph No. 50, Paris (1992).

FAO. 1997. Manual on the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed. FAO, Rome.

FAO. 1990. Guidelines on producing pesticides residues data from supervised trials. FAO. Rome.

FAO/WHO. 1993. Portion of Commodities to which Codex MRLs apply in Codex Alimentarius, 2 nd ed., Volume 2. Pesticide Residues, Section 4.1. Joint FAO/WHO Food Standard Programme. FAO Rome.

FAO. 1986. Guidelines on pesticide residue trials to provide data for the registration of pesticides and the establishment of maximum residue limits. FAO. Rome.

Codex Alimentarius, Volume 3, 1994, Residues of Veterinary Drugs in Food, Part 3.
United States of America Code of Federal Regulations 21, Part 58, sections A to K.

*Quantifying Uncertainty in Analytical Measuremen*t. EURACHEM/ CITAC Guide, 2 nd Ed.
Statistical Intervals. A Guide for Practitioners. Gerald Hahn and William Meeker. John Wiley and Sons, Inc, 1991.

Agricultural Compounds and Veterinary Medicines Act 1997.
ACVM Registration Standard-Information Requirements
ACVM Registration Standard-Information Waivers
ACVM Registration Guideline for Residue Data: Plant Compounds
ACVM Registration Standard and Guideline for Chemistry

This standard and guideline has been prepared to advise and assist applicants in the preparation of their application.

2. INFORMATION REQUIREMENTS

Each application to register a trade name product or to very the registration conditions on a trade name product where the MRL is already gazatted in the NZ Mandatory Food Standard Table of MRLS or the Table of maximum Permissible Levels (of residues) issued under the Animal Products Act, the Meat Act or the Dairy Act, must supply the information required to support a WHP determination at the prescribed level of conformance. The applicant may propose a WHP based on their interpretation of the data and their evaluation of any deficiencies in the data set.
However, the ACVM Group will make the final assessment of a WHP based on an overall risk assessment which may include consideration of other issues and a different interpretation of the significance of any non-compliance with this standard.

The data assessment report must identify all non-compliances with the standard, preferably by section number.
The data assessment report may include comment on the perceived significance of any identified non-compliance and the effect that may have on any conclusion that could reasonably be obtained from the data contained in the residues dossier.
The residues dossier must contain an index of contents and an unambiguous page numbering that corresponds with the index of contents.
All waivers and or exemptions pertinent to the application for a WHP must accompany the application and copies must be included with the residue dossier.

2.1 **Standards**

2.1.1 All experimental trial data within applications but excluding:
those research approvals that request a clearance for sale of produce into the human food; or
when a default WHP is requested under the relevant ACVM standard must be collected according to the principles of GLP as specified in either of the codes specified under the definition of GLP in section 1.3 if the data is supplied with the intent of obtaining an assessed or allocated WHP.

This requires that all non-compliances with the code must be documented.

2.1.2 This standard refers to internationally accepted standards for the collection, reporting and interpretation of residue data. Where a dossier includes information collected and interpreted under any different standard it is the registrant™s obligation to show equivalence to the standards and procedures herein.

3. PHYSICAL AND CHEMICAL PROPERTIES

Ancillary residue information
A summary of data elements from other dossiers is required as part of the WHP assessment. Information from the Chemistry, Efficacy and Safety dossiers is required.

Template

A data sheet summarising the separately required elements is documented in this standard (see Annex I) and is also available on the ACVM website under ‚Forms™.

4. DATA ASSESSMENT REPORT ON RESIDUE TRIALS

Residues DA Template

A data sheet summarising the required elements is documented in this standard (see Annex II) and is also available on the ACVM website under ‚Forms™.
(Applicants are advised that lack of availability to Assessors of these data in summary form may result in increased assessment costs owing to the extra time involved in data retrieval.)

5. PROPOSED USE PATTERN

The use pattern of a trade name product affects the level and nature of residues that will occur in food or primary produce. It is essential, therefore, that submissions include the complete and detailed use pattern proposed for the product, to supplement the proposed label directions.

The registrant must address any new risks arising from a new use of a substance in a registered trade name product. Examples of such new risks are:

different metabolites with different quantitative relationships

different marker compound.

The new use of a substance in regard to route of application shall require the registrant to furnish proof of the identity of both the marker residue and the marker tissue, and to identify any metabolites that may be relevant to the residue definition.

5.1 **Use situation**

The proposed use situation should be clearly identified, including an indication of the species, sex, growth stage(s) involved, e.g. weight ranges or age ranges of the animals involved and the situations or conditions/diseases for which the remedy is intended to be used. Details and characteristics of the individual animals used in the trial, their health, feed, housing and clinical status during the trial should be documented:

for topically applied ectoparasiticides, description of the weather conditions at the time of application and for 5 days thereafter if housed outside;
meteorological parameters required are temperature and range, RH, cloud cover, rainfall;
the proposed prescription medicine status or other restricted access to, or proposed controls on, the trade name product where this may impact on the probability of conformance with the WHP.

5.2 **Application method**

The mode of application of the intended treatment must be described fully. The site or placement of the product on or in the animal must be described fully.

5.3 **Application rate**

The dosage for each animal must be reported in mg (of the active ingredient)/kg live body weight as well as total mass and/or volume of the trade name product administered. The ACVM Group shall not prescribe an upper limit to dose volumes/animal. Each case must be supported on its merits. Residue data must be reported on the largest volume of any range proposed; residue data must be reported on the largest dose of any range reported. All maximum dosages reported in the residue trials must also be reported in the safety and efficacy trials if the injection site lesion residues from those trails are to be used in WHP assessment.

Applicants may stratify WHP by dose regime and dose volume. Applicants should note that there exists evidence that residue persistence may increase significantly with dosage and dose volume, and is more marked with subcutaneous and intramuscular administration. However, this may not necessarily result in an increase of WHP in any particular instance.

5.4 **Application and timing**

The frequency and timing of repeat doses administered during the proposed treatment interval must be reported. If Good Agricultural Practice requires that cycles of application be used over the course of a year, then the timing (when) and frequency must be reported.
If the use of the product is such that it is likely to be used in conjunction with, or immediately following, the use of a different veterinary medicine this must be documented.

5.5 **Proposed withholding period**

For liver, kidney, muscle and fat (all species) WHP will be assessed from any of the following permissible WHP: days up to and including 21 days and in weekly intervals thereafter.
For eggs, WHP will be intervals of 1 day, commencing at day 0 (i.e. a nil WHP), thereafter in 1 day increments.

Milk WHP will ordinarily be expressed in hours. This is predicated on treatment being applied immediately after a milking. A nil milking WHP equates to a nominal 12 hr milk WHP, for example based on two milkings per day schedule.
PNTI will be in weeks only.

Any risks associated with practical or accidental non-compliance with proposed label directions should be noted. This includes, for example, studies done with subcutaneous injections (risk of intramuscular) on large animals or for whole herd treatments and injuection at unusual sites, i.e. non neck.

6. SUPERVISED RESIDUE TRIALS

Supervised trials serve as the primary source of information for determining residue levels. Specific information on the numbers of trials, time points, animals per time point and tissues required are specified in the tables or in footnotes to the tables in the appendices to this standard. The residue risks are considered different for pioneer uses and non-pioneer or generic uses. These are listed separately in Appendix 1.2 and 1.3.

Two trial options are possible:

Option 1. Three or more time points with the specified number of animals (see Appendix 1) at each time point. This option allows a limited extrapolation of data beyond the data time points supplied in the trial.

Option 2. One time point only. Election of a proposed WHP and selection of the specified number of animals (data points see Appendix 1.4) for the trial to enable ACVM Assessors to be assured that the required residue conformance is met at the assessed WHP. If this is so, then that time point (if it is between permitted WHP) or the next permissible one after it becomes the assessed WHP. No other extrapolation is permissible in this electable option. For example, if MRL conformance is not met at, e.g. a 5 day time point, then the ACVM Group will assess a suitable WHP based on a conservative interpretation of the data. It is very unlikely that the (long) default WHP would be offered but each case would be judged on its merits. Trial data presented under Option 2 with fewer than the specified number of animals will also be interpreted conservatively as specified for an inallocated WHPll and waiver situation unless the supplementary documentation in the waiver is sufficient to remediate the data deficiency.

Registrants should note that Option 1 must be followed for pioneer uses-with limitations (see section 12).

Where there is potential for plant compounds to produce residues in food producing animals through ingestion of treated fodder, feeds or soil then residue trials in crops and animals may need to be carried out.
Refer to the *ACVM Registration Guideline for Residue Data: Plant Compounds* for trial procedures. Refer to the Meat Act Residue Regulations, Animal Products Act Regulations or the Dairy Act Regulations D 107 for the relevant MRLS or MPLs.
All trail design and execution must be conducted in compliance with GLP.

6.1 **Trials in GLP accredited facilities**

6.1.1 Any analytical processes carried out in GLP accredited facilities and carried out according to GLP do not need to supply full documentation of the procedure. A brief summary is sufficient. However, the actual formulation used, the interval elapsing between manufacture and use, and the storage conditions subsequent to manufacture must be documented.

6.1.2 Any processes carried out in a GLP accredited facility and carried out according to GLP do not need to supply any raw data records associated with the procedure.

6.2 **Trials in non-GLP accredited facilities**

6.2.1 Where any part of the study is not conducted in a GLP accredited facility the registrant must supply all of the following:
Full documentation of all physical aspects of the facility;
Full documentation of other accreditations held by the facility;

Full documentation of the CV of any auditors employed for the study and the audit schedule;
Full CV of all staff involved in the study;
All raw data produced within the non-accredited facility pertinent to the study;
Full documentation of any audits or peer reviews of the facility conducted within 1 year of the commencement of the study;
The foregoing applies to all subcontractors who contributed to any element of the study;
Documentation showing complete traceability of all relevant physical and observational data generated by the study.

6.2.2 Applicants should note that after 1 January 2003 applications under 6.2 will not be compliant with ACVM policy. Applications under this option must be accompanied by a valid waiver application.
Applicants are reminded that a waiver may not necessarily be accepted.

Reporting requirements are much less onerous for trials in GLP accredited facilities.

6.3 **Residue trials and primary products**

Residue trials should aim at giving as accurate as possible a measure of the residues likely to occur in edible portions of the crop or in other food commodities such as products of animal origin (edible tissues, milk, milk products, eggs). A residue trial may be in the form of obtaining a residue decay curve (depletion over time) or residue measurements at one time point. In particular dose rates in the trial must not be less than label does rates. If it can be demonstrated that bioavailability is a direct and linear function of dose, then results from higher dose rates may be extrapolated to (inferred) levels at the label dose rate for doses not exceeding 3 times the label doses rate.

6.3.1 **Milk**
For milk residues the trial data must be generated on, and reported from, individual trial animals generally at the maximum dosage/animal. Where intra-mammary treatments do not in treat all teat canals or quarters then the following shall prevail:
If milk is aggregated at milking then the assigned residue level for any sample so collected will be adjusted pro-rata for the proportion of teat canals treated in the animal.
If teat canals are treated and milk collected and the residues analysed separately then the residue will be taken as the mean of those separate values.

Any factors such as partial udder treatment and partial herd treatment in a given situation, which could result in a reduction in the milk WHP (with suitable registration conditions), may be alluded to by an assessor and may be taken into account by NZFSA at the time the registration is granted.
For residue assessment and WHP purposes, milk will be assessed as pertaining to that bulked product obtained from the test group (i.e. a herd) at a given milking.

6.3.2 **Meat, (including fish), eggs and honey**
Analytical data must be reported on the produce from individual animals, eggs or hives* as the case may be.
* Honey from individual frames or combined from one hive

6.4 **Design of residue trials**

6.4.1 **Treatment frequency, dose and timing**
The dose and frequency of application and the interval between treatments should be the same as specified on the label. The dose should be the maximum of any electable dose specified on the label.
If the trial conditions differ from those specified on the label or from those currently in farm practice in New Zealand, then this should be addressed in the report. All procedures applied to animals prior to application of the formulation must be documented in full (e.g. cleaning, clipping, sterilising).

6.4.2 **Field component of residue trials**

It is not required that residue trials are conducted on animals suffering from the disease for which the trade name product is (claimed to be) a remedy. The definitive residue depletion study must be conducted on animals certified as free of clinical disease. However, where pharmacodynamics and kinetics of the active ingredient(s) are known or suspected to be affected by disease states for which the veterinary medicine is indicated or by some unrelated disease, then this must be addressed in separate clinical/metabolism studies with reference to any published literature.
Any research results obtained for other purposes and which shows any interaction or otherwise between the ADME of the active substance and the disease state for which it is a remedy or any other disease present in New Zealand livestock will assist assessors in ascertaining a more accurate risk profile of the residues.

While in general the time points selected should cover the rise, plateau and decay phases of the residue depletion curve for WHP assessment, only the depletion phase is significant for the purpose of setting a withholding time.
Bioequivalence trial results normally used to demonstrate *equivalent bio-effectiveness* (e.g. by comparative measurements on plasma) between a reference and a test product may, by themselves, be insufficient to show that, in the case where bioequivalence is proven, the WHP of the reference product is applied directly to the test product. The *power* of the data analysis is usually insufficient to obtain the required degree of conformance for residues.

6.5 **Samples and sampling**

6.5.1 **Sampling procedures**
The procedure for taking samples for residue analysis must be fully documented with particular attention to the practical avoidance of contamination of samples. Failure to comply fully with this provision may result in inclusion of outlying (high and possibly arising from contamination) data points unnecessarily in the evaluated data set. This may result in the imposition of an unnecessarily conservative WHP.

6.5.2 **Sample storage**

The storage of the samples must be fully documented from the time of removal from the animal to receipt within the laboratory, up to and including analysis, and then for storage until the study is completed. The sample packaging must be shown to be free from components that interfere with the residue analysis.
Samples taken in non-GLP accredited facilities must supply all raw data sheets, sampling protocols, and freezer and transport logs.

6.5.3 **Sample types**
Tissues are on a wet weight basis.
For residue studies:
meat is muscle (voluntary, e.g. not heart) obtained from any of the major muscles; the correct anatomical name is required (e.g. *latissimus dorsi)* from a specified part of the animal;
fat is omental or renal fat;
kidney is homogenised whole kidney with fat trimmed;
liver is any part of the liver;
eggs are homogenised whole eggs without shell;
muscle is with fat trimmed off;
fish meat is without skin/scales.
It is not required to report (residues) on kidney of fish or poultry.

A minimum of 100 g of any one tissue must be homogenised from which the requisite subsample must be taken (excluding eggs). Where this condition cannot be met because of the immaturity of the animal or small organ size, the organ mass must be reported.
A minimum of 100 ml of milk must be taken from each animal from which the requisite subsample is taken. In the case of trade name products for application into or on the udder, then the milk must be identified as either originating from either specified quarter(s) (treated udder) or combined with milk from untreated quarters from the same animal.
All samples should be taken in duplicate (the second as a reserve sample).

6.6 **Residue data from other countries**
Registration data in support of a withholding period for a veterinary medicine does not necessarily have to be generated from trials conducted in New Zealand **except** in the case of topically applied parasiticides on sheep. One New Zealand trial on cross-bred sheep is required for each of the claimed use patterns, e.g. off-shears and or long-wool use.

7. METHODS OF RESIDUE ANALYSIS

Analysis in GLP accredited facilities
Any analytical processes carried out in GLP accredited facilities and carried out according to GLP do not need to supply full documentation of the method. A brief summary is sufficient.

Any analytical processes carried out in a GLP accredited facility and carried out according to GLP do not need to supply any raw data records associated with the sample analyses.

Any analytical processes carried out in a GLP accredited facility and carried out according to GLP do not need to supply any raw data associated with the method of validation. It is sufficient to tabulate the performance specifications obtained during the validation.

Registrations under this option must provide copies of the laboratory™s accreditation status, any audit reports and any action arising from deviations and amendments to the study plan.

A document detailing the study participants, their role and experience must be supplied (section 4, Annex II).

Analysis in non-GLP accredited facilities
Any analytical processes carried out according to GLP but not in a GLP accredited facility must supply the following:

a complete copy of the method Standard Operating Procedure (SOP);
a copy of the method SOP validation, the results of the validation and any algorithms used (with justification) in calculating and validation parameters;
representative raw data records from within the validation. Where the analytical method involves an instrumental determination such as spectrophotometry, HPLC, or gas-liquid chromatography, specimen output charts showing blank determination and recovery determinations should be provided to assist in the evaluation of the method;
all raw data pertaining to the samples/sample analysis;
all records relating to traceability of physical measurements;
all audits and results pertaining to the study;
brief CV of study contributors.
If any component of the method SOP differs from that specified in the validation, any adverse impact on data quality must be discussed.
Applicants should note that after 1 January 2003 applications under 7.2 will not be complaint with ACVM policy. Applications under this option must be accompanied by a valid waiver application. Applicants are reminded that a waiver may not necessarily be accepted.

Analytical validation
The method must:
be validated in accordance with the principles of GLP; or
be validated according to ISO Guide 17025; or
be validated according to, or equivalent to the procedures and specifications outlined in Eurachem/CITAC Guide *Quantifying Uncertainty in Analytical Measurement, 2 nd Edition.*
Data supplied from analytical methods lacking documentation of appropriate validation will not be assessed.

Analytical methods

The method must:
possess a high degree of specificity for the compound(s) reported under the residue definition;

possess an acceptable accuracy for incurred residues for those residues that are specified as part of the residue definition.

This second point in 7.4.1 may be particularly difficult to demonstrate. Registrants using either:
reference methods issued by CAC; or
reference methods approved by the CVM (FDA) or EMEA
shall not be required to provide any further evidence. However, if the method reported in the registration application differs in any material way from the reference method, the validity of the change must be supported.

Registrants using ‚in-house™ methods supported by, or referenced to, radiometric tracer studies elaborating the disposition of residues shall not be required to provide any further evidence.
Registrants using ‚in-house™ methods not supported by the reference methods or radiometric evidence as described above must supply sufficient evidence that the method presented is capable of measuring the residues as specified in any of the regulations in 1.2.1.
The method should:

have a Limit of Quantitation at a level considerably lower (at least ½ MRL) than any MRL (or MPL) proposed for finite residues. Where this is not possible for technical reasons, values reported as < LOQ may be interpreted as ½ LOQ unless the applicant provides a valid method for censoring data <LOQ. Where data is reported as < LOQ or less than < LOD registrants are encouraged to seek advice from a statistician for appropriate methods of data reduction;
in respect of any sample analytical results made there from, be substantiated by adequate quality control evidence in the form of blanks, recovery and exhaustive extraction data, to show that the method was applied effectively for the determination of the residues in the substrates analysed, and at the levels under consideration.
Attribute data such as positive or negative response on a limit test, if supplied, as critical data at any level of residue testing is deemed of lower quality than numerical data. It may attract a more conservative WHP assessment than if quantitative data were to be supplied for the trade name product.

Analytical methods for compliance purposes

It is not proposed at this time as part of this standard to require and specify data requirements for methods suitable for compliance monitoring of the residues in question.

Storage stability tests for analytical samples

Where sample extracts have been stored prior to analysis, the stability of residues must be demonstrated with recovery studies performed under similar conditions. The results of stability tests for residues in stored analytical samples of representative substrates must be documented. The duration of the study must cover the interval between taking the samples and the end of the analytical phase.
In all cases samples with incurred residues are preferable and in some instances is the only way of showing the required stability of the marker residue.
Where a matrix with incurred residues cannot be provided a surrogate may be provided. Registrants should note that where a marker residue is not wholly the active ingredient then the study must include the other components in the form as specified in the residue definition.

The study conditions must reflect those to which the samples from the residue trials have been subjected.

8. LABORATORY DATA HANDLING AND STATISTICAL ANALYSIS

General requirements
The purpose of this section is to provide a means of analysing and reporting the residue data by a relatively simple and standardised procedure to enable the necessary residue conformance requirements to be met. A table of g™ factors used to estimate upper conformance values from the mean and the SD are in Appendix 1.5.
The g™ factor is a parameter used to obtain tolerance interval (a predictive interval) of a population from the mean of a restricted data set. It is a refined form of the t-statistic for confidence intervals of a mean for a data set.

If a different statistical procedure from that in this standard is used to estimate a WHP, then it should be fully documented to show that the WHP concluded from the statistical analysis will satisfy the conformance criteria for the MRL. In particular any different procedure should be sufficiently documented to show that it gives a conformance outcome not less than that obtained by the documented procedure.

Response parameters and units used to report any results must be consistent within the residue report. Where the option of a trial is to present a depletion curve and claim extrapolation the linearity of the curve with the data transform selected must be consistent with a correlation coefficient of 0.97 or more.

8.1.1 For sample concentrations where analytical data points are reported as ‚zero™, ‚nil™ or ‚negative™ in the analytical record, registrants must set these at ½ of the LOQ reported in the method validation. This ‚data censoring™ is not required if a probabilistic method of estimating the tolerance level is used.
Where a regression curve is the chosen mode to determine WHP extrapolation of individual animal data, to complete a data set where some elements are < LOD or < LOQ is permissible if the requirements of the last paragraph of section 8.1 are met. Extrapolation is permissible for only 1 time point* beyond the last data point. Registrants should note that trial data must be tabulated as found. If in the WHP calculation interpolated data (or amended data) is used then that detail should be noted separated with the substitutions clearly noted.

* In this context the permissible extrapolated time is the least of any of the time intervals over which linearity is established (see 8.3.5).

8.1.2 Where a sample is analysed more than once in the same batch, the analytical results are recorded separately but the sample value used shall be the average of the replicates. Where two replicates of the sample are analysed in two separate batches, the foregoing applies unless the results differ by more than 2 SD (as cited in the validation document) when the measurement obtained first is to be used in the WHP calculation unless there is a reason specified why it is invalid. If three replicates are done and any one differs from the mean by more than 2 SD as per the validation document, then that recorded data point is not used in the WHP calculation but an explanation for the aberration should be included.

8.1.3
If an internal standard and/or surrogate standard is used to normalise the analytical (concentration) data and to compensate for any unanticipated mechanical, extractive or derivatisation losses, then the analytical results should report both corrected and uncorrected data. Whichever set gives the better correlation coefficient for the calibration curve should be used to calculate the sample residue concentrations.
8.1.4

Mathematical transforms of individual data time point sets for regression analysis must document the validity of the transform in the particular application, with literature reference where applicable.

8.1.5

In general it is preferable that the time points selected bound the proposed WHP but this standard recognises that this is sometimes impossible to achieve. However, with the expectation that registrants understand the properties of their formulation extrapolation of residue data using a supportable regression relationship to proposed WHP 1 relevant time unit (see list of permissible WHPs) beyond the last data point is permissible.

8.1.6
For animals in a feedlot situation where medicated feeds may be administered the minimum first sampling time must reflect current industry practice, e.g. in the poultry industry a first slaughter time of 3 hrs is possible and will be taken to represent a ‚nil™ WHP.

Meat, eggs and honey

The treated population conformance characteristics are:
Meat, liver, kidney, fat, edible offal of ruminants and horses; honey
- *P* is 0.9
- 100 (1-) is 95%

Meat, liver, kidney, fat, edible offal of poultry, pigs, emus, ostriches; meat, liver, fat of farmed fish; eggs
- *P* is 0.95
- 100 (1-) is 95%

For data analysed by regression the minimum number of time points and analytical data points specified in tables A1.1-1.4 must be met or a waiver supplied. For WHP data reliant on one time period only the animal numbers specified in table A1.3 are applicable. It will be assumed for tissue and egg analytical data sets that all
the data points corresponding to any one time point are distributed normally.

Data reduction includes (one tailed) application of the g™ parameter to the standard deviation. The relevant value is entered into the equation:
UCL = mean + g™*SD

The factor g™ is obtained from tables of statistical intervals but a selection for different values of N, *p* and a are listed in Appendix 1.5. The upper confidence value for each of the time point sample means is calculated. This will generate a new set of concentration data for entering into the regression equation. The locus of the curve will intercept the concentration axis equal to the MRL at the minimum time for withholding. This time can be calculated by entering the MRL value into the equation and solving for time parameter and gives the *calculated WHP* (note extrapolation restrictions above). This is not the *assessed* WHP, which is the next specified time after this value. Registrants should note that this assessed WHP is not necessarily that which will be allocated to the trade name product; peer review and other external risk factors considered after assessment may result in an adjustment to the assessed WHP.

The time/ UCL data set should be analysed to determine if it fits a linear or linear transformed (e.g. log) depletion model. A regression equation relating residue concentration and time is of the form:
T = m*c + b
at the upper conformance level and T is the time. The correlation coefficient for the association must be documented. If the transformed equation does not give a linear relationship, then the predictive power of the relationship must be justified by reference to relevant literature or the mathematical model used.

Registrants should note that this equation is written in the reversed form from the way it is conventionally expressed. T is the independent variable to be estimated.
Non-finite data such as that bounded by LOQ and or LOD may be analysed by a probabilistic risk assessment process to determine the (probable) residues present at the required conformance or conversely show that the required conformance is met at a particular WHP.

Milk
The treated population conformance characteristics are:
p is 0.99
100 (1-) is 95%
Applicants should note that where part herd treatment can be justified in terms of New Zealand farm practice for that trade name product then where a limiting proportion of a herd can be identified, documented and supported assessment may take that (dilution) into account when assessing whole herd residues. Product registration conditions will then specify any such maximum proportion for users to manage.

General requirements for milk data
Milk WHPs are assessed on pooled milk from a treated cohort. In principle analytical samples could be prepared for each time point and consist of milk aliquots from each cow mixed according to each cow™s milk yield at that milking as a proportion of the total for the treated cohort at that treatment time.
However, while this would give only the required one value per time point the pooling loses information on variance as only the mean value is computed. Thus while milk pooled in this fashion may be used to track residue depletion prior to the time points of interest (see table A1.4) it will not be used for assessing the residues at the final WHP. For this individual cow, information on volumes and residue concentrations are required. Time at which herd milkings occur post-treatment must be reported as hours not numbers of milkings.

The ACVM Group requires that individual animal data are required for the time points used in the determination of the WHP, whether by regression or single point.
All animals must be treated to the maximum of the recommended dose regime on the label. Cows treated at less than the maximum dose rate will have residue data adjusted pro-rata the dose and the number of quarters treated.

The WHP is based on the residues that are determined in the pooled milking from the treated. If the regression method is used then the animal numbers as specified in table A1.2 or table A1.3 are applicable. If the single time point option is elected then the animal numbers specified in table A1.4 are required.

Milk WHP will be set in hours with a nil WHP as the first possible WHP. This is predicated on treatment being applied immediately after a milking. A nil milking WHP equates to a nominal 12 hr milk WHP, e.g. based on two milkings per day schedule.

Time dependent trial data must be manipulated to establish the relationship between the marker residue concentration and time. If the relationship is linear, a degree of extrapolation to an assessed WHP is permissible. Anova and regression analysis will provide an estimate of the distribution of residues in treated herds by concentration and time from which the WHP can be assessed with the required conformance and confidence.

For milk samples at the three critical time points the mean residue concentration is the sum of the individual animal residue concentration multiplied by the corresponding milk yield, and this total is divided by the total milk yield for that milking from the treated animals, that is:
$C_m = (Ca*Va + Cb*Vb \text{ —..} Cn*Vn)/(Va + Vb + \text{–.} Vn)$

Where *C*a, *Cb* are the residue concentrations of cow # *a, b* etc. and *V*a, *Vb* are the milk volumes from that milking which correspond with the respective concentrations of cow # *a, b* etc.; the sample trial mean is denoted by cm, then the upper conformance level of herd milk residue concentration is:
UCL = cm+g™*SD/ v(N)

Where g™ is the factor relating N, SD and the mean at the conformance level of ,cm™ (%) using a one tailed test. A table of g™, N, *p* and α are listed in table A1.5.
Registrants should note that the manipulations required in 8.3.4 may be conveniently done using a spreadsheet such as EXCEL.

The mean data points and the upper conformance values (UCL) are displayed as a continuous graph and the point of intersection with the MRL located. This is the minimum calculated WHP. The minimum assessed WHP is the next multiple of 12 hrs (or one milking) after this time (the WHP is the time at which milk may be taken). The allocated WHP is that to be applied to the product after consideration of any other risk factors. The time/ UL data set should be analysed to determine if it fits a linear or linear transformed (e.g. log) depletion model. A regression equation relating residue concentration and time is of the form:
T = m*UCL+b

The correlation coefficient for the association must be documented. Note that time should not be expressed in milkings in this equation as the interval may not be the same between milkings.
Registrants should note that this equation is written in the reversed form from the way it is conventionally expressed. T is the independent variable to be estimated.
Extrapolation of the regression curve to the MRL (or MPL) but which embraces one extrapolated data set time point is permissible; that is, if the reported points are in weeks then extrapolation is one week, if days then one day, if in milkings then one milking. If the intervals are not equal then extrapolation will be restricted to the least interval.

Non-finite data such as that bounded by LOQ and or LOD may be analysed by a probabilistic risk assessment process to determine the (probable) residues present at the required conformance or conversely show that the required conformance is met at a particular WHP.

Calves

Treatment of pregnant dams can result in calves being born with residues acquired pre-natally that may exceed the residue thresholds. Registrants should also note that calves feeding on treated dams may also acquire residues from the colostrums. Both sources of residues must be evaluated for an application for registration involving calves and particularly bobby calves. Trial data sets shall consist of tissue analyses of at least 4 days old calves (3 days old calves are acceptable) with tissue concentrations stratified according to PNTI as per sections 8.2.2 Œ 8.2.4. A trend of decreasing tissue
residues with increasing PNTI will be apparent from which an appropriate PNTI for the trade name product for that use may be estimated. It is not required that there be an equal number of calves attributable to any particular PNTI in the trials because of the accepted practical difficulty in predicting birthdates.

To enable an acceptable degree of confidence in the estimation of the PNTI it is required that not less than 20 calves contribute residue data and are more or less spread over the interval of interest. The same data extrapolation restrictions apply as outlined in section 8.

Applicants should note that a PNTI to meet residue thresholds for both meat and milk should be estimated. The greater of these shall be the one presented for approval.

Dry cow therapy
Treatment of dry cows prior to commencement of milking may also result in violative residues in the milk, even after 4 days of mandatory withdrawal. In this case the trial data set will as in 8.3.1 above consist of milk analyses with the results stratified according to pre-natal treatment time. A trend of residue depletion with increasing pre-natal interval will be apparent from which the required pre-natal withholding time to achieve acceptable milk residues can be estimated as per the method specified under 8.3. Assessed PNTI for dry cow treatments must always be done by trials reporting residue depletion. Extrapolation to a quantised WHP beyond the last data point is permissible.

This standard does not specify the exact number of animals to be included in such a trial but some general guidelines can be outlined (see table A1.3). As the PNTI is specified in weeks only the number of animals in any one week spread of brithdates should not be less than 7. With a minimum of 3 time points to be reported, a minimum of 21 successful mother/neonate births must be reported. However, often due to practical difficulties in managing birthdates these may not be evenly spread or, as is preferable, for these clustered proportionately closer to the proposed PNTI
Each application will be examined on its merits with weight given to trial design, birhtdate distribution over the trial interval and the degree of clustering around the proposed PNTI.
To enable an acceptable degree of certainty in the estimation of the WHP it is required that not less than 20 cows take part in the trial and that the withholding period claimed lies within the pre-natal treatment interval range.

Injection site residues (ISRs)
Although there is no CAC standard for the reporting and assessment of ISRs, the ACVM Group requires reporting of such data. Where the ISRs are less than 10 times the meat MRL, ISRs will not at the present time be used by the ACVM Group to set a WHP. Where some ISRs reported show residues in excess of 10 times the meat MRL the ISRs may be used in conjunction with the other tissue residues to set a WHP. This data is required only for intramuscular or subcutaneous administration. Risk assessment on the significance of any ISR above the ACVM threshold is contingent on the number of data points supplied and the proportion of those below the threshold. Applications are advised to supply as many ISR data points at the proposed WHP as possible. This is especially so if any ISR >10X MRL (meat) where the final decision WHP will take frequency and concentration into account although this knowledge is often available only from post-registration residue surveys.
Registrants must identify any factors associated with their product that may impact on the incidence of ISR arising from the field use of the product.

9. SUMMARY AND CONCLUSIONS

The registrant of the trade name product must comment in the application, with reference to the withholding period claim, on:
the significance of the statistical variation in the data;
the effect of sampling procedure on the analytical results;
the effect of storage and transport of samples on the analytical results;
the interpretation of outliers, the method and validity of that method for dealing with them;
the significance of variability within the analytical method itself on the reported residue concentrations;
the extent to which any departure from the guidelines affects the estimation of the withholding period; and
any deviations and amendments to the study plan and all other non-compliances with this standard.

FOR MILK WITHHOLDING TIMES NO ALLOWANCE SHOULD BE MADE FOR APPLICATION OF TRADE NAME PRODUCTS TO LESS THAN 100% OF A HERD IN THE APPLICANT™S REPORT OR SUMMARY UNLESS THE APPLICANT DEMONSTRATES THAT THIS IS ‚GOOD AGRICULTURAL PRACTICE™ AND THAT AN APPROPRIATE RESTRICTIVE CONDITION ON THE LABEL IS PRESENTED FOR APPROVAL.

10. MAXIMUM RESIDUE LIMITS OR MAXIMUM PERMISSIBLE LEVELS

The MRL or MPL relevant to each application must be reported from the New Zealand Mandatory Food Standard Table of MRLS for the named substance or the Meat Residue Regulations Notice 2000 of MPLs or the Dairy Residue Regulations, as appropriate. The residue definition (marker residue) must be listed opposite that named substance as well as the primary product to which these pertain.

11. PROCEDURE TO BE FOLLOWED FOR REGISTERED TRADE NAME PRODUCTS WHERE THE MRL (OR MPL) IS CHANGED

Increased MRL (or MPL)

Where the MRL (or MPL) is increased and notified through the New Zealand Mandatory Food Standard Table of MRLs or the Meat Residue Regulations or Dairy regulations, registrants may apply to the ACVM Group for a change of WHP. In these instances only data that has been generated in accordance with this residue standard may be used to support the application. A reduction in WHP will be granted only where the existing data in support of the application is primarily that of Option 2 (see section 6), i.e. by a depletion curve. However, no extrapolation to a WHP which is outside the data range is permissible. (Outside in this context means to an assessed WHP shorter than the first time point, or outside the linear range of extrapolation of the regression relationship to an MRL [or MPL] higher than found for the UCL of the sample sets.) Applicants are advised to note this when designing any residue trials.

Decreased MRL (or MPL)

Where the MRL (or MPL) is decreased and notified through the NZ Mandatory Food Standard Table of MRLS or the Meat residue Regulations or Diary Regulations, then the registrant has a number of options available.

Otherwise, the ACVM Group will assess the existing data held on file and make an allocated WHP.
Option A:
The existing data set supporting the current registration consists of a trial, conducted according to the ACVM standard, with the data analysed as a residue depletion curve. The UCL of the penultimate or last data point must be less than the new MRL (or MPL) and then WHP assessment is facile and an assessed WHP can be easily determined.

Option B:
The new MRL (or MPL) is less than the last data point but linearity of the depletion curve is demonstrated whereby extrapolation of the depletion curve (UCL) according to the requirements of this standard will give the necessary residue conformance at the next permissible WHP.

Option C:
The existing data does not meet the requirements of the depletion curve of Options A or B above. In this case, trial data to support the claim must be supplied. If the data to support the existing registration with the superseded MRL (or MPL) was generated according to the ACVM standard, then only the absent data sets need to be supplied.
The applicant may elect to use Option 2 specified under section 6 for trial data Œ single time point data.

The applicant may elect to support an ACVM allocated WHP based on a combination of data supporting the current registration and/or a mix of new data and published information supplied with a data waiver. However, data supplied under this option will be assessed conservatively by the ACVM Group for the allocation of a WHP as specified in this standard.

12. A2 APPLICATIONS: PROCEDURES TO BE FOLLOWED

New use patterns for active ingredients that have an MRL are considered to present a residue risk no less than if they were in a pioneer substance. Although formulations of this type will have an MRL for the active ingredient entered into the NZMFS where one is required, they pose significantly more risks than B1 or B2 applications or C8 and C4 applications.

Residue trials for these applications must be conducted according to this standard but also and only to the particular requirements in sections 6.1, 7.1 and 8 but noting that the single time point trial option is not permissible for trials under A2 applications.

Data extrapolation by means of regression analysis is not permissible under A2 applications.
The sampled time points must bracket the proposed WHP. Extrapolation only to fill data points at <LOQ or <LOD is permissible on individual animals for one time point past that for which finite residue data is obtained. Confidence parameters for the extrapolation must be documented.
Residues in all edible tissues (kidney, liver, muscle and fat) must be presented unless a supportable waiver is presented.

No waivers in respect of minimum trial numbers and time points will be accepted in respect of A2 applications except for horses where a default WHP is electable.

SPECIFICATIONS FOR TRIALS AND ANIMAL NUMBERS FOR ASSESSMENT OF WHP

Table A1.1
Minimum trial sets to establish a residue depletion curve

Category	**Number of Trials**
Topical parasiticides (long wool) Topical parasiticide (off shears) All other trade name products	2 (sheep only/goats) 1 (sheep only) 1

Notes

1 Trials to establish a meat WHP must be carried out on each of merino and cross-bred sheep for long wool application. One New Zealand trial on cross-bred sheep is required for the claimed use pattern, e.g. long wool. No substitution for this is permissible. Applicants would be advised to use a climatic zone significantly different from that in any one of an overseas sourced residue data report.

2 Pre-ruminant animals under one month of age are considered to be a separate category of stock for orally administered trade name products. Residue data cannot be extrapolated from the ‚adult™ category. Separate residue trials are required.

3 Bobby calves are a separate category of pre-ruminant animals. Residue trial data cannot be extrapolated from the ‚adult™ or ‚pre-ruminant™ categories. Separate trials are required for bobby calves and for pre-ruminant animals where a use is claimed.

4 Default withholding periods have been set for food producing animals (including horses as food producing animals). Where applicants consider these to be inappropriate for their trade name product, trial data must be supplied (see following tables). Waivers for significant elements of this standard for a WHP application must meet the ACVM Standard for Waivers.

5 An application for a trade name product requiring a milk withholding time will always require that a meat withholding time also be set and trial data to support the meat withholding time must be submitted unless the applicant elects the default WHP or can support an allocated WHP shorter than the default WHP.

Table A1.2

Minimum number of data sets (time points) to establish a residue depletion curve

Table A1.2 specifies the minimum number of data sets or time points that must be reported upon at a given time point in a residue depletion trial for meat, edible offal, fat, eggs and milk. The requirements are specified according to the model of application of the trade name product.

Number of Time Points						
	Ruminants/Deer/ pre-ruminants	Ruminants	Pigs	Horses	Birds	Fish
Model of application	Meat	Milk	Meat	Meat	Meat Eggs	
Oral Non Systemic	4	4	4	3	4 4	3
Topical Systemic	4	4	4	2	3 3	3
Topical Non Systemic	4 3	4 3	4 3	3 2	4 4 3 3	3 3
Parenteral Preparations (2)	4	4	4	2	3 3	0
Intrauterine Preparations	2	3	NA	NA	NA	NA
Intramammary Lactating Animal Preparations	3	3	NA	NA	NA	NA
Intramammary (Dry)	3	See 8.5.1 (PNTI)	NA	NA	NA	NA
Animal Preparations	1	1	1	*	NA	0

Gaseous Anaesthetics					0 0	

Notes

1 Pre-ruminant animals, e.g. bobby calves and, separately, calves under 1 month of age, for the purposes of this guideline are treated as a separate class of stock from ‚ruminants™ (refer notes 3 and 4 attached to table A1.1). This particularly applies when prenatal treatment is applied to dams (see section 8).

2 Trade name products subject to WHP restrictions and administered by subcutaneous injection must generate a data set where administration is by intramuscular injection. However, for this aspect of residues **only the marker tissue residues** are required at the claimed WHP.

3 For intramuscular and subcutaneous administration injection site residue data must be supplied particularly for those samples that bracket the proposed or assigned WHP.

4 Waiver from these requirements may be applicable where ADME data is highly temporally compressed.

Table A1.3
Minimum number of data elements at one time point to establish a residue depletion curve.

Table A1.3 specifies the minimum number of animals that must be included and reported upon at any sampling given time point in a residue decay trial for meat, edible offal, fat, eggs and milk. The requirements are specified according to the mode of application of the trade name product.

	Ruminants/Deer/ pre-ruminants	Ruminants	Pigs	Horses	Birds	Fish
Model of application	Meat	Milk	Meat	Meat	Meat Eggs	
Oral Systemic	5	9	5	1	5 3	3
Oral Non Systemic	4	5	3	1	4 3	3
Topical Systemic	5	9	4	1	5 3	3
Topical Non Systemic	4	4	3	1	4 3	3
Parenteral Preparations (2)	5	9	5	2	3 3	0
Intrauterine Preparations	3	5	NA	NA	NA NA	NA
Intramammary Lactating Animal Preparations	3	9	NA	NA	NA NA	NA
Intramammary (Dry) Animal Preparations	3	= 7 per week (PNTI) see 8.5.1	NA	NA	NA NA	NA
Gaseous Anaesthetics	1	1	1	NA	NA NA	NA

Notes
1 Pre-reminant animals, e.g. bobby calves and separatly calves under 1 month of age, for the purposes of this guideline are treated as a separate class of stock from ‚ruminants™ (refer notes 2 and 3 attached to table

A1.1). This particularly applies when prenatal treatment is applied to dams (see section8).
2 Trade name products subject to WHP restrictions and administered by subcutaneous injection must generate a data set where administration is by intramuscular injection. However, for this aspect of residues **only the marker tissue residues** are required at the claimed WHP.

3 See section 12 for exceptions.

Table A1.4
Minimum number of data points for single time point assessed WHP
Table A1.4 specifies the minimum number of animals that must be included and reported upon at a given time point in a residue decay trial for meat, edible offal, liver, kidney, fat, eggs and milk. The requirements are specifie according to the mode of application of the trade name product.

	Ruminants/Deer/ pre-ruminants	Ruminants	Pigs	Horses	Birds	Fish
Model of application	Meat	Milk	Meat	Meat	Meat Eggs	
Oral Systemic	9	19	9	3	9 9	5
Oral Non Systemic	4	10	4	21	5 5	5
Topical Systemic	9	19	9	3	9 9	5
Topical Non Systemic	4	19	4	2	5 5	5
Parenteral Preparations (2)	9	19	9	4	9 5	0
Intrauterine Preparations	5	5	0	*	0 0	0
Intramammary Preparations					0 0	
Gaseous Anaesthetics	9	19	0	*	0 0	0
	2	1	21	*		0
						NA

Notes
1 Pre-ruminant animals, e.g. bobby calves and separately calves under 1 month of age, for the purposes of this guideline are treated as a separate class of stock from ‚ruminants™. This particularly applies when prenatal treatment is applied to dams.

2 Trade name products subject to WHP restrictions and administered by subcutaneous injection must

generate a data set where administration is by intramuscular injection. However, for this aspect of residues **only the marker tissue residues** are required at the claimed WHP.

Table A1.5
Factors* g™ (1- , p, N) for calculating normal distribution one-sided 100(1-)% tolerance bounds

	p = 0.90			*p* = 0.95			*p* = 0.99		
1-	0.9	0.95	0.99	0.9	0.95	0.99	0.9	0.95	0.99
N									
2	10.025	20.581	103.02	13.09	26.26	131.43	18.5	37.094	185.62
3	3	6.155		5.311	7.656	17.37	7.34	10.553	23.896
4	4.258	4.162	13.995	3.957	5.144	9.083	5.438	7.042	12.387
5	3.188	3.407	7.38	3.4	4.203	6.578	4.666	5.741	8.939
6	2.724	3.066	5.362	3.092	3.708	5.406	4.243	5.062	7.335
7	2.494	2.755	4.411	2.894	3.399	4.728	3.972	4.642	6.412
8	2.333	2.582	3.859	2.754	3.187	4.285	3.783	4.354	5.812
9	2.229	2.454	3.497	2.65	3.031	3.972	3.641	4.143	5.389
10	2.133	2.355	3.240	2.568	2.911	3.738	3.531	3.981	5.074
	2.066		3.048						

*Hahn and Meeker, Statistical Intervals. Wiley and Sons, 1991.

ANNEX 1
TEMPLATE FOR OTHER DATA ELEMENTS SUMMARY

1 **CHEMISTRY DOSSIER**
1.1 Formulation: ingredients and content in % or g/L (or ml/L); purpose of ingredient

1.2 Formulation type
(if a suspension, median particle size and range)

1.3 Specific gravity, freezing temperature of formulation

1.4 Viscosity in centipoise units at a specified temperature (any information on viscosity-temperature relationship)

1.5 Impurities chemically related to any component of the marker residue; identity and concentration over the proposed shelf life claimed

2 **EFFICACY DOSSIER**

2.1 Dose rates at which efficacy is established

2.2 Label dose rates

2.3 Relevant environmental conditions over the duration of the efficacy trial (place, month, weather, sunlight)

3 **SAFETY DOSSIER**

3.1 Numbers and proportion of treated animals showing injection site lesions (for parenteral products)

3.2 Documentation on size and persistence of lesions (for parenteral products)

3.3 Any other adverse effects noted, including numbers and proportion, that will impact on residues conformance at a proposed WHP, e.g. skin irritation (increased permeability), photo-sensitivity (increased permeability)

3.4 Relevant environmental conditions over the duration of the safety trial (place, month, weather, sunlight)

ANNEX II
DATA ASSESSMENT TEMPLATE FOR WHP RECOMMENDATION

1 **Identity**
1.1 Applicant
1.2 Trade name of product
1.3 Registration number
1.4 Formulation details
1.5 Active ingredient(s) and impurities related to residue definition
1.6 Status and application type

2 **Proposed use pattern**
2.1 Use situation
2.2 Condition(s) being treated
2.3 Application/administration method and site
2.4 Application rates/dosage
2.5 Number and timing of treatments
2.6 Applicant™s proposed withholding period
2.7 Changes to agricultural practice (if any)

3 **MRLs**

Insert the exact MRL statement for the stated active ingredient as documented in the New Zealand Mandatory Food Standard Table of MRLS or the Meat Residue Regulations or the Dairy Residue Standard.

4 **Residue trial data supporting information**
Provide a concise statement on the quantity, quality, validity and completeness of the supporting data. Record that the appropriate marker residue was determined. Note the appropriateness and validity of any procedure in the residues dossier report. Note any deviations and amendments to the study plan that may adversely affect the residue profile as documented. Note any non-compliances with GLP or GAP that may impact on the validity of any individual data points, the trial and residues profile as a whole, and which includes any break in traceability of any data elements.
Report on each study separately, according to the number of studies the registrant elects to supply. Document the accrediation status of all organisations participating in the residue studies. Identify the principal individuals together with their roles and qualifications. Report all audits carried out that relate to the residue study. Identify the auditors. Document the method validation parameters.

5 **Residue trial data**
Tabulate the uncorrected data points. Having noted the comments in section 4 above document any adjustments, corrections or manipulations to the data points and tabulate. Note the particular reason(s) for any data point adjustment. Using the method as described in the standard construct either a depletion curve or a table of the UCL. If a different data reduction method is used the additional information as documented in the Standard must be included. Note the relationship of the UCl to the MRL at time points of interest. Report on all methods used.

Tissue Residue Study No XXX
Tissue Residue Study No XYZ
Milk Residue Study No AAA
Eggs Residue Study No ABC
Within each study comment on the clinical and analytical phase separately.

6 **Results from data reduction**

7 **Comments**

8 **WHP**

List assessed, allocated or default WHP for meat, lactating cows, dry cows, chickens, eggs, fish, honey separately; list PNTI separately.

9 **Conformance**
Estimate the degree of conformance of the treated population with the MRL using the method as outlined in the standard if more than 99/95%.

10 **Further advice to the applicant**
Note any inconsistencies and non-compliances in the dossier.
Include any explanatory notes in support of the recommendation or conclusion.

11 **Further advice to the ACVM Group**

Note any inconsistencies in the dossier.
Note any inconsistencies in the standard.
Note any issues or areas not addressed by ACVM standards as a consequence of this review.
Assessor™s name/organisation: _____
Signature: _____
Date: _____
Peer reviewed/organisation: _____
Date: _____

ANNEX III
ACTIVE INGREDIENTS WITH WHP EXEMPTION

LIST OF SUBSTANCES FOR WHICH NO RESIDUE THRESHOLD IS SPECIFIED WHEN USED ACCORDING TO THE CONDITIONS OF REGISTRATION UNDER THE ACVM ACT. (THESE HAVE TO BE GAZETTED TO TABLE 3 OF THE NZMFS AND THE USE RESTRICTION SPECIFIED.)

Named substance*	**Therapeutic/Zootechnical use Use**
Oestradiol-17 and its esters or conjugates	To aid in initiation of cycling in cattle Anoestrus in sheep, goats, sows, metrits, pyometra, dystocia, retained placenta in cows
Testosterone and its esters or conjugates	In all food producing animals for aging, debility, crypto-orchidism, deficient sex drive
Prostaglandin F_2	To control and synchronise oestrus, sub-oestrus, pregnancy termination, chronic endometritis in cattle

Androstendione and its esters or conjugates	De-fleecing of sheep
Epidermal growth factor for sheep	Control of oestrus, anoestrus, induce cycling
Progesterone, alpha-hydroxyprogesterone (deoxycortisone) Norgestomet	Oestrus synchronisation in cows
Zinc Sulphate/Zinc oxide/Zinc	Facial eczema
Salicylic acid or any of its esters	Topical keratolytic, pruritis
Oxytocin	Aid in parturition, uterine prolapse, milk letdown, post-partum haemorrhage in pigs, goats, horses and cows Farrowing fever in pigs
Buserelin/buserelin acetate	Anoestrus, cystic ovaries, induction of ovulation, increase conception rate
Isoxsuprine Gonadorelin, Deslorelin	Treatment of cystic ovaries, prevention of delayed ovulation, improve fertility rate in cattle Induction of ovulation in horses Induction of spawning in finfish
Gonadotrophins Ovine and porcine FSH	Induction of superovulation in cattle, anoestrus, treatment of cystic ovaries Induction of superovulation in sheep and goats Induction of superovulation and anoestrus in horses

Propantheline Eugenol	Oestrus induction in pigs Spawning induction in finfish Sedative for finfish

* Trade name products with any of the named substances as the active ingredient will not attract a WHP when the claim for use is as listed against that named substance.

Note: The ACVM Group will issue a procedure by which substances are evaluated for entry to this list.

ANNEX IV
RESTRICTED SUBSTANCES
LIST OF SUBSTANCES FOR WHICH SPECIAL REGULATORY PROVISIONS APPLY

Any **cattle, deer, goats, sheep, llamas, ostrich, emu** or **fish** treated with the following substances or any product derived from any of the cited animals that has been treated with the following listed substances may never be sold for entry into the human food trade where it cannot be assured that the animals or their edible tissues do not enter a market where the substances are prohibited from use on food producing animals.

Prospective registrants should seek advice from the ACVM Group on the likely restrictions that would apply and the registrant™s responsibilities in the management of these substances.

Chloramphenicol
Colchichine
Chloroform
Nitrofurans (including but not limited tonitrofurazone, nihydrazone, furazolidone, furaltodone)
Nitroimidazoles (including but not limited to dimetridazole, ronidazole, metronidazole, carnidazole)
Chlorpromazine
Dapsone
Substances with the pyrazolidone moiety within the chemical makeup for example, but not restricted to, phenylbutazone, ramifenazone, dipyrone
Arsenilic acid
Nandrolone

ANNEX V
STANDARDISED WHP SPECIFICATIONS

Standardised WHPs apply for the products that meet the stated criteria provided the dose rates for the active ingredient for which efficacy is claimed do not exceed 105% of the reference product. Applicants are not obliged to accept the default WHP for their product but if they elect not to do so they must comply with all provisions of this residue standard. Standardised WHPs are a subset of previously assessed WHPs falling within the general framework of pharmaceutical equivalence. The specification applies to the meat of all species intended for human consumption except horses and bobby calves or where specific exceptions are noted.

1 Oxytetracycline crèmes, gels, oblets, pessaries, solutions or suspension formulations for intra-uterine use not exceeding 2 g of active within a 10 day period, containing no other active ingredient(s) for intra-uterine use:
10 days meat WHP for cattle
Oxytetracycline formulations for oral use at dosages less than 25 mg/kg bw for sheep and goats, 45 mg/kg bw/day for pigs, and 12 mg/kg for calves, and containing no other active ingredient(s) regulated by an MRL:
10 days meat WHP for cattle, sheep, goats, pigs, poultry
2 Tetracycline crèmes, gels, oblets, pessaries, solutions or suspension formulations for intra-uterine use not exceeding 2 g of active within a 10 day period and containing no other active ingredient(s) regulated by an MRL:
10 days meat WHP for cattle
Tetracycline formulations for oral use at dosages less then 25 mg/kg bw for sheep and goats, 45 mg/kg bw/day for pigs, 20 mg/kg bw/day for poultry and 12 mg/kg for calves and containing no other active ingredient(s) regulated by an MRL:
10 days meat WHP for sheep, goats, pigs, poultry and calves

3 Chlortetracycline crèmes, gels, oblets, pessaries, solutions or suspension formulations for intra-uterine use use not exceeding 2 g of active within a 10 days period and containing no other active ingredient(s) regulated by an MRL:
10 days meat WHP for cattle
Chlortetracycline formulations for oral use at dosages less than 25 mg/kg bw for sheep and goats, 45 mg/kg bw/day for pigs, 20 mg/kg for poultry and 12 mg/kg for calves for oral use, and containing no other active ingredient(s) regulated by an MRL:
10 days meat WHP for sheep, goats, pigs, poultry and calves
Chlortetracycline formulations for oral use at dosages less than 45 mg/kg bw/day for pigs, containing no other active ingredien(s) regulated by an MRL except tiamulin at less than 6.75 mg/kg as the hydrogen tartrate salt:

10 days meat WHP for pigs
4 Xylazine aqueous solutions by parenteral administration for sedation at dose rates not exceeding 4 mg/kg bw for deer, 0.4 mg/kg for sheep and goats, and 0.35 mg/kg for cattle and containing no other active ingredient(s) regulated by an MRL, nor any excipient added to prolong persistence:
3 days meat WHP for cattle, sheep, goats and deer
nil WHP for cattle, milk
5 Dexamethazone sodium phosphate aqueous solution by parenteral administration. The formulation must contain no other active ingredient(s) regulated by an MRL, no liquid other than water and no excipient intended to prolong persistence:
1 day meat WHP for cattle and deer
2 milkings WHP for cattle
6 Praziquantel oral solutions or suspensions for sheep to be given at dose rates not exceeding 7.5 mg/kg bw. The formulation must contain no other active ingredient regulated by an MRL and no excipient intended to prolong persistence:
7 days meat WHP
7 Fenbendazole oral formulations at dose rates to not exceed 7.5 mg/kg bw for cattle and 5.0 mg/kg for sheep, goats and deer and containing no exipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:
Febantel, oxfendazole and fenbendazole sulphone at a.i. inclusion rates within limits required by the *ACVM Chemistry Standar*d;
Levamisole at concentrations to not exceed 8.1 mg/kg bw as the base;
Praziquantel at concentrations to not exceed 7.5 mg/kg bw:
10 days meat WHP for cattle, sheep, goats, deer
8 Oxfendazole oral formulations at dose rates to not exceed 7.5 mg/kg bw for cattle and 5 mg/kg bw for sheep, goats and deer and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:
Fenbendazole, its sulphone and febantel at a.i. inclusion rates within limits as required by the *ACVM Chemistry Standar*d;
Levamisole at concentrations to not exceed 8.1 mg/kg bw as the base;
Praziquantel at concentrations to not exceed 7.5 mg/kg bw:
10 days meat WHP for cattle, sheep, goats, deer

9 Levamisole oral formulations for sheep and goats at dose rates to not exceed 8.1 mg/kg bw (as levamisole base) and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:
Albendazole or albendazole sulphoxide at concentrations to not exceed 10 mg/kg bw for cattle and deer and 5 mg/kg for sheep and goats;
Fenbendazole or oxfendazole at concentrations to not exceed 7.5 mg/kg bw for cattle and deer and 5.0 mg/kg bw for sheep and goats;

Praziquantel at concentrations to not exceed 7.5 mg/kg bw:
10 days meat WHP for cattle, sheep, goats, deer
10 Albendazole oral formulations at dose rates to not exceed 10 mg/kg bw for cattle and deer or 5 mg/kg bw for sheep and goats and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:
Albendazole sulphoxide, the sulphone and hapasil at a.i. inclusion rates within limits as required by the *ACVM Chemistry Standar*d;
Levamisole at concentrations to not exceed 8.1 mg/kg bw (as the base);
Praziquantel at concentrations to not exceed 7.5 mg/kg bw:
10 days meat WHP for cattle, sheep, goats, deer
11 Albendazole sulphoxide oral formulations as dose rates to not exceed 10 mg/kg bw for cattle and deer or 5 mg/kg bw for sheep and goats, and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:
Albendazole, its sulphone and Hapasil at a.i. inclusion rates within limits as required by the *ACVM Chemistry Standar*d;
Levamisole at concentrations to not exceed 8.1 mg/kg bw as the base;
Praziquantel at concentrations to not exceed 7.5 mg/kg:
10 days meat WHP for cattle, sheep, goats, deer