APVMA REGULATORY GUIDELINES
Seeking comment on the APVMA draft regulatory guidelines

Available content:

- Using the regulatory guidelines
- Application types
- Make an application
- Information guidelines and standards
  - Monitoring and reporting
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In response to feedback during consultation, the APVMA has generated a printable version (PDF) of the regulatory guidelines to assist with review and preparation of submissions. This product is only available during the consultation process.

The printable version is provided in seven parts, reflecting the primary headings used in the website. It includes a table of contents to assist with navigating the document, however, the functionality to click through to related content is not available.

To provide feedback on the regulatory guidelines, please reference the consultation page number which appears above each section of content as follows:

The following content can be found at http://new.apvma.gov.au/node/XX
If making a submission, please reference page number: XX


Submissions on the regulatory guidelines are invited to address comprehensiveness, readability, errors, as well as usability of the website located at http://new.apvma.gov.au. Consultation closes 31 March 2014.

Disclaimer: the Commonwealth accepts no responsibility for the accuracy or completeness of any material contained in this document. Material in this document is only guidance and is made available for the purposes of consultation on the understanding that the Commonwealth is not providing professional advice. The full disclaimer is available at http://new.apvma.gov.au/node/986.
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Information guidelines and standards

Guidance on the submission of data to address the safety, efficacy and trade statutory criteria associated with applications. Includes the relevant standards used in our assessment processes.

Data guidelines

Guidance on the registration and provision of data relating to agricultural and veterinary chemical products and the approval of active constituents.

Veterinary drug residues—Comparative metabolism studies, selection of marker residues and ratios of marker residues to total residues

This guideline is based on the International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products guidelines (VICH GLs) 46 and 47. These were intended to provide a general description of the criteria that have been found by the European Union, Japan, the United States, Australia, New Zealand and Canada to be suitable to identify the metabolites of veterinary drugs produced by laboratory animals and target animals in comparative metabolism studies.

VICH GLs 46 and 47 are two of a series developed to facilitate the mutual acceptance by national and regional regulators of residue information for veterinary drugs used in food-producing animals. They were originally prepared after consideration of the current national and regional requirements and recommendations for evaluating veterinary drug residues in the European Union, Japan, the United States, Australia, New Zealand and Canada.

While VICH GLs 46 and 47 cover most of the Australian recommended considerations in terms of comparative metabolism data for laboratory species and target animal species, there are some additional considerations that are unique to Australia. These additional considerations are detailed in this document.

Guidance on metabolism studies

Scope

This guidance is intended to provide recommendations for procedures to identify the metabolites of veterinary drugs produced by laboratory animals. The purpose of the comparative metabolism studies is to compare the metabolites of the laboratory animals used for toxicological testing to the residues of the veterinary drugs in edible tissues of food-producing animals. The studies aim to determine if the laboratory animals used for toxicological testing have been exposed to the metabolites to which humans can be exposed (that is, as residues in products of food-producing-animal origin).

The pharmacokinetic profiles of the veterinary chemical and its metabolites in the target animal species should be qualitatively comparable with those of the laboratory animal species used to establish the health standards, to verify the relevance of the toxicological effects and the no-observed-adverse-effect levels and/or no-observable-effect levels, and thereby validate the dietary exposure assessments.

Overview

Metabolism studies are used to assess the fate of the chemical in target animals and to assess the nature and disposition of chemical residues in food-producing animals. The composition of a residue (parent and metabolites) and the target tissue(s) or food commodities in which it is present (for example, meat, offal, milk, eggs) should be known, so that residue depletion trials and analytical methods deal with the relevant residue components.

Metabolism and kinetics studies in both target animals and laboratory animals help assess:

- user safety (as in toxicology and occupational health and safety)
- consumer safety (as in residues).
Introduction

The human food-safety evaluation of veterinary drug residues helps ensure that food derived from treated food-producing animals is safe for human consumption. As part of the data collection process, you should conduct studies to:

- characterise the metabolites to which laboratory animals are auto-exposed during the toxicological testing of the veterinary drug. The purpose of these studies is to determine whether the metabolites that people will consume from tissues of target food-producing animals are also produced by metabolism in the laboratory animals used for the safety testing. It is understood that, if the laboratory animals produce substantially similar metabolites to those produced by the food-producing animal, the laboratory animals will have been auto-exposed to the metabolites that humans will consume from tissues of treated food-producing animals. Auto-exposure of metabolites will ordinarily be taken as evidence that the safety of metabolites has been adequately assessed in the toxicology studies.
- permit an assessment of the quantity and nature of residues in food derived from animals treated with a veterinary drug. These metabolism studies provide data on:
  - the depletion of residues of concern from edible tissues of treated animals at varying times after drug administration
  - the individual components, or residues, that comprise the residues of concern in edible tissues
  - the residue(s) that can serve as a marker for analytical methods intended for compliance purposes (that is, monitoring of appropriate drug use)
  - the ratio of marker residue to total radioactive residues
  - the identification of target tissue(s).

Types of metabolism studies

Demonstration of metabolites from the laboratory animal can be generally accomplished in one or more in vitro studies or in an in vivo study. You can conduct one or more in vitro laboratory animal metabolism studies (for example, laboratory animal liver slice metabolism) for comparison to the metabolism in the food-producing animal to demonstrate that the relevant laboratory animal produces the metabolites that are found as residues in the edible tissues of the target food-producing animal. Conducting in vitro studies can avoid the use of in vivo laboratory animal studies, reduce the number of animals that are euthanased, and reduce the cost of comparative metabolism studies. If the in vitro or in vivo studies do not demonstrate the metabolites produced by the target food-producing animal, you should address by other means the relevance to consumer safety of the food-producing-animal metabolites.

Laboratory animal in vitro and in vivo metabolism studies are most often accomplished using radiolabelled drugs. These studies are capable of monitoring all of the drug-derived residues resulting from the administration of test material (note: generally only the major metabolites should be identified). This guidance, therefore, recommends procedures for metabolism studies conducted with radiolabelled drugs. However, alternative approaches (that is, when not using radiolabelled drugs) to characterise the metabolites in laboratory animals can be suitable when the metabolites produced by the target food-producing animal as residues in edible tissues are readily identified in urine or tissues of the laboratory animals by chemical means.

You should conduct metabolism studies in compliance with applicable good laboratory practice.

Metabolism studies in laboratory animals

Generally, auto-exposure has been adequately demonstrated if laboratory animals produce each of the major metabolites of the residue that people will consume from edible tissues of treated food-producing animals. You should report qualitative information on the metabolites in laboratory animals. Quantification of the metabolites found in urine, fluids or tissues of laboratory animals is not generally an objective of the comparative metabolism studies. Generally, only the major metabolites found as residues in the food-producing animal should be identified in the laboratory animals. Metabolites observed in laboratory animals that are not observed in the food-producing animal are not relevant to the objective of assuring that the laboratory animals are auto-exposed to the residue metabolites that humans will consume.

Test materials

Drug

The chemical identity (including, for example, the common name, chemical name, CAS-number, structure, stereochemistry and molecular weight) and purity of the drug substance should be described. The test drug should be representative of the active ingredient to be used in the commercial formulation.

Radiolabelled drug

Nature and site of label

Carbon-14 \((^{14}\text{C})\) is the label of choice because intermolecular exchange is not an issue. Other isotopes, such as \(^3\text{H}, ^{32}\text{P}, ^{15}\text{N}\) or \(^{35}\text{S}\), might be appropriate. Tritium (3H) might be considered suitable if a rigorous demonstration of the stability of the tritium label is provided; for example, the extent of exchange with water is assessed and found to be equal to or less than 5 per cent.

You should indicate the position(s) of the radiolabel. The drug should be radiolabelled in a site, or in multiple sites, to assure that the portions of the parent drug that are likely to be of concern are suitably labelled. The radiolabel should be placed in a metabolically stable position(s).

Purity of radiolabelled drug

Radiolabelled drugs should have a high level of purity, preferably of approximately 95 per cent, in order to minimize artifactual results. You should demonstrate radiochemical purity via appropriate analytical techniques (for example, by using two chromatographic systems).

Specific activity

You should state the specific activity of the synthesised radiolabelled drug in the study report. The specific activity should be high enough to permit...
tracking of the residue of concern in edible tissues. The sensitivity should be determined by the potency of the drug. You can adjust the specific activity by mixing the radiolabelled drug with an unlabelled drug. To facilitate analytical measurements and conserve radiolabelled drugs, you can dose animals to be euthanised at early withdrawal periods with a drug of a lower specific activity, while animals to be euthanised at later withdrawal periods can be dosed with a drug of a higher specific activity.

Analytical standards

Analytical standards should be available for the parent drug and, if possible, for metabolites known or expected to exist, for use in the chromatographic comparison of drug metabolites. The metabolites can be isolated from tissues generated in the target food-producing-animal metabolism study.

In vitro test systems

You can use single or multiple in vitro metabolism test studies as an alternative for the in vivo comparative metabolism studies.

The laboratory animal species used in the comparative metabolism study should preferably be the same species (and for rodents the same strain) as was used in the pivotal study for determining the toxicological acceptable daily intake of the veterinary drug. In case another species is used, you should justify the choice of species in terms of relevance. You should report on the sources of the animals, their weights, health statuses, ages and sexes.

Various test systems have been published and are widely used. In vitro systems for comparative metabolism studies include primary hepatocytes, liver microsomes, the S9 sub-cellular fraction, cytosol, liver slices and whole cell lines. Protocols for these in vitro studies have not yet been standardised (for example, by the Organization for Economic Co-operation and Development), therefore some strengths and weaknesses of each of these systems are discussed below:

- **Primary (fresh or cryopreserved) hepatocytes**: primary hepatocytes are liver cells that are useful in evaluating phase-I and phase-II metabolism and have the added advantage of taking membrane transport effects into account. These hepatocytes can be prepared in suspension, monolayer culture or sandwich cultures. The sandwich cultures have the advantage that they maintain enzyme activities for a longer duration of time. If the food-producing-animal residue metabolites are demonstrated in a primary hepatocytes system, then comparative metabolism has generally been demonstrated. Use of a primary hepatocytes-based system can be complementary to one or more of the other in vitro systems to demonstrate the metabolism for a laboratory animal species.

- **Liver microsomes**: liver microsomes include most of activities of cytochrome P450 and flavin-containing monooxygenase systems for evaluating phase-I metabolism, along with uridine diphosphate-glucuronosyl-transferase for phase-II glucuronidation. If the food-producing-animal residue metabolites are demonstrated in a liver microsomal system, then comparative metabolism has generally been demonstrated. Use of a liver-microsome-based system can be complementary to one or more of the other in vitro systems to demonstrate the metabolism for a laboratory animal species.

- **S9 sub-cellular fraction**: The S9 sub-cellular fraction contains the same phase-I and phase-II enzymes present in liver microsomes, as well as additional systems such as sulfotranferases and N-acetyltransferases. The S9 sub-cellular fraction is suitable for evaluating phase-I and phase-II metabolism or phase-I metabolism followed by phase-II conjugation. If the food-producing-animal residue metabolites are demonstrated in a S9 sub-cellular fraction system, then comparative metabolism has generally been demonstrated. Use of a S9 sub-cellular fraction-based system can be complementary to one or more of the other in vitro systems to demonstrate the metabolism for a laboratory animal species.

- **Cytosol**: this represents the supernatant fraction that remains following microsomal centrifugation. It contains some of the phase-II conjugation systems, but otherwise represents a relatively incomplete matrix for metabolic work. In general, the use of cytosolic systems alone is unlikely to provide a complete comparative metabolism profile, but if the food-producing-animal residue metabolites are demonstrated in a cytosol system, comparative metabolism has generally been demonstrated. Use of a cytosol-based system can be complementary to one or more of the other in vitro systems to demonstrate the metabolism for a laboratory animal species.

- **Liver slices**: the use of whole liver slices for metabolism research is possible; however, the liver cell viability and corresponding enzyme activities decrease rather rapidly compared with the other alternatives. You should not conduct comparative metabolism studies using liver-slice methodology unless you can demonstrate cell viability and enzyme activity. However, if the food-producing-animal residue metabolites are demonstrated in a liver-slice system, then comparative metabolism has generally been demonstrated. Use of a liver-slice-based system can be complementary to one or more of the other in vitro systems to demonstrate the metabolism for a laboratory animal species.

- **Whole cell lines**: use of whole cell lines is not currently recommended because the enzymatic activity is generally low. However, if the food-producing-animal residue metabolites are demonstrated in a whole cell line system, then comparative metabolism has generally been demonstrated. Use of a whole-cell-line-based system can be complementary to one or more of the other in vitro systems to demonstrate the metabolism for a laboratory animal species.

- **Whole cell cultures**: if the target-species metabolic profile includes evidence of both phase-I and phase-II biotransformation, you should consider investigating multiple options (for example, microsomes and S9) to reproduce the complete metabolic profile.

Although many variations in test conditions have been reported in the literature, the following represents some general guidance for conduct of in vitro comparative metabolism studies:

- **Test molecules are usually incubated in the in vitro system at 37 °C.**
- **The concentrations of target molecules are typically lower than 100 μM.**
- **The incubation time is dependent upon the rate of metabolism of the target molecules and should be adjusted accordingly.**

Cofactors of phase-I and phase-II metabolism are scientifically necessary for incubation of liver microsomes and S9, such as NADPH (nicotinamide adenine dinucleotide phosphate, NADPH regeneration system) for phase-I metabolism, UDPGA (uridine diphosphate-glucuronosyl-transferase) for glucuronidation, and PAPS (3′-phosphoadenosine 5′-phosphosulfate) for sulfation.

When more standardized in vitro system metabolism study protocols become available, the general guidance above can be replaced according to the standardized protocols.

In vivo test systems

Animals
Laboratory animals: the laboratory animal species used in the comparative metabolism study should preferably be the same species (and for rodents the same strain) as was used in the pivotal study for determining the toxicological acceptable daily intake of the veterinary drug. In case another species is used, the choice of species should be justified in terms of relevance. You should provide the sources of the animals, their weights, health statuses, ages and sexes.

Target animals: there are some national or regional differences regarding the designation of major and minor species, particularly for turkeys and sheep. These differences can affect national or regional data collection requirements and recommendations. In Australia, sheep are considered to be a major species, while turkeys are minor.

In certain instances, the total residue and metabolism data for a drug’s use in a major species might be extrapolated to the minor species. When a national or regional authority calls for a total residue and metabolism study for a minor species, or for a species considered to be major in one region but not another, the study design outlined in this guidance should be acceptable.

Animals used in the metabolism study should be representative of commercial breeds and of the target population. You should provide the source of the animals, their weights, health statuses, ages and sexes.

Ordinarily, a single study can be performed in pigs (around 40 to 80 kg), sheep (around 40 to 60 kg) and poultry. For cattle, a single study in beef cattle (around 250 to 500 kg) could apply to dairy cattle, and vice versa. Generally, the results of a metabolism study in adult cattle and sheep can be extrapolated to calves and lambs, respectively. However, a second study might be appropriate for pre-ruminating animals if there is sufficient reason to believe the pre-ruminating animal will have significantly different metabolism from the adults. You should perform a separate study to demonstrate the total residue in milk of dairy cows.

If the study is intended to support a withdrawal period, the study parameters should address the worst-case study conditions (for example, animal weights and associated maximum injection volume).

**Animal handling**

Animals should be allowed adequate time to acclimatise. You should apply normal laboratory animal caretaking or husbandry practices. It is recognized that these studies might call for metabolism cages, a departure from ‘normal’ practices; therefore, you should only use metabolism cages if the study is intended to collect urine and excreta, or other specifications.

Animals should be healthy and, preferably, should not have been previously medicated. However, it is recognized that animals might have received biological vaccinations or prior treatment, for example with anthelmintics. An appropriate wash-out time should be observed for the animals prior to enrolment in the actual trial. Animals should have a known history of medication.

The feed and water supplied to the animals should be free from other drugs and/or contaminants and you should ensure that environmental conditions are adequate, consistent with animal welfare, and in accordance with applicable national and regional regulations.

Animal caretaking practices and disposal of animals and tissues from animals should be in compliance with all applicable national and regional laws and regulations.

**Numbers of animals**

Laboratory animals: enough animals should be treated with the drug in the comparative metabolism study to provide enough composited tissue or excreta for analysis. The samples of like material from different animals can be composited for a single analysis. There is no minimum number of animals for a comparative metabolism study; however, four animals of each sex are often used (but less can be used) to assure there is enough sample material. Demonstration of comparative metabolism is not generally conducted in animals of each sex; therefore, the samples of like material can be pooled (without regard to sex) to increase the likelihood of demonstrating the metabolites of interest when sex differences in metabolic ratios might exist.

Target animal species: at least four groups of animals, evenly-mixed as to sex if the drug is intended for use in both males and females, should be euthanised at appropriately spaced time points. The following numbers of animals are recommended:

- large animals (cattle, pigs, sheep)—three or more per euthanasia time
- poultry—three or more per euthanasia time
- fish—10 or more per euthanasia time
- lactating cattle for milk collection—eight or more for representative multiparous cattle of high and low milk production
- laying birds for egg collection—sufficient to collect 10 or more eggs per day
- honey—five honey samples, each from a separate hive.

Australia does not subscribe to the concept of a ‘practical zero withdrawal period’. Therefore, if a zero day withholding period is being sought, one of the euthanasia time points should be at zero hours withdrawal.

A sufficient amount of control tissues should be available to permit a determination of background concentrations and combustion efficiency, and to provide tissue for testing of related analytical methods.

**Drug formulation**

You should describe the drug formulation, the method of dose preparation, and the stability of the drug in the formulation during the treatment period in the study report. For studies in laboratory animals, it is not critical that the formulation used in the comparative metabolism studies is the same as the commercial product. However, in contrast, target animal studies should involve treatment with the intended final formulation whenever possible. Given that metabolism studies can be conducted well in advance of definitive formulation decisions, treatment with representative or prototype formulations can also be considered appropriate.

**Route of administration**

Laboratory animals: in studies with laboratory animals, you should administer the drug orally. Gavage or bolus dosing can be used to ensure that animals receive the complete dose and to minimise environmental concerns.

Target animal species: for metabolism studies with the target animal species, you should administer the drug via the intended route of administration (for example, orally, dermally, intramuscularly, subcutaneously). For drugs that are intended for oral administration, especially via feed
or drinking water, you can use gavage or bolus dosing to ensure that animals receive the complete dose and to minimise environmental concerns.

For drugs that are intended for oral and parenteral administrations, you should usually conduct separate metabolism studies. Ordinarily, a single study with a parenteral route will be applicable to cover all parenteral routes including intramuscular, intramammary, subcutaneous and topical. Similarly, a single study with an oral route will ordinarily be applicable to all potential oral formulations (for example, drinking water, in-feed and quick-release tablets).

Dosing

Laboratory animals: the dose should be high enough to result in concentrations of metabolites in excreta or tissues for comparison. You should administer the dose daily, for enough time that the drug undergoes all relevant metabolic events, including those associated with enzyme induction. Normally, administration for five days is used unless there are data to show that a longer time of administration can better demonstrate the formation of the metabolites of interest. You can use doses near the minimum toxic dose to generate high concentrations of the metabolites of interest in tissues and urine, but you can also use lower doses.

Target animal species: the dose should be the highest intended treatment concentration, and you should administer it for the maximum intended duration or for the time required for steady state to be achieved in edible tissues. Pre-dosing of animals with an unlabelled drug, followed by administration of a radiolabelled drug, is not recommended.

For continuously administered drugs, a separate study to determine the time for residues to reach steady state in edible tissues might be appropriate. When a drug administered in a single dose is intended to have zero withdrawal, you should demonstrate that the absorption phase has been completed.

When gavage dosing for the feed and water routes, you should divide the dose and give it in the morning and afternoon to better approximate actual-use conditions.

Animal euthanasia

Laboratory animals: you should humanely euthanise all animals. Chemical euthanasia can be used unless it will interfere with analysis of the metabolites of interest.

Animals should be euthanised for metabolite analysis at a single time point, usually 2–4 hours after the last dose of the test substance. Multiple days of dosing provides the presence of metabolites resulting from sequential metabolism of the parent drug over time, and therefore additional euthanasia time points are not called for.

Target animal species: you should euthanise animals using commercially applicable procedures, making certain to observe appropriate exsanguination times. Chemical euthanasia can be used unless it will interfere with analysis of metabolites of interest.

Sample collection

Laboratory animals: before euthanasia, urine, faeces, and blood can be collected for analysis. The samples should be analysed immediately or stored frozen (unless freezing causes a stability problem for the metabolites of interest) until analysis. Freezing of the samples is to reduce microbial and host metabolism from altering the metabolic profile. If the samples are stored after collection, the sponsor should ensure that the radiolabelled compound remains intact throughout the storage period.

Comparative metabolism can be demonstrated with one or more excreta or tissues. Samples that are typically taken for qualitative metabolite analysis can include blood or blood fractions, excreta, liver, bile, kidney, fat or other tissues. Enough tissue of each type should be taken from each animal for analysis.

Target animal species: following euthanasia, samples of sufficient amounts of edible tissues should be collected, trimmed of extraneous tissue, weighed, and divided into aliquots. If the analysis cannot be completed immediately, the samples should be stored under frozen conditions pending analysis. If samples are stored after collection, you should ensure that the radiolabelled compound remains intact throughout the storage period.

Table 1 lists how the recommended samples should be taken from the target animal in the metabolism study.

<table>
<thead>
<tr>
<th>Edible tissue type</th>
<th>Sample description by species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Injection site tissue</td>
<td>Core of muscle tissue ~500 g 10 cm diameter × 6 cm deep for intramuscular 15 cm diameter × 2.5 cm deep for subcutaneous</td>
</tr>
<tr>
<td>Liver</td>
<td>Cross-section of lobes</td>
</tr>
<tr>
<td>Kidney</td>
<td>Composite from combined kidneys</td>
</tr>
<tr>
<td>Fat</td>
<td>Peri-renal and subcutaneous back fat</td>
</tr>
<tr>
<td>Skin/fat</td>
<td>N/A</td>
</tr>
<tr>
<td>Milk</td>
<td>Whole milk</td>
</tr>
<tr>
<td>Eggs</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A: not applicable

You should analyse the tissues shown in Table 1. Additional tissues should be collected and analysed to provide information on the one additional tissue to be analysed in the marker residue depletion study. As appropriate to species, the additional tissues you might analyse include heart (cattle, pigs, sheep, poultry), small intestines (cattle and pigs) and gizzard (poultry). Furthermore, it might be appropriate to collect and analyse other
edible offal from the various species if it is deemed important for a safety assessment (for example, offal with expected high residue concentrations or with residues having slow depletion rates).

Excreta and blood are not always collected during metabolism studies with target animal species. However, analyses of these samples can be useful from several perspectives:

- analyses of the excreta and blood allow an estimate of the mass balance, a valuable tool in assessing the quality of the study
- the samples of excreta can be a good source of metabolites
- the samples can be of use in conducting an environmental risk assessment.

If you decide to collect such data, we recommend that you collect urine and excreta from selected animals on a daily basis.

Blood samples can be taken from selected animals at various time points and at euthanasia. Data on the total residue in blood can provide valuable pharmacokinetic information.

**Determination of total radioactivity**

Laboratory animals: determination of total radioactivity in samples and accounting for the mass balance of the radioactivity are not normally conducted for the in vivo metabolism studies conducted with laboratory animals. When total radioactivity is to be determined, you should follow the procedures presented below (for target animal species).

Target animal species: you should determine the total radioactivity in samples using established procedures, which might include, for example, combustion followed by liquid scintillation counting, solubilisation and counting, or direct counting, depending on the nature of the sample. You should completely describe the details of the radioassays, including the preparation of analytical samples, instrumentation, and data from standards, control tissues, fortified tissues, and incurred tissues. You should also demonstrate the ability of the procedure to recover radioactive material added to control tissues.

The results of analyses of samples for radioactivity should be reported on a wet weight basis and on a weight/weight basis, with micrograms per kilogram (µg/kg) as the preferred units. You should describe the sample calculations showing conversion from counts per minute/weight (cpm/weight) or disintegrations per minute/weight (dpm/weight) to the weight/weight basis in the study report.

**Separation and comparison of metabolites**

Commonly available analytical technology, including, for example, high-performance liquid chromatography, high-performance thin layer chromatography, gas chromatography, and mass spectrometry, enable separation of the total residue into its components and identification of the drug-derived residues.

**Analytical methods**

You should provide a complete description of the procedures used for chromatographic and chemical characterization of the drug residues in the report. The description should include the preparation of standards, reagents, solutions, analytical samples; the extraction, fractionation, separation and isolation of the residues; the instrumentation; and the data derived from standards, control tissues, fortified tissues, and incurred tissues. The analytical method should be validated at least to demonstrate the recovery, the limit of detection and the variability. You should also demonstrate the repeatability of the retention times for the analytical method.

**Extent of characterisation of major metabolites**

Laboratory animals: characterisation and structural identification of the metabolites and demonstration of the tissue extraction efficiency during the comparative metabolism study are not normally conducted when the comparison of the chromatographic retention time(s) demonstrates the presence of the metabolites of interest in the laboratory animal.

Target animal species: the degree of characterisation and structural identification depends on several factors, which include the amount of residue present, the concern for the compound or for the class of compounds to which the residue belongs, and the suspected significance of the residue based on prior knowledge or experience.

In general, characterisation and structural identification of major metabolites should be accomplished using a combination of techniques and might include chromatographic comparison to standards or mass spectrometry. As a point of reference, major metabolites are those comprising 100 micrograms per kilogram or more, or 10 per cent or more of the total residue in a sample collected at the earliest euthanasia interval (or following attainment of steady state, or at or near the end of treatment for continuous-use drug products). In some cases, chemical characterisation rather than unequivocal structural identification for a major metabolite will be appropriate (for example, when a conjugate is present or if mass spectrometry information indicates the likely biotransformation pathway, such as M+16 for hydroxylation). Ordinarily, no differentiation of the radioactivity below these levels (that is, of the minor metabolites) would be recommended unless there are toxicological concerns over residues occurring at the lower levels.

**Non-extractable metabolites**

Laboratory animals: characterisation of non-extractable metabolites in comparative metabolism studies in laboratory animals is normally not performed. You should only do a characterisation of the covalently bound metabolites of a veterinary drug in laboratory animals when the non-extractable residue contains a metabolite of interest that is not present in enough quantity for characterisation in the easily extractable portion. In that case, you should follow the procedures identified for target animal species below.

Target animal species: the use of veterinary drugs in food-producing animals can result in residues that are neither extractable from tissues using mild aqueous or organic extraction conditions nor easily characterized. These residues arise from:

- incorporation of residues of the drug into endogenous compounds
- chemical reaction of the parent drug or its metabolites with macromolecules (bound residues), or
- physical encapsulation or integration of radioactive residues into tissue matrices.
Those non-extractable residues shown to result from incorporation of small fragments of the drug (usually one or two carbon units) into naturally occurring molecules are usually not of significance.

Characterisation of the bound residues of a veterinary drug is usually prompted when the bound residue comprises a significant portion of the total residue or when the concentration of bound residue is so high as to preclude the assignment of a practicable withdrawal period for the drug (that is, the total residue does not deplete below the residue of concern because of the amount of bound residue). The extent of data you should collect on the bound residue depends on a number of factors, including the amount of bound residue, the nature of the bound residue and the potency of the parent drug or metabolite on which the acceptable daily intake is based. You may need to investigate the nature of bound residues in certain situations. The information obtained from such an investigation might warrant the discount of some of the residues from the total residue of concern.

Characterisation of the bound residue: the characterisation of bound residues is usually difficult, involving vigorous extraction conditions or enzymic preparations that can lead to residue destruction or artefact formation.

However, the biological significance of residues of veterinary drugs in foods usually depends on the degree to which those residues are absorbed when the food is ingested. Therefore, the determination of the bioavailable residues that result when tissue containing bound residue is fed to test animals can be a useful characterisation tool.

### Reporting of data—outcomes of the metabolism assessment

#### Comparative metabolism studies

Assessment will involve review of the absorption, distribution, metabolism and excretion of the drug in laboratory animals and target animal species.

Absorption: the primary purpose of absorption studies is to assess the bioavailability of the veterinary chemical, which relates to the rate and extent of absorption. The same considerations of absorption apply, regardless of the route of administration.

In the case of veterinary chemicals where it is proven that systemic absorption is negligible (that is, where metabolism studies demonstrate that the levels of total radioactive residues in edible commodities are below the limit of quantification of the analytical method used for monitoring and surveillance purposes), further residue studies are not required. However, if there is significant systemic absorption and total radioactive residues in any of the edible commodities are above the method limit of quantification, you should provide full residues studies.

Absorption involves estimation of:

- the rate of absorption (such as plasma $T_{\text{max}}$ reached within time of treatment)
- the extent of absorption
- the absolute bioavailability of the drug.

Distribution: following absorption, the veterinary chemicals are distributed throughout various tissues and organs of the target animal species. The results of distribution studies are useful in identifying the target tissue(s).

Distribution involves consideration of:

- where in the body the drug residues partition into the relative rank order of total radioactive residue(s) distribution in standard tissues from different species
- the extent of protein binding that occurs.

Metabolism: different biotransformation products may possess different toxic potentials. Therefore, you should provide information on the chemical nature, concentration, and persistence of the total residues. The purpose of the metabolism study in the target animal species is to provide the necessary information on the metabolic fate of the veterinary chemical in the edible tissues, and to enable the establishment of the marker residue(s).

These studies are also necessary to establish whether the metabolite(s) found in target animals are the same as those found in the laboratory animals used for toxicity testing. This is referred to as comparative metabolism, and determines whether the metabolites that people are exposed to when consuming tissues from treated animals are also produced in the laboratory animals used to establish the health standards. To validate the approach to assessing dietary exposure and the potential risk to human health, this information should be provided.

Metabolism involves consideration of:

- the profiles of total radioactive residues in excreta (urine, faeces), and tissues (muscle, liver, kidney, fat, skin fat$^1$, or injection sites) from treated animals
- the characterisation of total radioactive residues, and identification of the main residues components
- the postulation of the routes of metabolism of the drug in animals.

Ideally, the outcome of the comparative metabolism assessment is that the biotransformation pathways for a veterinary drug are qualitatively (if not quantitatively) similar in laboratory animals and target animal species. It is understood that, if the laboratory animals produce substantially similar metabolites as those produced by the food-producing animal, the laboratory animals will have been auto-exposed to the metabolites that humans will consume from tissues of treated food-producing animals. Auto-exposure of metabolites will ordinarily be taken as evidence that the safety of metabolites has been adequately assessed in the toxicology studies.

If the conclusion of the comparative metabolism studies is that laboratory animals are not exposed to all significant metabolites, you should provide bridging toxicity studies where laboratory animals are dosed with the significant metabolite that is not auto-exposed in the laboratory species.

Excretion: Information on the route(s) of excretion reflects the pathways by which the veterinary chemical is metabolised. It is recommended that you provide data on excretion in target animal species, including renal and faecal excretion. You should also consider other routes of excretion when appropriate (for example, milk).

Excretion involves examination of:

- the extent of recovery of administered dose in excreta (over a certain time frame)
- the estimation of the terminal plasma half-life, used as an indicator of residues persistence
- the comparison across the different species.
Selection of marker residue(s)

You should report the components of the total residues in each tissue for each collection time point, for comparison to the total residue concentrations. The components of the total residues (parent drug plus metabolite[s]) should be examined to select the marker residue. The marker residue might be the parent compound. However, the marker residue might also be defined as a combination of parent compound plus a metabolite(s) or as a sum of residues that can be chemically converted to a single derivative or fragment molecule.

After consideration of the metabolism data, it should be possible to select the marker residue. An appropriate marker residue has the following properties:

- there is a known relationship established between the marker residue and the total residue concentration in the tissue of interest
- the marker residue should be appropriate to test for the presence of residues at the time point of interest; that is, adherence to the withdrawal period
- there should be a practicable analytical method to measure the marker residue at the level of the maximum residue limit at a level that is acceptable to Australia’s major trading partners.

Selection of a target tissue

The target tissue is the edible tissue selected to monitor for the total residue in the target animal. The target tissue is usually, but not necessarily, the tissue with the slowest depletion rate of the residues.

Ratios of marker residues to total residues

You should report the total residue concentration for each tissue for each collection time point. Also provide the amounts of total residue radioactivity extracted (percentage extractable) using various treatments (enzyme, acid). You should present the data so that it is possible to determine the ratios of marker residue to total residue ratio in each tissue, without extrapolation. These ratios are an integral part of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives approach to establishing maximum residue limits for veterinary drugs.

Agricultural—Efficacy experimental design and analysis

Evidence provided in support of a proposed label claim for efficacy must demonstrate strong correlation between application of the product and the claim. Well-designed, well-conducted efficacy trials are critical to building your portfolio of evidence for submission to the APVMA.

The experimental design and analysis must be able to demonstrate that it is the application of the product that is having the measured effect, rather than some other variable. If a trial is poorly designed, even the most skilled statistician will have difficulty in applying appropriate and meaningful statistical analysis to prove that the product works as claimed.

Poorly designed trials and incorrect statistical analyses introduce doubt about the efficacy of a product and could result in the APVMA being unable to be satisfied against the prescribed criteria that the product is efficacious. Therefore, you should carefully consider both trial design and analysis before commencing any trial.

This guideline provides advice about designing efficacy trials and may be used as a checklist of design principles. It is not intended to replace the considerable information available on the subject elsewhere and does not include all matters relating to trial design and analysis. We encourage you to seek advice from a professional biometrician or statistician when planning trials.

The guideline draws heavily on Design and analysis of efficacy evaluation trials, which is published by the European and Mediterranean Plant Protection Organization (EPPO) (PP 1/152(4), 2012).

When designing efficacy trials for registration purposes, you should consider the following matters in order to generate data that are both reliable and robust:

- objectives and scope
- design type and analysis requirements
- treatments and controls
- randomisation
- replication
- statistical power
- plot and sample size
- managing contamination between plots
- variables
- measurement methodology.

The type of analysis that can be conducted on trial data is heavily dependent on the trial design. Therefore, it is crucial that the trial design and type of analysis be considered together.

Objectives and scope

The objectives and scope for a trial should be clearly defined. The trial design should not be more complicated than is required to meet the objectives. Trial objectives may even place constraints on the trial design.
The main objective of any efficacy trial is to demonstrate that the product will be efficacious when used in accordance with the proposed label instructions. However, the final label instructions (for example, instructions on rates and frequency of use) may not be obvious if pilot studies have not been conducted to determine the likely rate(s) or number of applications. Pilot studies are often designed differently from pivotal studies for this reason.

An example objective could be: *To demonstrate that product A will provide control of pest B in situation C, using commercially available equipment, at a level deemed commercially acceptable and no less than current industry standard D.*

Trial objectives lead to the scope of the trial. The scope of the trial encompasses all reasonable variables that could affect the trial objectives and ultimately the product’s intended use. The scope must be sufficient to cover all important possibilities and variables and allow a statistical analysis to demonstrate a strong correlation between the application of the product and the measured effect.

Limitations on the scope should also be considered. For example, sometimes objectives can only be met by conducting a number of separate trials, and environmental factors affecting efficacy can vary from plot to plot and over time. The scope of the trial or groups of trials should address these issues to ensure that the design allows for adequate randomisation of treatments, replication of treatments and repeats of trials. Other scope parameters include variation in the testing environment, using the appropriate rates and application methods of the new product and applicable industry standards.

**Design type**

There are many trial designs, each with benefits and constraints. The best design allows the true extent of a product’s efficacy to be assessed by an appropriate statistical analysis. It will take account of any variability in parameters in the study and allow their influences to be measured or ranked in importance. A good trial design will also minimise the probability of any result, efficacious or not, being the consequence of chance.

Efficacy trials should be designed to allow valid and appropriate statistical analyses of the data generated. The most appropriate experimental design will depend on the pest or situation, and you should consider those factors and the test objective when designing the experiment. Treatment group sizes and the number of replicates depend on treatment differences for each pest situation and may need to be determined in preliminary range-finding studies.

Most efficacy trials (especially laboratory trials and field-based trials of agricultural pesticides) include the test product(s), reference product(s) and an untreated control (the treatments). Further details on treatments are provided below. The trial design determines how many of each treatment type are required (that is, replicates), where each treatment is placed in relation to others (for example, randomisation) and how they are placed in relation to the trial environment (for example, blocks of treatment sets). It is the pattern of all these features that makes up the trial design and determines the type of analysis possible.

Common designs used in efficacy trials include randomised complete block designs and Latin squares.

In a randomised complete block design, the block is a group of plots within which the environment is homogeneous, and each block contains only one of each treatment, placed in a random order within the block. This design is useful if the trial area is variable (heterogeneous) but there are patches of homogeneity where a block of treatments will fit. The placement of the blocks should aim to control the variability of the site by ensuring that each treatment is compared against all other treatments under the same trial conditions within the block. Examples of areas where randomised complete block designs are suitable are plantings of horticultural crops grown in areas of varying topography or soil.

Latin squares are a modification on a block design. The design is formed on the basis of a square matrix in which one axis of the matrix is a treatment and the other axis represents another variable, such as time, space or a person. Each treatment appears once in each row and each column. For example, Figure 1 shows a square matrix with four treatments (A, B, C and D):

![Figure 1: Latin squares design of a square matrix with four treatments.](image)

**Analysis**

The type of analysis to be conducted depends on the purpose and design of the trial and the type of observations made. Statistical analysis is not required in all cases; nor is it appropriate in certain situations. However, when a comparison between two products or between one product and no treatment is required, statistical analysis must be provided to support the interpretation of the data. Novel statistical analysis submitted in support of experimental data should be accompanied by the raw data and the published literature that references the statistical technique. This guideline cannot describe all analytical approaches for all trial designs, but aims to provide some principles of analysis to assist applicants. If you are not confident of your knowledge in this area, it is highly advisable to seek the assistance of a competent statistician before starting trial work.

Typically, it is the variable that determines which broad type of analysis is required (that is, parametric or non-parametric). If the variable is quantitative (binary, binomial, discrete or continuous), parametric statistical methods should be used, such as analysis of variance or linear or logistic regression. If the variable is qualitative (nominal and ordinal methods, such as ranking or scoring), non-parametric methods are required.

Before conducting a parametric analysis of variance, three assumptions should be met to ensure that the analysis is valid:

- additivity of effects
- homogeneity of variance
- normality of the error.
Information guidelines and standards

If these three assumptions cannot be met, non-parametric methods may be preferred.

**Parametric tests**

Additivity requires that the sources of variability (eg treatments) are independent of each other. Independence results in an additive (eg multiplicative or logarithmic) effect on the response variable (eg pest population). The more variables interact with each other, the greater the chance that the observed response is not the result of the individual treatments may invalidate the observed results. Sometimes, effect results are not on a natural scale and must be transformed to different scales (for example, probit or logit) to meet additivity requirements. Methods to test additivity are available (such as Tukey's test of additivity).

Homogeneity of variance requires that all the populations tested contain the same level of variability. The less homogeneity between variances of populations being compared, the less likely it is that a parametric method will be able to accurately produce a significant result. There are many tests used to test homogeneity of variance, each with advantages and disadvantages.

Normality requires the distribution of errors (variance around the mean) to be normal. Normal distribution is important because the further the distributions are from normal, the less validity any analysis of variance assessments will have, as there is a greater chance that a significant result will be false (and vice versa). Standard tests and graphical displays are available to demonstrate normality.

**Analysis of variance**

When reporting the results of an analysis of variance (ANOVA), you should present a table of means of each of the treatments, along with the standard error or confidence interval (the variability around the mean). Presenting means with the variability of results can overcome the difficulty of explaining statistically equivalent results when differences between means are large (and vice versa).

Formal statistical tests, often as F-tests, are usually also performed to demonstrate any significant results between treatments. Typically, study reports present an analysis to compare all treatment means against each other. In considering the original objective of the trial, this may not be necessary and may confuse the analysis and interpretation. For example, not all treatments need be compared against each other, especially if the comparison of interest is only a limited set of treatments, such as the new product versus the industry standard at proposed label rates. If the trial is designed for this purpose, these matters should be considered at the trial design stage (for example, t-tests may be appropriate). You should consult appropriate texts and professional statisticians if you are unsure of the most appropriate test or procedure.

**Non-parametric tests**

Non-parametric methods may be required and are preferred when the data are qualitative rather than quantitative or the three assumptions described above cannot be met. However, non-parametric methods should be used with caution when analysing small data sets. There are a number of different non-parametric methods, many of which are suitable only in certain situations. You may wish to refer to the EPPO's Design and analysis of efficacy evaluation trials (PP 1/152(4)) for references describing which test is relevant to a particular type of data set.

**Trial series**

You may need to conduct separate but closely similar trials at different locations and/or at different times. The series of trials can be analysed together in certain circumstances (for example, if they have the same methods, external impacting factors and pest abundance and similar standard error) and for particular reasons (for example, to estimate treatment effects over sites and years or to test potential confounding factors). Such an analysis should not be conducted unless it has been planned for at the trial design stage so that all requirements can be met. See EPPO guideline PP 1/152(4) for more details.

**Treatments and controls**

Trials often include multiple treatments to allow for comparisons between treatments of interest. These could be treatments using different rates of the same product to show any different rate effects or treatments using different products to show equivalence or differences between products. Applying no treatment at all is also very valuable, as it can highlight many issues within an experiment and allow different comparisons to be made (see below).

For a test to be acceptable for regulatory purposes, in most cases the test treatment should be compared to one or more control treatments. They can include:

- an untreated (negative) control
- a reference product standard (positive control).

The untreated control allows a comparison to be made by measuring the difference between the treatment and what happens if no treatment is applied. It also allows the effects of any other variables present in the trial to be measured. For example, an unexpected drop in temperature, a hailstorm or spray drift from another area could considerably reduce the population of pests in a crop trial and therefore have an impact on the trial results. By considering the measurements from the negative control, the magnitude of other effects can be determined. The untreated control results are also used to provide a modified, per cent control figure that is specific to the treatment and not any other influential factors. When the test treatment includes additives such as wetting agents, the untreated control can include the same additive so that the true effect of the active constituent can be determined.

In small-scale simulated trials, the inclusion of an untreated control is quite easy. However, the APVMA appreciates that in certain situations, such as large-scale field trials and public health situations, untreated controls may be uneconomic or inappropriate. In such situations, you may need to conduct longer pre-treatment monitoring to determine whether there are any extraneous reasons for population fluctuations. In addition, more trials may be needed to show consistent results, thereby discounting location- and time-specific reasons for population reductions.

The placement of untreated controls within the trial design depends on the specifics of the trial (product type, situation and pest) and the analysis. Untreated controls are most often placed just like any other treatment (included controls), but can also be placed next to every treatment (for example, by splitting individual plots into treated and untreated sections; that is, adjacent controls), by placing them outside the treatment group (excluded controls) or by systematically placing them between and within treatment groups to account for variability in the trial area (imbricated controls).

Positive controls can be used as an industry benchmark, thus providing an idea of how each product compares in equivalent situations. Statistically equivalent efficacy (with a low probability of a chance result) is the minimum aim in this comparison. Equivalent efficacy obtained under difficult
Randomisation

Every trial will have factors influencing the effect provided by the treatment applied. This could include variations in the trial environment, such as patchy pest abundance or physical parameters of the trial site. Assigning treatments to plots randomly (and having sufficient replication) is considered the best way of ensuring that any uncontrolled sources of variation affect each treatment evenly and that any bias in assigning treatments to certain plots is removed. Simply assign each treatment or plot to a number and use a random number generator to assign treatments.

Replication

Even when testing in what appear to be identical situations, the result of a pest control treatment will be variable due to differences between individuals or populations of the same pest species, slight differences in applications made and variations in environmental conditions. To allow an appropriate assessment, the extent of variation in performance needs to be understood, especially when comparing two products or when comparing against a negative control treatment. Therefore, repeat the same treatment a number of times to measure the likely variability, so that any difference between treatments can be deemed to be due to the treatments and not just chance.

If the nature of the trial does not lend itself to statistical analysis (for example, repeated commercial-scale field tests in separate locations or areas not considered equivalent for statistical purposes), the separate trials are not considered true replicates. Commercial-scale field trials are typically used to demonstrate that the product can be used on a commercial scale with commercial equipment. By themselves, such trials are usually insufficient because they are not designed to demonstrate that efficacy is due only to the treatment being applied. However, if control plots are included in each location, a statistical analysis could be done with these data.

If data held by you or a third party are insufficient to demonstrate an appropriate level of control, you should consider collecting data using a research permit.

Replication versus pseudo replication

True replication, not ‘pseudo’ replication, is essential in ensuring that the trial can be appropriately analysed. A true replicate involves a single and separate application of the treatment. Each separate treatment application should have one result per parameter measured or experimental unit. If multiple samples are taken from each single treatment they should be added, joined, composited etc, as appropriate to the analysis, to present a single value per replicate. A common error made by researchers is to make one large treatment application and take multiple replicate samples from the one treatment. These samples are considered to be ‘pseudo replicates’ and should not be used as replicates in statistical analysis, where it will be inconsistent with the assumptions used to validate the particular statistical method used (eg ANOVA).

It can be difficult, depending on the trial site and the pest being treated, to determine how best to create proper replicates. One way of ensuring this is to apply blocked separation of treatments and randomisation (see above).

The number of replicate treatments required is dependent on a number of factors, including how much statistical ‘power’ is required (see below), the precision of the measurements being taken (see below) and the variability (heterogeneity) of the test site.

Statistical power

The power of a statistical test is the probability that it will yield significant results (Cohen 1977) or the probability of detecting a given difference between treatments if such a difference exists (EPPO PP 1/152(4)). The main goal of determining statistical power is to allow the researcher to decide, while in the process of designing an experiment:

- how large a sample is needed to enable statistical judgements that are accurate and reliable
- the likelihood that the statistical test will detect effects of a given size in a particular situation.

If a design does not have sufficient power, the experiment might not be able to determine with any confidence that a significant result has occurred. A finding beforehand that a test has low power should lead to a review of the experimental design. A test found afterwards to have low power should convince the researcher to either perform the experiment again with a larger sample size or to at least consider what conclusions about demonstrating efficacy, if any, can be drawn from the experiment.

Researchers use the number of residual degrees of freedom (rdf) available in a trial design to determine whether the trial is likely to have sufficient statistical power. Statisticians also use rdf to describe the number of values in the final calculation of a statistic that are free to vary. Generally, the minimum accepted number of rdf required for a trial design to be considered adequate is 12 (EPPO PP 1/152(4)). However, this should be increased if there is low precision in the measurements taken. Table 1 gives the rdf in relation to a number of sites, treatments and replicates in a site. You may wish to obtain advice from an expert statistician about this aspect of trial design.

Table 1: Residual degrees of freedom in relation to number of sites, treatments and replicates in a site

<table>
<thead>
<tr>
<th>Sites</th>
<th>Replicates</th>
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<th>4</th>
<th>6</th>
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</thead>
<tbody>
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<td></td>
<td>Treatments</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<tr>
<td></td>
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<td>3</td>
<td>4</td>
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<td></td>
<td>8</td>
<td>14</td>
<td>21</td>
</tr>
</tbody>
</table>

The rdf for an estimate equals the number of observations (values) minus the number of additional parameters estimated for that calculation. As the number of parameters to be estimated increases, the degrees of freedom available decrease. It can also be thought of as the number of observations that are freely available to vary, given the additional parameters estimated.

When estimating a single population mean (for example, the average number of weeds per square metre from n-square-metre samples), the number of rdf is \( n - 1 \) (the \( 1 \) represents the mean around which all other sample measurements will vary). When estimating the difference between two population means (that is, a two-sample t-test), the number of degrees of freedom is \( n_1 + n_2 - 2 \) (or \( n_1 - 1 \) + \( n_2 - 1 \)).

In a completely randomised design trial with 5 treatments (for example, no treatment, 0.5x proposed rate, 1x proposed rate, 2x proposed rate and an industry standard) and 4 replicates, there are 15 rdf. This is calculated by the total df (that is, 5 x 4 – 1) minus the treatments df (5 – 1 = 4); that is, 19 – 4 = 15.

In a randomised complete block design trial with 3 treatments (for example, no treatment, full rate and an industry standard) and 7 replicates, there are 12 rdf (that is, total df (7 x 3 – 1) – treatments df (3 – 1) – blocks df (7 – 1) = 20 – 2 = 18 rdf).

In a completely randomised design trial with 3 treatments and 4 replicates repeated at 3 equivalent sites, there are 18 rdf (that is, total df (3 x 4 x 3 – 1) – treatments df (3 – 1) – sites df (3 – 1) – interaction treatment x sites df ((3 – 1) x (3 – 1)) – replicate df over sites (4 – 1) x 3 = 35 – 2 – 4 – 9 = 18 rdf).

We recommend that you consult a statistician or a compendium of appropriate experimental designs to determine the most suitable study design for each specific situation (host, pest, experimental purpose) and product type. Some product-specific guidelines that may be included in the regulatory guidelines suggest possible trial designs that suit the particular type of product and types of trials that are typically used for that type of product. Alternatively, you may seek an assessment of a proposed trial protocol from the APVMA.

**Experimental units (plots)**

The experimental unit is that part of the trial material to which a single treatment is applied and on which observations are made (EPPO PP 1/152(4)). For example, it could be a plot of wheat receiving a selective herbicide application, an apartment with a cockroach treatment, an arm of a person with a personal insect repellent or an apple tree receiving a fungicide treatment.

The experimental units should be representative of the population the trial is testing and representative of the likely situation the product being tested will be used in if registration is granted. Lack of environmental uniformity between units can sometimes be dealt with by blocking, as described above.

The size of an experimental unit must be uniform between treatments and between trial sites if comparison is required. The size required is dependent on the variables of the trial. The ‘bigger is better’ rule is true for most situations, as accuracy increases with plot size, but only while the environmental variables of the plot remain uniform. The plot size should be appropriate to allow a treatment to be applied that replicates or simulates real use and allows an adequate sample size to be taken. Where specific product type guidelines exist, they may include experimental-unit size recommendations.

Interference between plots is also of considerable importance. Individual plots need to be sufficiently separate from each other to ensure that there is no interference or contamination of treatments (or pests) from one unit to another. For example, in situations where pesticides are sprayed on a crop, spray drift can carry chemicals from one treatment plot to another if there is insufficient protection or distance between plots.

Untreated buffer rows between plots can be added to the experimental design to reduce effects such as drift from one treatment to another. Depending on the situation, the rows may be of a taller or denser species or a more disease-resistant or spray-tolerant cultivar. Physical barriers such as plastic sheets can also be used at the time of application. Plots may also be planted farther apart to provide a distance break. Application equipment must also be suitable for this purpose. Alternatively, plots may be large enough to allow for factors such as drift, and the effect of the treatment is only done where those factors are unlikely to be present; for example, a plot size is 5 m x 20 m but only the middle 3 m is used for assessment.

Where the pest of interest is very mobile (such as vertebrate pests or certain insects), it may also be necessary to ensure that units are sufficiently separate or protected so that individuals in one treatment are not able to move out of the treatment area or into another treatment area, thereby affecting each treatment result.

Other types of interference depend on the product, pest and situation being tested. You should document any possible interference issues and explain how they were managed.

**Variables and methods of measurement**

The nature of the variable being observed for change as a result of a treatment is important because it usually influences the statistical method used to interpret the results of a trial (EPPO PP 1/152(4)). Variables can be binomial (for example, yes/no or presence/absence of damage), nominal (for example, non-ordinal descriptions such as species present or type of damage—root, stem or leaf), ordinal (for example, ordered but not measured, or qualitative descriptions such as levels—bad, good, best) or quantitative (that is, measured and ordered results).

Any observations made should be of a type that can be consistently accurate, relevant to the aim of the trial and, wherever relevant, allow an appropriate statistical analysis.

Observations on variables can be in the form of measurements, visual estimations, ranking and/or scoring. Different types of observations require different analysis (that is, parametric versus non-parametric) and in certain situations may not provide suitable evidence for demonstrating efficacy.

There are certain benefits to visual estimation, scoring and ranking, such as speed of observation and possibly lower cost, but you should take care that the type of observation does not limit the choice and power of the statistical method. For example, determining the effect of an ant poison by estimating the number of ants present within 20 cm of a food station at a point in time can be difficult. One method would be to estimate whether the number was less than 10, between 10 and 30, between 30 and 100 or more than 100. This method, while easy, quick and inexpensive, will be unlikely to provide the type of information that will allow a powerful statistical analysis. However, taking a photo and counting ants individually or measuring the amount of food consumed in a particular period may provide the type of information required for an appropriate analysis.

Observations that will best support a statistical analysis will have:

- precision—a combination of accuracy (an absence of any bias by the observer) and reliability (they will have low variability)
- sensitivity—an ability to detect small changes in the parameter observed (measured) in the experimental unit
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- repeatability—able to provide the same or a closely similar value to the same observer with identical experimental units
- reproducibility—with the same or closely similar value for a different observer with identical experimental units.

Often, it is necessary or beneficial to make more than one type of observation to determine the effectiveness of a pesticide. In addition, there are usually many ways a product’s effect can be observed and measured. This can lead to different analysis options and, as discussed above, different probabilities of detecting differences in treatments where they exist.

It is critically important, however, that the type of observation made can support the product label claims being proposed. For example, an efficacy trial of pesticide for use in crops can look at both the effect on the pest concerned and any effect in crop yield. Together, these results provide much more information than either alone. Although crop yield is usually the most important end result for the user, for regulatory purposes it needs to be demonstrated that it is the particular pest being observed that is having the yield effect.

It is imperative that the type of observation to be made is considered along with the trial design and analysis before the trial is conducted, and that the observations support the claims to be made on the label. We recommend that you seek professional advice if you are unsure.

References


European and Mediterranean Plant Protection Organization (EPPO), Design and analysis of efficacy evaluation trials (PP 1/152(4)).


Veterinary chemical products—Residues (Part 5A)

The Agricultural and Veterinary Chemicals Code Act 1994 specifies that the APVMA must be satisfied that foodstuffs obtained from animals treated with an active constituent or chemical product must not contain residues of the active constituent or chemical, or its metabolites as they might constitute a health hazard for the consumer.

Therefore, when applying to register new veterinary chemical products to be used in or on food-producing animal species, in support of your application you should submit appropriate pharmacokinetic, residue kinetic and residues depletion data, or relevant scientific argument. Pharmacokinetic and residue kinetic data are used for maximum residue limit determinations, while residue depletion data are used to establish withholding periods and export slaughter intervals.

Types of data

Pharmacokinetic, residue kinetic and residues depletion data are submitted to enable maximum residue limits, withholding periods and export slaughter intervals to be established. As the APVMA is responsible for registering both agricultural and veterinary chemicals, it has a harmonised approach to assessing the intake of residues as part of its evaluation of safety. In the interest of obtaining outcomes that are aligned with those of other countries for maximum residue limit decisions for veterinary chemicals, the APVMA follows the procedure used by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives for estimating maximum residue limit values, but retains its internally harmonised approach as an additional way of estimating residue intakes.

Pharmacokinetic data comprise information on the absorption of a veterinary chemical, its distribution in tissues, its metabolism or biotransformation, and excretion over time. The purpose of pharmacokinetic studies is not one of mass balance (that is, to achieve quantitative recovery of the administered dose), but rather to provide information on the concentration–time profile of the veterinary chemical and its metabolites in the target animal species, and on subsequent planning of residue depletion studies. The recommended considerations when performing pharmacokinetic studies are described in Veterinary drug residues—comparative metabolism studies, selection of marker residue(s), and ratios of marker residues to total residues.

Additionally, the pharmacokinetic profiles of the veterinary chemical and its metabolites in the target animal species are compared qualitatively with those of the laboratory animal species used to establish the health standards, to verify the relevance of the toxicological effects and the no-observed-adverse-effect levels, and thereby validate the dietary exposure assessments.

Residue kinetic studies provide information on the concentration profile of total residues in edible tissues over time, and the corresponding concentration profile of marker residue(s). These data are used to:

- define the relationship between the marker residue(s) and total residues in edible commodities at any time after treatment
- calculate maximum residue limits.

The recommended considerations when performing residue kinetic studies are described in Veterinary drug residues—comparative metabolism studies, selection of marker residue(s), and ratios of marker residues to total residues.

Food-safety (marker residue depletion) data are used to

- establish maximum residue limits
- demonstrate compliance with existing maximum residue limits
- determine appropriate withholding periods
- determine appropriate export slaughter intervals.

The guideline Food-safety studies for veterinary drugs used in food-producing animals provides study design recommendations that will facilitate the generation of food-safety data that are likely to satisfy the data recommendations for establishing maximum residue limits and recommending appropriate withdrawal periods for a specific product.
Residues data submissions

The types of pharmacokinetic, residue kinetic and marker residue(s) depletion data that should be provided in support of an application to register a veterinary chemical product will depend on whether:

- the veterinary chemical has been previously approved by the APVMA
- the APVMA-approved veterinary chemical has been previously registered in a product for use in or on the target animal species
- the dose form, treatment regimen, and route of administration of the veterinary chemical product has been considered previously by the APVMA.

Details of the types of data that should be submitted to address the veterinary residues aspects of an application are provided in Table 1.

Table 1: Pharmacokinetic and residues data needed based on type of product application

<table>
<thead>
<tr>
<th>Registration status</th>
<th>Use of veterinary chemical in target animal species</th>
<th>Dose form, route of administration, and treatment regimen</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>New veterinary chemical (not currently approved by the APVMA)</td>
<td>N/A</td>
<td>N/A</td>
<td>Full pharmacokinetic, residue kinetic and residue depletion package</td>
</tr>
<tr>
<td>Existing veterinary chemical (previously approved by the APVMA)</td>
<td>Not currently registered</td>
<td>N/A</td>
<td>Full pharmacokinetic, residue kinetic and residue depletion package</td>
</tr>
<tr>
<td>Existing veterinary chemical (previously approved by the APVMA)</td>
<td>Currently registered by the APVMA</td>
<td>Not currently registered</td>
<td>Full pharmacokinetic, residue kinetic and residue depletion package</td>
</tr>
<tr>
<td>Existing veterinary chemical (previously approved by the APVMA such as a generic registrations)</td>
<td>Currently registered by the APVMA</td>
<td>Currently registered</td>
<td>Residue depletion package only</td>
</tr>
</tbody>
</table>

N/A = not applicable

Application layout

A checklist of data for Part 5A (pharmacokinetics and residues) of an application for veterinary chemical products is shown in Table 2, along with a brief description of how the data should be set out.

Table 2: Data submission checklist for Part 5A

<table>
<thead>
<tr>
<th>Submission</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of contents</td>
<td>List the sections included in the submission and their page numbers</td>
</tr>
<tr>
<td>Pharmacokinetic and residue kinetic studies (for the determination of marker residue, marker residue to total residue ratios and maximum residue limits):</td>
<td>A single summary of all pharmacokinetic and residue kinetic studies, along with an interpretation of the results, clearly outlining the reasons for the proposed marker residues and target tissues, and the proposed maximum residue limits for each edible commodity. Full copies of each of the studies should be provided in the appendices. Where maximum residue limits have already been established, details of the previously established marker residues, target tissues, ratios of marker residues to total residues, and maximum residue limits should be provided.</td>
</tr>
<tr>
<td>Food-safety (marker residue depletion) trials (for the estimation of withholding periods and export slaughter intervals):</td>
<td>A single summary collating all the relevant residues decline data, along with an interpretation of the results, which give rise to the proposed withholding periods and export slaughter intervals. Full copies of each of the residue decline studies should be provided in the appendices.</td>
</tr>
<tr>
<td>Analytical methodology:</td>
<td>Copies of the full reports for each analytical method, including validation reports, should be provided in the appendices.</td>
</tr>
<tr>
<td>Appendices:</td>
<td></td>
</tr>
</tbody>
</table>
Information guidelines and standards

• copies of the full reports for pharmacokinetic, residue kinetic and residue trials, along with complete details of the analytical methods and validation reports.

The following content can be found at http://new.apvma.gov.au/node/360
If making a submission, please reference page number: 360

Agricultural—Preparing a study report (Efficacy and safety)

Applicants planning and conducting efficacy and crop safety trials should consider how the trial data will be collected, documented and prepared for presentation to the APVMA to support an application to register or vary a product. This guideline provides basic advice about the presentation of study reports that may be included in an efficacy dossier. You may use this advice and accompanying template, but are also free to use any alternative format. If you use an alternative format, you are responsible for ensuring that your template addresses all the features described below so that the report can be easily reviewed and understood by a reviewer.

This guideline should be read in conjunction with other APVMA guidelines, including any relevant product-specific guidelines and the guidelines on preparing an efficacy dossier and experimental design and analysis.

Further details about each section of the report template are also provided to assist applicants preparing reports.

Figure 1: Study report template

<table>
<thead>
<tr>
<th>Study/Trial identification</th>
<th>Quality assurance statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study summary/Executive summary/Abstract</td>
<td>Scope/Introduction/Background</td>
</tr>
<tr>
<td>Methods and materials Study particulars Experimental design Treatments Assessment methods</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>• Raw data • analysis</td>
</tr>
<tr>
<td>Conclusions and discussions</td>
<td>Appendixes</td>
</tr>
<tr>
<td>Additional information/References</td>
<td></td>
</tr>
</tbody>
</table>

Guidance on report features

Study identification

Include an identifying study or report number that is unique to the report. This is especially important when there are a number of trials following the same protocol or with similar titles, as they can be easily confused, particularly during the creation of the data list and over the life of the application.

Provide the study or report title and the names of the primary author(s), editors and any other people involved, and details of their roles in the study. Include the date the report was finalised (for example, approved for release by the person responsible).

Study summary, executive summary or abstract

Provide a brief summary of the investigation, including a statement of the objective, general methods, results and conclusions. If the study was conducted for the purpose of registering a product in Australia, it should include reference to how the results support the product’s efficacy and proposed label instructions for use. Any constraints, such as economic, meteorological or animal welfare issues, should also be detailed.

Scope, introduction and background

The purpose of the study should be briefly stated to make it clear and set the scene for the reviewer. If the study is introducing new technology, methods, other unusual matters or different designs, including a brief explanation in the introduction and providing the details in the relevant sections would be appropriate. Alternatively, if the particular design has been used successfully in previous APVMA applications, it may be useful to provide some background on this for the reviewer, who might not be aware of past assessments. It may be of benefit to include the previous reviewer’s report as an attachment. The efficacy reviewer can only assess what is in the dossier provided, so you should include all relevant aspects of the trial and any ‘industry’ information that will be needed to understand the conduct of the trial and the particular use pattern.

Methods and materials

General

Trial results and the conclusions drawn from them have little value if the report does not adequately explain how the trial was conducted. If the trial followed protocols previously agreed with us, or published methodology such as APVMA or internationally accepted guidelines, this should be stated and explained where necessary. If the trial methodology is detailed or lengthy, it can be included as an appendix to the main report; provide only the main points in the body of report.
**Study particulars**

Details of the research establishment, the study coordinator, other personnel, the exact location and the dates of commencement and completion of the trial must be recorded and documented in the submission. Provide scientific (Latin binomial) names for any crops, pests, weeds or other organisms discussed (common names, though useful, are imprecise and too variable to be used by themselves). Where necessary, provide relevant meteorological information (rainfall, temperature, humidity, etc.) and agronomic details (soil type, cultivars, crop rotations, etc.) for both local and overseas studies. These details could be presented in table format with each study and may be included as an appendix.

**Experimental design**

Full details of the experimental design (for example, small plot, replicated, randomised complete block design), numbers of replicates and plot sizes should be provided for each study. The following will provide useful information for the reviewer:

- definition of the null (for example, no difference between treatments or products) and alternative hypotheses (for example, the proposed new product is better than the existing product) and the appropriate level of statistical significance for rejecting or accepting the hypothesis (for example, p < 0.05)
- methodology for the statistical or biometrical analysis proposed, statistical justification for numbers of animals or groups used (including the need to replicate), statistical power and confidence level of the data
- standard operating procedures that are study-specific and other records, which may be appended to the submission
- details of controls used as comparisons in the statistical analysis (it is important for the reviewer to be assured that controls have been exposed to similar environmental conditions and study conditions).

For further details on experimental design, refer to the *Efficacy experimental design and analysis guideline*.

**Treatments**

Give details of the test product(s) and of any standards or reference products (controls) included in the studies (such as the product name or experimental code, active constituent name and content). This should also include the active constituent level and/or formulation details of the reference product and any other products used in the trial.

Provide full details of all treatment applications. It is important that the treatments are consistent with current agricultural practice. This could include information such as:

- application rate in terms of product per unit or active constituent per unit (including per unit canopy row)
- frequency of applications and application intervals
- details of any other products used, either separately or in combination
- carrier volume (L/ha) and type (for example, diesel or water)
- type of application equipment
- other application details, such as nozzle type, spray quality, pressure (kPa, bar) and boom height
- date of application
- crop growth stage at application and crop part treated
- pest population or developmental stage or infestation level at time of application.

If you use an experimental code, explain how the coded product relates to the proposed product. If more than one formulation has been used in development studies, give full formulation details and, where relevant, details of bridging or bioequivalence studies. If earlier formulations of the product or other products containing the same active constituent(s) are cited in supporting evidence, explain the relevance of this evidence to the current formulation.

**Assessment methods**

All assessment methods should be documented, explained and, where relevant, appropriately referenced.

Examples of critical information that could be documented include:

- date or interval after application, or interval prior to harvest
- for crop uses, crop growth stage key (for example, Zadok’s scale)
- efficacy assessment method (for example, European Weed Research Council rating scale, or number of individuals in the monitoring area counted per 30 seconds)
- sample size (such as 20 tillers per plot or 5 soil cores per plot)
- sample method (for example, random or fixed)
- harvest date for crop applications
- harvest method (for example, small plot combine)
- harvested commodity measurements (such as weight and moisture content)
- expression of yield (for example, tonne per hectare at 85 per cent dry matter)
- explanation of any abbreviations used.

For crop protection products, you should provide yield data for all treatments (including standards and controls) to demonstrate the effect of the product on yield. An acceptable argument or explanation should be provided if yield data are not included.

**Results**

**General**

All relevant data should be presented and reported. Providing results from a ‘typical sample’ is not acceptable. When only means, percentages or other presentations of results are given in the results section of a report, all ‘raw’ data should be provided in an appendix.

If negative or unusual results have been recorded, they must be included together with a discussion (below) about how or why they may have occurred. This information can help in determining optimal application conditions.
Information guidelines and standards

Statistical analysis

You should conduct a statistical analysis of the results whenever relevant or if you are required to demonstrate differences or equivalence between treatments.

Provide full details of the statistical methods used, including a justification or validation for the method chosen. Include information about how the underlying assumptions of the statistical method have been met in the justification for the method selection. Include any reasons for not carrying out a statistical analysis if you have not done one. The results of the statistical analysis (for example, degrees of freedom, F-values and p-values) should be presented in table format with each study. If there are many such analyses, they could be provided as an appendix. Novel statistical analysis submitted in support of experimental data should be accompanied by the raw data and the published literature that references the statistical technique.

Presentation

If a study produces many separate results (for example, from different treatments and assessment times), the data are best presented in a table or matrix format. This allows a quick and easy comparison of results.

If graphs or other methods of presentation are used, they should be appropriately labelled with measurement details, including the relevant units. The type of presentation of results should be similar to that expected in a peer-reviewed journal. Original or raw data should be included and may be submitted as an Appendix to the report.

Any abbreviations or indications of statistically significant results used in a table must be explained as notes to the table. Examples of useful table formats are shown below in Table 1 and Table 2:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Result prior to treatment (unit of measurement)</th>
<th>Result after treatment (unit of measurement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product A, rate 1</td>
<td>11a</td>
<td>5b</td>
</tr>
<tr>
<td>Product A, rate 2</td>
<td>13a</td>
<td>1a</td>
</tr>
<tr>
<td>Product B</td>
<td>12a</td>
<td>2a</td>
</tr>
<tr>
<td>Product C</td>
<td>13a</td>
<td>1a</td>
</tr>
<tr>
<td>No treatment control</td>
<td>12a</td>
<td>11c</td>
</tr>
</tbody>
</table>

Table 1: Example of a simple comparison of before and after treatments

Note: Results with different letters within a column denote a statistically significant difference.

Table 2: Example of a more complex comparison of multiple results per treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Measurement of two related results (for example, % control/g weight loss)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
</tr>
<tr>
<td>A1</td>
<td>%</td>
</tr>
<tr>
<td>A2</td>
<td>%</td>
</tr>
<tr>
<td>B</td>
<td>%</td>
</tr>
<tr>
<td>C</td>
<td>%</td>
</tr>
<tr>
<td>NI control</td>
<td>%</td>
</tr>
</tbody>
</table>

DAT = days after treatment.


The report should include text that highlights the important results or significant outliers, including any significant differences that are important to testing the study hypothesis (or lack of them). Ideally, this should be located close to the relevant table and include a reference to the table. Descriptions of results should be concise, and the discussion or interpretation of the results should be left to the discussions and conclusions section (see discussions and conclusions).

Discussion and conclusions

Each trial should be appropriately analysed, the results interpreted and a relevant conclusion about the purpose and hypotheses of the study stated. Conclusions must be clear, specific and, wherever possible, related to the proposed use of the product as instructed on the product label (for example: ‘The results of the trial support a label use rate of x g/100 L when applied via ground application equipment; another application may be required after 14 days if monitoring indicates pest numbers will exceed thresholds, etc.’). Do not present conclusions that are not relevant to the purpose of the study.

This section is where any unusual or unexpected results should also be discussed. If possible, explain how they occurred. It is not unusual for an efficacy dossier to include trial reports in which there is considerable variability in trial results. Issues such as unusually low or high pest abundance or other confounding factors (for example, weather effects or soil types) may need to be discussed to allow a proper interpretation of the results.

We might not consider variability of results negatively if the variability can be adequately explained. Variability of results may lead to label instructions that advise users of the possibility of variable results and how they may avoid them. This section could also discuss the integration of the proposed product with current pest management practices. Economic action thresholds for specific crops should be detailed to allow the assessor to evaluate the likelihood of repeated use.

This section could also discuss the integration of the proposed product with current pest management practices. Economic action thresholds for specific crops should be detailed to allow the assessor to evaluate the likelihood of repeated use.
Appendixes

Appendices can include raw data, detailed statistical analyses and any other details that are important in supporting the report but that are not needed in the body of the report.

Additional information and references

Full copies of any reports, studies or other supporting information referenced in the report should be provided if they are used to justify a claim. They should be logically ordered in terms of their purpose and listed in a table of contents for easy reference.

Veterinary—Efficacy standards for ruminant anthelmintics in Australia

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (also known as VICH) was officially launched in Paris in April 1996, as a cooperative effort between members of the regulatory authorities and the veterinary chemical industry from the European Union, the United States and Japan. The program aims to harmonise technical guidelines for veterinary product registration, and has drawn on the experience of the human pharmaceutical harmonisation initiative, ICH.

The regulatory authorities of Australia and New Zealand have observer status on the VICH Steering Committee.

To evaluate the efficacy of anthelmintics in ruminants (bovine, ovine and caprine), the APVMA has adopted guidelines developed by the VICH process, including:

- **VICH GL7 (Anthelmintics General): Efficacy of Anthelmintics: General Requirements**
- **VICH GL12 (Anthelmintics: BOVINES): Efficacy of Anthelmintics: Specific Recommendations for Bovines**
- **VICH GL13 (Anthelmintics: OVINES): Efficacy of Anthelmintics: Specific Recommendations for Ovines**
- **VICH GL14 (Anthelmintics: CAPRINES): Efficacy of Anthelmintics: Specific Recommendations for Caprines**

These guidelines are to be used in conjunction with the APVMA’s Part 8 Efficacy and Safety Guidelines, as well as the World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of anthelmintics in bovine, ovine and caprine ruminants.

Because of Australia’s unique environmental and geographical features, farm management practices, animal breeds and parasite burdens and their population dynamics, there are some differences between VICH/WAAVP recommendations and recommendations for products that are to be registered in Australia.

Therefore, the following additional guidance is provided for applicants proposing the registration of ruminant anthelmintics in Australia:

- Due to the prominence of *Haemonchus contortus* and its pathogenicity at low numbers, you should demonstrate persistent effectiveness at a level of greater than 99 per cent to support your proposed claims.
- Because of Australia’s history of parasite resistance selection, we recommend that most of the confirmatory field efficacy work be conducted within Australia under typical farm management practices covering relevant geographical regions.
- If you have efficacy data generated overseas, submit those data at the time of the product registration application.

We encourage you to use the efficacy standards shown in Table 1 when generating data for ruminant anthelmintics in Australia. These criteria are usually sufficient to give us confidence in the product’s efficacy in Australia’s unique conditions. For your reference, Table 1 is specifically related to:

- Section 5, Standards for effectiveness of VICH GL7; and
- Section 4.1, Criteria to grant a claim of VICH GL12, 13 and 14.

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Host species</th>
<th>Claim for treatment/control</th>
<th>Claim for persistent effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal helminths</td>
<td>Sheep/goats</td>
<td>&gt;95%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>and lungworm</td>
<td>Cattle</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Liver fluke</td>
<td>All</td>
<td>&gt;90%</td>
<td></td>
</tr>
</tbody>
</table>

Note on geometric versus arithmetic means

In relation to Section 4.2 Geometric versus arithmetic means of VICH GL7, the geometric mean is appropriate for statistical tests where data is non-normally distributed. However, the geometric mean may underestimate the biological significance of worms in the animals with the highest worm burdens. We consider that the current information on statistics does not support the adoption of geometric means as the sole means of interpreting trial data. If the arithmetic mean for the data provided in efficacy trials shows marked variance from the geometric mean, we may take the arithmetic mean into consideration (that is, we are likely to give more weight to the arithmetic mean when there is variability in the trial data).

The VICH guidelines can also be accessed from the VICH website.
efficacy and safety of teat sanitisers

This is a guideline about the sorts of information an applicant can submit to address the safety and efficacy criteria for teat sanitising products. It also provides guidance on how the information might be presented and analysed. For further information on the safety and efficacy criteria, refer to the Make an application guidelines.

The data provided to the APVMA should demonstrate that the product will be:

- safe for the animal
- effective in reducing the incidence of infectious and environmental mastitis in the herd.

These guidelines pertain to pre- and post-milking teat sanitisers (dips, sprays, udder washes and related entities). These guidelines are based on principles recognised by the scientific community as appropriate for collecting scientific data. They are by no means complete. They deal with the product-specific issues discussed below.

The key areas are irritancy to teat and udder skin and bactericidal efficacy of the teat sanitiser. These guidelines should be read in conjunction with Part 8: Efficacy and target animal safety. All trial protocols should be approved by an animal care and ethics committee before any animal experimentation.

These guidelines do not include public health (including milk residues) or environmental safety considerations.

Testing teat sanitisers for irritancy

The applicant should demonstrate that the proposed product is safe to the target animal under normal Australian climatic conditions. This does not necessarily mean that the product will improve the skin condition of teats or maintain them in good condition during periods of adverse weather. The pH of the final solution should be between 4 and 6. An applicant who wishes to make a label statement for inclusion of extra emollient during periods of adverse weather should provide efficacy data for use of the product with the extra emollient.

Safety of teat sanitisers under normal conditions

Selection of herds, teat, cows and quarters

The product should be tested for at least six weeks in at least two herds using a minimum of 10 normal multiparous (multiple pregnancy) cows and 10 normal primiparous (single pregnancy) cows in each herd. Tests should be carried out on lactating cows with mainly light-coloured teats. Half of each group should be at early lactation and half at late lactation. Cows with grossly deformed teats should not be included in the trial. A description of each test animal should be submitted, stating the animal’s number, breed, age, lactation stage and daily milk production. Cows should be under constant supervision during trial periods. Any adverse reaction and consequential treatments between these times must be recorded.

Experimental design

Teats should be examined for skin reaction one week before and one day before the beginning of the trial.

All four udder quarters should be treated at the same time according to the manufacturer’s instructions.

Examination of the teats should be done by a veterinarian or other competent investigator familiar with the anatomy and normal and abnormal appearance of cows’ teats. Examinations of the teats should be done before milking by the same person.

Teats should be examined for skin reactions every 48 hours during the treatment and post-treatment periods (days 8 through 42).

Evaluation of skin reactions

At each examination before milking, the condition of each teat should be recorded as follows:

The occurrence and severity of any of the following lesions should also be recorded:

- erythema (redness of skin)
  - skin visibly normal: 0
  - very slight erythema (barely noticeable): 1
  - well-defined erythema (clearly visible): 2
  - moderate to severe erythema: 3
  - severe erythema (beetroot redness): 4
- oedema formation
  - skin visibly normal: 0
  - very slight oedema (barely noticeable): 1
  - slight oedema (edges or area well defined by definite swelling): 2
  - moderate oedema (swelling raised approximately 1 mm): 3
  - severe oedema (swelling raised more than 1 mm and extending beyond the area of product exposure): 4.

The occurrence and severity of any of the following lesions should also be recorded:

- drying, roughening and/or scaling of the teat skin
- lesions on the teat barrel. A lesion is defined as a fissure or other abnormality (such as an ulceration or blister) in which there is a break in the epidermis
- lesions of the teat end. These include ulceration or eversion of the teat orifice as well as skin lesions occurring within 1 cm of the teat orifice
- any degree of skin tenderness on touch.

Evaluation of milk quality
I

of

or 'Direct microscopic somatic cell count in milk' reported in the Journal of Milk and Food Technology, vol. 31, no. 11, November 1968, and 'Design of eyepiece reticules for use in the direct microscopic somatic cell count method' reported in the same volume (Appendix 3), are appropriate for estimating individual cow cell count. Electronic cell counting may also be used. Somatic cell counts should be consistently determined in aliquot samples taken from the total milk production of each quarter. The method of collection of the sample should be stated. A bucket milker or similar device is recommended. Milk samples should be collected for quality evaluation every 48 hours during the treatment and post-treatment periods (days 8 through 42). Animal data sheets should include a copy of the laboratory report with the technician's signature and the dates of the analyses.

**Trial treatment periods**

The pre-treatment period is the week (days 1–7) before the product is administered. Baseline observations are made to confirm that all test animals are normal. During this period, two milk samples, 24 hours apart, should be taken for culture and cell count from all four quarters. This procedure will help to distinguish udder irritation due to a pathogenic organism from irritation caused by the product.

The treatment period begins at the second week (day 8) and lasts for four weeks (day 35).

The post-treatment period begins at the eighth week (day 36) and lasts for one week (day 42).

**Trial treatment periods**

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The treatment period begins at the second week (day 8) and lasts for four weeks (day 35).

The post-treatment period begins at the eighth week (day 36) and lasts for one week (day 42).

**Data collection**

Information to be documented for the pre-treatment, treatment and post-treatment periods should include teat condition, milk cell count, animal identification, farm site, trial number, date, test day and hour (am/pm), milk production, body temperature (where appropriate) and any other obvious clinical condition. Whenever possible, the documentation should include photographs of a representative selection of both groups at the start of, during and at the end of the trial.

Any transient deterioration in teat condition during the immediate assessment period should be noted for use in subsequent technical information. Any observed adverse reaction resulting from application of the product in the clinical studies should be reported. The submitted data should be statistically analysed.

**Safety of teat sanitisers under adverse conditions**

If no irritancy has been recorded for the product under normal conditions and the label refers to specific instructions for use under adverse weather conditions, a repeat of the trial should be carried out under such adverse weather conditions.

**Determining the efficacy of a teat sanitiser in reducing the incidence of naturally occurring new intramammary infections**

Guidance on what data should be submitted will vary depending on the method of product application. For new actives, applicants should submit the results of properly designed and conducted laboratory and field-scale scientific studies. In vitro studies are generally not suitable as the sole basis for claims of efficacy.

**Antiseptic determination**

The proposed product formulation (final solution) should qualify as an antiseptic by in vitro testing. One or more of the following tests are recommended:

- the phenol coefficient method for phenolic compounds
- the use-dilution method for disinfectants miscible with water to determine the maximum dilution that kills test organisms
- available chlorine germicidal equivalent concentration method for water-miscible chlorine disinfectants.

These three methods are complete end-point methods that require, within the experimental error, 100 per cent kill of the test organism. Each of these methods is fully described in the Official methods of analysis of the Association of Official Analytical Chemists, 15th edn, 1995.

The common mastitis-causing pathogens are Staphylococcus aureus, Streptococcus agalactiae, Streptococcus uberis, Streptococcus dysgalactiae and Pseudomonas aeruginosa.

**Clinical studies (field trials)**

**General guidance**

The efficacy of the product should be investigated in the target species.

Product formulation and use patterns used in the clinical studies should be identical to those being proposed for registration. An applicant who wishes to make a label statement for inclusion of extra emollient should provide data for use of the product with the extra emollient.

Trials should be repeated if a new method of product application is recommended—for example, teat dip, teat spray or automatic spray systems.
Trials should be repeated if variable levels or types of teat emollients are recommended, as levels of active constituents ingredients may be modified by such changes.

If the product is diluted with water, the quality (pH, hardness and alkalinity) of water used in the trial should be determined and clearly stated on the product label. Extra experiments should be considered if a range of parameters of water quality are to be recommended.

Efficacy data should be collected for each pathogen for which a claim is made. The crucial parameter for the effectiveness of the product is the results of bacteriological cultures.

‘For the reduction in the herd incidence of infectious mastitis caused by …’ is generally an acceptable label claim.

Any concurrent antibiotic or non-antibiotic therapy administered to a study animal should be fully described.

The following baseline data are recommended for each herd: herd size, number of animals currently lactating, percentage of lactating animals affected by mastitis, age structure of the herd, stage of lactation, and mastitis vaccination history.

**Experimental design**

A split herd design is recommended. Under this design, all teats of half of the cows are treated before or after milking (depending upon the label claim), with the final teat sanitiser formulation according to label instructions. The remaining cows serve as untreated controls.

The number of new intramammary infections that occur in all quarters of all cows, both treated and control (untreated), should be determined. The experimental unit is the individual teat and its associated quarter.

**Selection of experimental herds, cows and quarters**

Data should be collected in a minimum of six herds in at least two geographic locations, with at least two independent investigators supervising the trial.

Trials should be conducted in herds in which 10–20 per cent of the animals are expected to be infected in at least one quarter with the target organisms.

Only quarters that are free of infection with major mastitis pathogens should be included.

Cows with teats that are damaged before and during the study should be excluded.

Cows diagnosed as infected during the trial and subject to appropriate treatment should be removed from the trial. However, their records should be included in the results.

**Duration**

The length of an efficacy study will depend on the number of uninfected quarters available initially, on the rate of new infection in the control group, and on the percentage reduction in infections in the treated group. However, trial duration should be a minimum of one year.

**Culturing**

A pre-study culture/somatic cell count survey should be undertaken. It should include milk samples from all lactating quarters on all cows in the herd in order to establish the baseline incidence of clinical and subclinical mastitis in the herd. The survey should take place within the two-week period before initiation of the treatment.

Single quarter milk samples should be cultured monthly during the entire trial.

All quarters for the common infectious mastitis pathogens should be cultured.

Appropriate bacteriologic culture methods of isolation are described in the most recent version of Microbiological procedures for the diagnosis of bovine mastitis, National Mastitis Council.

Milk should be grossly examined at each time of sampling for signs of clinical mastitis and the type of clinical mastitis encountered should be recorded.

**Criteria for diagnosing infections**

A new intramammary infection is diagnosed in a previously uninfected quarter when:

- the same bacterial species is isolated from two consecutive samples taken during the trial, or
- a single bacterial species is isolated from a single sample from a quarter with clinical mastitis.

Clinical infections should be accompanied by the cardinal signs of inflammation, a high somatic cell count and an attempted milk culture.

A bacteriologically negative clinical case occurs when consecutive samples do not agree.

**Presentation of data**

The following information should be included in the final trial report:

- duration of the trial
- numbers of quarters in the study pre-treatment and each subsequent sampling
- the number of infected and non-infected quarters in the initial survey
- the number of new or recurrent infections detected monthly or bimonthly with somatic cell counts in the control and treated group
- the percentage differences in new infections from each pathogen species and the type of mastitis that occurred in the treated and control groups
Several farmed fish species are kept in areas where the water temperatures can vary considerably during the year. Laboratory studies should use "degree-days" should be used wherever relevant.

Quality points for consideration are homogeneity and segregation of these products. To account for fish being poikilothermic animals, the term feed to high temperatures and pressures, which can cause the degradation of active constituents, excipients or other feed constituents. Other conditioning and pelleting are the main factors affecting stability during the manufacture of medicated feedstuffs. Those processes can subject the feed to high temperatures and pressures, which can cause the degradation of active constituents, excipients or other feed constituents. Other quality points for consideration are homogeneity and segregation of these products. To account for fish being poikilothermic animals, the term ‘degree-days’ should be used wherever relevant.

Several farmed fish species are kept in areas where the water temperatures can vary considerably during the year. Laboratory studies should use "degree-days" should be used wherever relevant.

**General considerations**

We encourage you to standardise study protocols and study reports as far as possible to facilitate the comparison of study results and the possible extrapolation between different species of fish.

If the product is intended for in-feed administration, you should consider and, if appropriate, investigate the possible impact of the feed composition. The feed composition and manufacturing process may influence the medicinal product because of physico-chemical compatibility. Fish have very marked senses of taste and smell. To ensure that they will accept the final product, we recommend that the palatability of the active substance and, if relevant, the excipients be investigated prior to clinical trials.

Conditioning and pelleting are the main factors affecting stability during the manufacture of medicated feedstuffs. Those processes can subject the feed to high temperatures and pressures, which can cause the degradation of active constituents, excipients or other feed constituents. Other quality points for consideration are homogeneity and segregation of these products. To account for fish being poikilothermic animals, the term ‘degree-days’ should be used wherever relevant.

Several farmed fish species are kept in areas where the water temperatures can vary considerably during the year. Laboratory studies should...
**Information guidelines and standards**

Therefore, be carried out to cover the relevant temperature range. The optimal temperature for the disease should also be taken into consideration when planning the studies. Normally, studies should be carried out at two water temperatures. You should justify your choice of water temperature(s) in relation to the fish species, product and indication. If you do not carry out studies at two different temperatures, you should justify that choice.

More limited investigations may be acceptable for a compound previously authorised for use in another relevant species. This is elaborated under the appropriate topic (see 'Safety in the target species' and 'Clinical studies').

When justified, data from non-aquatic species can be used as supportive information.

The origin and genetics of the experimental fish are important to obtain valid and reproducible results, and any variation should be addressed. All finfish species should be identified by their colloquial name, followed in parentheses by the Latin or Linnean description.

**Study reports**

All experimental techniques should be described in such detail as to allow them to be reproduced. You should also establish their validity and describe in detail each experimental trial or field trial and the conditions under which it was performed. You should provide separate reports on all trials, whether the results are favourable or not. Adequate summaries of groups of trials based on the same protocols may be provided.

Refer to Brattelid and Smith (2000) for detailed guidance on the contents of the study report.

You should report adverse events in sufficient detail to enable a proper assessment of safety in the target animal. You should explain non-specific mortalities and comment on any physical or behavioural abnormalities.

For clinical studies, you should clearly state the onset and the duration of relevant disease outbreaks. This information will allow the evaluation of coincidental mortality data and its potential threat to the statistical power of the study. You should explain how the data continues to be valid and fit for purpose.

**General study design**

As water quality has been identified as an important element for maintaining healthy fish and ensuring valid experimental results, water quality parameters such as temperature and salinity should be addressed in detail.

You should state the efficacy of the veterinary chemical product as a function of dose, frequency and duration of treatment. The criteria used for the evaluation of efficacy in the trials should be pre-determined. In confirmatory clinical trials, you should usually identify one primary efficacy endpoint and you may report one or more secondary endpoints. The primary endpoints should accurately reflect the intended benefit of the product. You should present the results in a way that is suited for adequate statistical evaluation. The clinical trials should cover all claimed indications, and each indication should be discussed and reported separately. You should perform statistical analysis of the results whenever relevant.

You should justify the observation unit (such as individual fish or cage) and the number of samples collected on each sampling occasion. The sample sizes should be sufficiently large, statistically justified and based on clinically relevant endpoints.

In studies of products intended for use against aquatic one-host parasites (such as sea lice on salmon), we recommend sampling a limited number of fish from many cages instead of many fish from a small number of cages in order to take into account clustering, which occurs naturally with such parasites.

**Preclinical studies**

The objective of preclinical studies is to characterise the active component or formulation, either to collect information of relevance when designing clinical trials or to document that clinical data obtained previously could be used for a new formulation, a new route of administration or administration in new temperature or salinity conditions.

When deciding which preclinical studies are relevant for efficacy and safety, you should take into account the mode of action (if known) and route of administration. For example, for waterborne products acting directly on ectoparasites, neither pharmacodynamic nor pharmacokinetic parameters in the target species are relevant from an efficacy point of view. However, it is important to know the mode of action and the effective concentration for the parasite.

On the other hand, for ectoparasiticide administered orally, pharmacokinetic parameters of the target species are relevant, as the active substance needs to reach the site where it is presented to the parasites (for example, blood, tissue fluids or mucus layer) in sufficient amounts.

Great care should be taken to ensure that the fish receive the intended dose. For single-dose studies of orally administered products, we recommended that you administer the test substance orally by gavage. For repeated dose studies of pre-mixes intended for medicated pellets, examples of applicable control methods are as follows:

- Small number of test fish: Count the pellets before they are given to the fish. After dosing, count the uneaten pellets and then calculate the average dose received.
- Large number of test fish: Small X-ray-dense glass beads (ballotini) can be incorporated when manufacturing medicated feed pellets for the trial, at a known concentration of beads per pellet (this can be determined by X-raying the pellets). When the number of beads per pellet is known, a representative number of fish can be X-rayed to reveal the average number of pellets ingested by the fish. It is also possible, by using small and large pellets alternate days, to reveal how many pellets were ingested on two different days in a row.

**Pharmacodynamics**

You should describe the pharmacodynamic (PD) effects, including the mode of action of the active ingredient(s), as the basis for the recommended use of the product. In some cases, this information will be available in the safety part of the dossier.

You should present all available relevant data (such as published references), including data from other animal species, where appropriate.

For antimicrobials, microbiological studies in vitro should be carried out according to the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances. State the study parameters in detail. Notably, temperature and possibly salinity in the medium may affect minimum inhibitory concentration (MIC) values and should be stated. In vivo studies to investigate the mode of action are generally not recommended.
Information guidelines and standards

For antiparasiticides, the mode of action could be investigated in vitro according to standard protocols. For in vivo studies, the principles of VICH GL7 (Efficacy requirements for anthelmintics: General requirements) apply.

Because fish are poikilothermic and significant temperature-related effects can be expected, you should justify your choice of the temperatures at which in vivo studies are conducted. In addition, in the case of topically administered products, other water quality parameters such as water salinity, pH and hardness should be taken into account.

Note that southern bluefin tuna can maintain selected tissues at temperatures above the environmental temperature and are considered to be heterotherms (Crockett and Londraville 2006).

Pharmacokinetics

We recommend that pharmacokinetic studies in finfish be carried out in accordance with the principles in the CVMP guideline for the conduct of pharmacokinetic studies in target animal species, as far as they may be applied to finfish. That guideline describes all relevant steps for pharmacokinetic studies, regardless of species. The main difference in fish is that repeated samples from the same fish may not be possible. Thus, samples from different fish at different time-points may be necessary. When modelling the results, all fish sampled are regarded as one ‘mega-fish’. Statistical methods are available to determine confidence intervals for pharmacokinetic parameters, such as bootstrapping (see, for example, Nordgreen et al. 2009).

You should submit pharmacokinetic studies where there is a need to document the residue depletion profile. However, we also strongly recommend that you consider pharmacokinetics as a tool to help reduce the total amount of clinical data—and hence the number of test fish needed.

In experimental studies in which systemic pharmacodynamics or tolerance is documented, pharmacokinetic data recorded in the study will increase the total amount of information, as effects could then be linked to exposure rather than to dose only. Also, in studies in which the individual dose is not known (as in the case of group oral medication), this will allow the estimation of an exposure–effect relationship at the individual level.

Pharmacokinetic data can also be used for bridging purposes. For instance, if clinical data are recorded in a study in which a certain formulation is used, those data could also be relevant to support the therapeutic performance of another formulation, provided there are comparative pharmacokinetic data to show that the two formulations are similar in terms of exposure.

Comparative pharmacokinetic studies could also be considered to bridge data between different environments, such as different salinity or different temperatures (the high and low ends of natural variation).

Performance of tests

You should perform pharmacokinetic studies under relevant conditions (such as salinity and temperature) because kinetic parameters, such as bioavailability, may be significantly affected by such factors.

The choice of study design will depend on the objectives of the study. Because it is difficult to collect a comprehensive set of data from an individual fish, analysis on a group level is normally used. Standard pharmacokinetic parameters could be calculated based on data from groups of animals sacrificed at different time points.

When using studies of distribution to support efficacy (for example, for substances that require distribution to skin or mucus for effect), studies should be planned with the combined use in mind. You could use either standard chemical analyses or methods using radiolabelled substances (such as whole body autoradiography and scintillation counting).

Sampling fish out of a small group may cause stress and produce effects such as decreased food uptake among the remaining fish, which may affect the outcome of the study, so you should take measures to reduce the animals’ stress. We recommended that the group be large enough to avoid stressing the remaining fish during all sampling procedures throughout the study. You should justify the group size chosen for each study.

Resistance

You should discuss the mechanism for resistance and the frequency of resistance and include information on possible transmission. Possible cross-resistance to other active substances used in farmed fish should be stated.

For ectoparasiticides, experience of the development of antiparasitic resistance should be included, if relevant. Experience related to the development of resistance from other areas of use (for example, as pesticides) should also be included when available.

Safety in the target species

You should determine target animal safety in all of the target species, as you have defined them, unless you can justify not doing so. Studies performed in one species of fish may be considered relevant for the evaluation of safety in a second species of fish of the same genus or taxonomic family, provided that they are kept under the same environmental conditions. In such a case, there should be supportive safety data from clinical trials in the second species. For example, it may be considered unnecessary to carry out formal target animal safety studies in trout if such studies have been carried out on other species of salmonid, and if supportive safety data from clinical studies in trout are available.

Excipients normally used in pharmaceutical products for terrestrial animals might not be well tolerated by aquatic species. You should determine the safety of excipients and justify any lack of appropriate data.

It is important to take into account possible adverse effects on development (malformations) if the medication is applied to young fish (embryos, larvae and juveniles) and the product can easily interfere with growth. Indicate the range of sizes and weights of fish recruited for the trial, as the same treatment might not have the same effect in fish of different sizes.

Studies of repeated dose tolerance are relevant only for products intended for repeated dose administration.

Test product

This and the following points apply to all target animal safety studies.

We recommend that you use the final formulation of the medicinal product. If the formulation used in studies differs from the final commercial formulation, you should demonstrate that the bioavailability of the formulations is the same. Substances administered by gavage should have a
suitable formulation (for example, solution, suspension, capsule or in feed). All formulations used in the tests should be assayed for the concentrations of the active substances before the start of the trials.

**Negative control groups**

Studies with in-feed medication should be carried out with the medicated group (preferably using the final formulation of the test product) and an untreated (feed-alone) group.

In all tests, the test product and placebo should be administered in the same manner as intended for the finished product. Handle untreated controls identically to treated fish.

For studies other than in-feed medication, the control substance should be either saline or vehicle (the finished product deprived of the active substance). You should justify your choice of control substance, taking into account that the excipients may have some effects of their own.

**Holding**

The fish to be tested should be in a normal physiological condition and be feeding well during two weeks of acclimatisation. You should allocate fish into groups randomly the day before the administration of the test product, using an appropriate method. To reduce stress caused by handling the fish, and for practical reasons, it could be acceptable to allocate and/or mark fish groups immediately before or during the administration of the test product, if justified. At sea, it may be difficult to allocate fish into cages. In this situation, allocation may be earlier than is mentioned above.

Acclimatisation is not applicable for embryonal stages.

The following conditions of exposure are recommended.

**Stocking density**

**Semistatic test**

- Waterborne administration: a maximum of 1 gram of fish per litre of water
- Oral administration: a maximum of 5 grams of fish per litre of water
- Parenteral administration: a maximum of 5 grams of fish per litre of water

These stocking densities are low and are suitable for tank-based operations. They may be adjusted for field studies.

**Flowthrough**

Higher loading is acceptable – that is, higher stocking density than quoted above may be used.

**Group size and number**

You should justify the numbers of fish per group, which should not be less than 10 with a minimum of 2 tanks per dose and 2 control tanks. If you choose to depart from this recommendation, you should consider applying to us for technical advice before beginning the trial. Trials with southern bluefin tuna should be conducted in a field situation, as it may not be feasible to hold this species in tanks.

**Fish size**

We recommend that you use fish of the most sensitive category (size or age and physiological status) for which the product is intended.

**Necropsy histopathology examinations and blood analyses**

As a minimum, tissues from all fish in the highest dose group and control group should be examined macroscopically and microscopically. Where the toxicity of the test product is expected to be relatively high, you should consider different necropsy schemes to include gross and microscopic examinations for all fish or for randomly preselected fish. If lesions are found in any tissue from the highest dose group, you should examine samples from fish in the second highest dose group macroscopically and microscopically, until a no-observed-adverse-effect level is determined. In addition, tissues from all fish showing systemic clinical signs should be examined macroscopically and microscopically.

Haematology and blood chemistry should be performed in laboratory studies on target animal safety. If blood chemistry and haematology parameters are unremarkable in the highest dose group, you may choose not to test in the lower dose groups.

You should justify the parameters you have chosen for testing. For substances already approved for other animal species, the decision on whether blood chemistry and haematology are performed should be based on the previous findings in those other species. You should include in the documentation a discussion or justification of the decision on whether blood chemistry was done, and, if so, of which parameters were chosen for testing.

**Dose justification and duration of dosage**

You should justify your choice of dose levels and the duration of exposure.

The chosen levels should be adequate to demonstrate a sufficient margin of safety for the product when it is used under field conditions. This means that the dosage levels should be high enough to account for the fact that varying degrees of unintended overdosing will commonly occur in practice with such types of medicinal products intended for waterborne or in-feed treatment.

For single-dose studies, at least three dose levels should be tested. The selection of dose levels should be based on the proposed therapeutic dosing regimen.

For repeated-dose studies, the selection of dose level(s) and the duration of the treatment period should be based on the proposed therapeutic dosing regimen and on results from single-dose studies.

**Oral administration**
You should provide detailed records of feed uptake and concomitant daily dose.

For solutions and suspensions given by gavage, adjust the concentration of the active ingredient so that, if possible, no more than 0.5 gram or millilitre test product per 100 grams of fish is used to achieve the required dose. These maximum dosage recommendations are based on the practical dosage limitations in fish.

**Waterborne administration**

Dipping and bathing are considered to be methods of waterborne administration.

Waterborne treatment should usually have a very broad margin of safety due to the difficulty of accurate dosing and estimating water volume in raceways or sea cages.

The duration of treatment should be equal to, or longer than, the proposed length of treatment. The dosage of a veterinary medicinal product (as in mammals) is principally a function of treatment concentration and exposure period. For sedatives and anaesthetics for use in finfish, the length of exposure is the main parameter available for adjustment during treatment.

**Parenteral administration**

Both the test and the control product should be administered by injection. The same volume of test solution should preferably be administered to the fish in both the test and the control groups. You should also provide the maximum volume of the product administered in one injection site and an assessment of the reaction in the injection site.

In some cases, investigating fewer than three dose levels could be justified because there are practical limitations to the volume that can be injected into fish. In addition, the test solution may have limited solubility, which restricts the maximum concentration in a restricted volume. This can make it difficult to obtain more than two dose levels with a significant difference.

**Clinical studies**

The main purpose of the documentation of efficacy is to prove the therapeutic value of a new veterinary medicinal product for farmed finfish and to define an optimal dose and dosage regimen.

Clinical trials should be conducted for each proposed indication and for all target species in which efficacy is claimed. For some products, such as waterborne treatments that act directly on ectoparasites and that are independent of the pharmacokinetics in the fish, you may choose not to submit clinical trials in a second species if the clinical data obtained for the main fish species can be shown to be relevant to the second species. In such cases, you should provide sufficient justification for the omission of clinical studies, together with documentation of target animal tolerance.

All studies should be performed under appropriate conditions according to the proposed method of use of the product. For example, the study should be carried out in water temperature(s) in which the test product is likely to be used, considering the different climatic conditions within Australia. The studies should be blinded, unless otherwise justified.

Normally, you should submit data from both laboratory and full-scale field trials. Where appropriate, you should justify the lack of relevant data.

The omission of field studies and the submission of challenge studies only may be accepted if you can adequately justify it. For example, in the case of a second species closely related to a first species for which the efficacy of the product is fully documented, challenge studies may be sufficient to document efficacy in the second species.

In all studies, the final formulation or an essentially similar formulation should be used and administered by the proposed route. If a similar formulation is used, bioequivalence should be confirmed.

The clinical trials should include control groups, and you should justify the choice of control group (positive or negative). If a positive control is used, you should explain how the study design has sufficient sensitivity to detect effects above placebo level. You should consider and discuss all variables likely to confound results and the methods used to reduce or avoid them.

You should remove fish from the trial when they show definitive signs of disease and/or when there has been pathological confirmation of disease in the holding unit, rather than wait for death to occur. Only where the removal of fish showing clinical signs would significantly diminish the value of the data should animals showing such signs be left in the enclosures. In all circumstances, humane endpoints should be applied.

You should monitor and record the nature and frequency of adverse drug reactions.

For oral medication, you should record the daily uptake of medicated feed together with the daily dose of the active substance, if possible. Premixes should be administered as medicated feed prepared by the procedure recommended by the manufacturer, preferably using a standardised feed.

**Laboratory studies**

The test conditions can be controlled and standardised in land- or sea-based test facilities. Experimental trials should be performed for the main target species.

The fish to be included in the trials should be of similar age and size, be susceptible to the disease in question and be of known origin and health status. The allocation of fish into groups should be done randomly using an appropriate method.

Every study should be designed to allow for appropriate statistical evaluation. You should present a sample size analysis. Significant differences might be found between different groups of fish kept under identical conditions owing to the fact that they are kept in separate tanks. Therefore, you should always use at least two groups kept under identical conditions but in separate tanks.

You should justify the choice of parameters recorded for evaluation and the statistical evaluation methods.

If negative controls are used, studies with in-feed medication should be carried out with the medicated group (using the test product) and an untreated (feed-alone) group. For products intended for other routes of administration, one negative control group is usually sufficient.
You should discuss challenge models (cohabitant, waterborne, injection) and their relevance to natural conditions (time of challenge, time of treatment, infection pressure, etc.).

The test animals should not previously have been exposed to the challenge organism, as such exposure has the potential to alter study results. You should provide specific justification if you use such animals.

The challenge organism should be of a strain relevant for the current disease situation. It should be isolated and characterised by the most appropriate method (preferably a standard method used by the national reference laboratory), which should be described in detail. The timing and performance of the challenge and the design of the study should be justified. You should report the results of the introduction of the challenge organism based on parasite counting, microbiological analyses or other pertinent investigations. If appropriate, a statistical analysis should be provided.

### Dose determination trials

Dose determination studies are normally laboratory trials with or without challenge. Their purpose is to determine the optimal dose, dosage interval and total period of treatment for the claimed indications. By integrating pharmacokinetic (PK) and pharmacodynamic (PD) data as a basis for the pre-selection of a treatment dose, the need for more extensive studies, such as traditional dose determination studies, might be reduced. The estimated dose should be confirmed by dose confirmation studies.

You should establish a dose–response relationship for therapeutic effect and, if possible, for adverse effects. Dose determination trials may be performed as field trials. Data from well-controlled experimental studies are preferred where relevant models are available, and field studies could then be used to confirm the findings from the controlled trials. The final dosage recommendations should be supported by documentation showing that satisfactory efficacy is obtained within the relevant temperature range.

Tests should be carried out in seawater and freshwater, if relevant to the proposed use, unless it is documented that the pharmacokinetics of the active substance are not affected by salinity.

If there are validated endpoints or models available, dose determination could be performed only as PK/PD modelling. In such cases, it is important that a sufficiently large exposure range is investigated, which implies that more than one dose level should normally be investigated.

For antimicrobials, MIC data could be used together with pharmacokinetic parameters to estimate the appropriate level of exposure. Such data could be used for dose determination, provided the PK/PD surrogate marker used is adequately validated. Note that these parameters differ between antimicrobials and bacteria, so you should justify the choice of parameter in each case. The pharmacokinetic endpoints should be derived from plasma, and the free (non-protein bound) fraction of active substance concentration should be used for calculations.

### Dose confirmation trials

Separate dose confirmation trials can be replaced by field trials performed with the final formulation of the product administered in the recommended dosage regimen.

### Field trials

The aim of field trials is to ensure that the product is efficacious and safe in the diversified conditions found in Australian aquaculture. The field studies should preferably be performed in accordance with good clinical practice.

If the trials use positive controls, a product that the APVMA has approved should preferably be used in the control group(s).

For products intended against diseases representing a potential threat to animal welfare, negative controls should only be used if no product is authorised for the claimed indication. The control group can be treated once an adequate estimation of difference in effect can be established.

### Selection of farms

You should justify the number and suitability of the sites selected for field trials. The sites should be geographically well distributed to maximise the possibility of diversified environmental conditions, disease situations and management practices. Each site should have several pens or tanks with fish of the relevant size or age and physiological condition (smoltification, sexual maturation, etc.) for the proposed use of the product. At least two pens or tanks of fish, and preferably 12–14 (that is, several pairs), should be used in the trial. The farmer should be experienced in keeping detailed records on all important factors concerning the farm and its fish. Records of the source of fish and the disease history in different pens or tanks should be kept. Previous medication and the use of chemicals and vaccines should be known. Daily records of outbreaks of disease, mortality and medication are required, as well as known and stable management practices concerning, for example, hygiene, feeding, handling and the use of feed additives or biocides. Daily records of water temperature should be kept.

### Selection of groups

All fish in one tank or pen are considered as one group. You should use a minimum of two groups in each trial, one of which should be a control group, which in most cases will be a positive control group. The groups should be allocated randomly, using an appropriate method. The prevalence of disease, daily mortality, clinical symptoms and other relevant parameters should be comparable in the treated and control groups at the start of the study.

### Trial procedure

Field trials in commercial fish farms should preferably be performed in spontaneous outbreaks of the diseases for which efficacy is claimed. Trials should thus be conducted at the time of year and under conditions in which a successful natural challenge can be defined by the investigator. Your report should include the method of identification of the causal agent. Information from trials performed with unsuccessful natural challenges may be provided, along with an explanation of the failures. All trials should be performed with adequate controls. Field trials with anaesthetics or other non-therapeutics should be performed with healthy fish. All trials should be planned so that suitable data are available for statistical analysis. You should choose clinical endpoints relevant for the proposed indication and specify primary and secondary endpoints.
Diagnostic criteria

You should confirm the presence of the investigated diseases in all groups included in the trial, and report the criteria for establishing an accurate diagnosis. Standard diagnostic methods should preferably be used. The same criteria are to be used in all trials and should include post mortem examination of a sufficient number of fish (at least six fish from each group). You should report the precise disease condition and the identification of any pathogenic organism.

Diseases caused by microorganisms should be diagnosed by isolating and characterising the pathogen by the most appropriate microbiological method (preferably a standard method), which should be described in detail. Samples from at least six fish per group are recommended.

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The following content can be found at http://new.apvma.gov.au/node/427
If making a submission, please reference page number: 427

Veterinary—Guideline for the evaluation of the efficacy and safety of coccidiostats

Introduction

This is a guideline about the sorts of information an applicant may choose to submit to address the safety and efficacy criteria for coccidiostat products. It also provides guidance about how the information might be presented and analysed. For further information on the safety and efficacy criteria, refer to the Make an application guideline.

The emphasis in this guideline is on simplicity. For a fuller treatment, refer to:

- reports from a coccidiosis symposium in ‘Methodology for the development, selection and testing of anti-coccidial drugs for use in controlling coccidiosis’,(1970) Experimental Parasitology, vol. 23, no. 1

Efficacy and safety studies cover three types of testing: battery, floor pen and field trials. All should be under the supervision of a qualified investigator, and battery and floor pen studies, particularly, should be designed so that the degree of efficacy can be shown to be repeatable.
Battery trials

A battery trial is usually carried out in the laboratory under controlled conditions, using susceptible chickens that are uniform for breed and sex and, when infected, are 2–2.5 weeks old. Treatments should be replicated.

You should develop data for each coccidial species for which a claim is made and also for mixed infections of those species.

It is desirable that the test coccidiostats be mixed by the testing laboratory into the basal ration, avoiding cross contamination with other coccidiostats.

This short-term trial usually runs for 8 days after infection. The infective dose of sporulated oocysts is usually administered 2 days after medication with the coccidiostat has commenced. Individual administration of oocysts directly into the crop of each chicken is recommended.

The test information you provide should contain significant responses relating to such factors as mortality, weight gain, lesion scores (0 to ++++) of chickens that die during the test and of those that are sacrificed at the completion of the test.

Artificial infections of *Eimeria tenella* and *E. necatrix* should aim to produce 25 per cent mortality in the controls, with smaller percentages for the less virulent species.

Anticoccidial indices may be used for expressing the efficacy of coccidiostats.

Floor pen trials

Floor pen trials should be designed to confirm the efficacy of the coccidiostat using unmedicated controls against coccidiostat-medicated test groups under natural or artificial coccidial exposure.

A suitable facility for such a trial would be an open-type shed with deep litter over a well-drained concrete floor, containing 8–12 pens on each side of a central passageway, each with a minimum capacity of 100 broiler type chickens. This will allow the testing of three potential coccidiostats and a control, and with 4–6 replicates, suitably randomised for each treatment. A treatment with a reference coccidiostat may be included, if desired.

Coccidial exposure, normally with mixed infections, should be sufficient to produce a clinical effect, but preferably with at least 10–15 per cent mortality in the unmedicated controls.

Artificial exposure is usually induced when chickens are 2.5–3 weeks old. A floor pen trial runs for about 8 weeks.

Efficacy can be evaluated by criteria such as:

- mortality, autopsy and lesion scores on dead chickens
- lesion scores on 3–5 randomly selected chickens from each pen at, say, 5–6 weeks of age
- weight gain and feed conversion ratios.

Field trials

Field trials should be conducted in two or three different climatic areas to demonstrate the utility of the anticoccidial agent under commercial conditions.

Commercial facilities normally available for such trials are not ideal for the accurate assessment of coccidiostats because there are marked variations in environmental conditions from farm to farm and from shed to shed. Field trials involve many sources of error, and one should recognise their limitations, but they are highly desirable to show that the coccidiostat can be efficiently mixed in commercial feed.

You should make every effort to secure uniformity of management and facilities, including housing, ventilation, brooding, and the type and distribution of waterers and feeders. As far as possible, the chickens should be uniform in strain, batch and sex. Most sheds take 5000 to 10 000 birds.

You should keep samples from every commercial feed delivery for check analyses of levels of coccidiostat to ensure that the feed has been mixed accurately.

The trial should be closely supervised and you should keep accurate records.

The following housing arrangements (listed in order of preference) can be used:

- two or three sheds of identical size, divided into three or more equal pens
- four equal sheds for cross-wise comparison of two coccidiostats
- two equal sheds, with one coccidiostat in each
- an equally divided shed to test two coccidiostats, with provision for some controls on non-medicated feed to be placed in each half in a secure enclosure.

Most field trials depend on natural exposure, and the replication of treatments and trials is highly desirable.

The following are the usual criteria for evaluation:

- mortality and autopsy findings
- lesion scores at 5–6 weeks on five randomly selected chickens from each group
- average weight at slaughter, feed conversion ratios, and the economic performance of each group.

Compatibility

Some evidence of the compatibility of the coccidiostat with various other feed additives is desirable. Overseas data may be considered.
Veterinary—Guidelines for registration of intramammary preparations for treatment of bovine mastitis

Part I: Introduction

This is a guideline about the sorts of information an applicant can submit to address the safety and efficacy criteria for intramammary preparations for the treatment of bovine mastitis. It also provides guidance on how the information might be presented and analysed. For further information on the safety and efficacy criteria, refer to the Make an application guidelines.

General comments

The following protocols are designed to serve as a guide for commercial organisations aiming to produce field trial data to support registration of intramammary products for the treatment of bovine mastitis.

The company applying for product registration should consider contracting the study investigation to an institution that can service the contract under the direct supervision of a consulting veterinary surgeon. The consulting veterinarian should have experience in mastitis research, investigation and, if possible, product testing, and should be responsible for the quality control of the treatment and milk collection procedures during the product evaluation.

Alternatively, a private veterinarian could accept the contract and then subcontract the microbiology and clinical pathology to a government, university or suitably accredited private pathology laboratory. Regardless of the arrangement for conducting the trial, the trial should be approved by an appropriate animal care and ethics committee.

The relevant local government adviser (veterinary officer, dairy adviser or animal health officer) and private veterinarian should be consulted during the design of the evaluation process and during selection of farmers and herds for the study. Farmer and herd selection should take into account the following factors:

- farmer’s cooperation (farmers should be fully informed about the experimental design and the procedures involved in the trial before they consent to cooperate)
- previous experience of the farmer in sterile milk collection
- herd size
- type of milking shed
- involvement in herd teating, bulk milk cell counting, individual cow cell counting (ICCC) for monitoring subclinical mastitis levels and antibiotic sensitivity patterns of isolates of *Staphylococcus aureus* from the herd
- availability of good records of cases of clinical mastitis and treatment (and response)
- active involvement in a mastitis control program supervised by a veterinarian
- active implementation of a culling policy
- availability of a regional veterinary laboratory or bacteriology laboratory with expertise and interest in veterinary mastitis research and/or investigation.

Use of seasonal calving herds, particularly for evaluation of dry cow products, may be more convenient for coordinating treatments and sample collection. However, herds calving year round may also be used.

Residue trials, if necessary, are best undertaken in experimental herds on dairy research institute farms and under veterinary supervision.

Principles

The trial should use cases of clinical or subclinical mastitis that can demonstrate the effectiveness, or otherwise, of the test product. Chronic or recurrent cases should be eliminated from the trial.

The number of false positive cases of clinical and subclinical mastitis included in the trial should be minimal. Effective use of herd records, farmer and laboratory expertise, and training in sample collection technique will minimise the inclusion of false positives.

Specified withholding periods should be based on trial data, and be consistent with maximum residue limits.

Label guidelines for intramammary infusions

The following are guidelines for labels of intramammary products. These guidelines should be read in conjunction with the Vet Labelling Code.

General

The label should clearly state, as part of the product name and in the label claim, that the product is for ‘lactating cows’ or ‘dry cows’.

Industry-accepted coloured lettering should be used in the product name, denoting ‘lactating cow’ in blue and ‘dry cow’ in red.

Applicants should propose a withholding period statement for both meat and milk. The statements should be worded in accordance with the Vet Labelling Code.

Dry cow products

The directions should clearly state that the product is formulated for use in cows at the end of lactation (that is, dry cow therapy).

Explicit directions should be given on the following points:
indication for treatment
- time for treatment (immediately after the last milking of the season)
- disinfection of the teat
- sanitary handling of the product (the wording may vary depending on the type of container)
- administration of the product, including instructions on milking out, or not milking out, the udder before administration
- massaging of teat and udder
- post-treatment precautions
- conditions for storage of the product.

Directions, based on residue analysis in a significant number of animals, should be given as to the minimum number of days of dry period.

The following restraint statement should appear on all labels below the directions for use heading:

**DO NOT USE** in lactating cows or within [...] days of calving.

Unless residue analysis to the contrary is provided, the label should have a statement to cover inadvertent use of dry cow therapy in lactating animals or before calving. This should appear in the directions of use information and read as follows:

If [product] is accidentally administered to a lactating animal or within [...] days of calving, contact the [product distributor/prescribing veterinarian] for advice.

The meat withholding period is to ensure that meat from treated slaughtered cows does not exceed the maximum residue level. Applicants should propose a meat withholding period statement for cows intended for slaughter in accordance with the Vet Labelling Code.

The statement on the appropriate milk withholding period for dry cows should read as follows:

**DO NOT USE** in lactating cows or within [...] days of calving. After calving, colostrum or milk from treated dry cows MUST NOT BE USED or processed for human consumption for [...] hours ([... milkings]).

Lactating cow products

The label should include directions on the following points:

- indications for treatment
- the optimal treatment regime (that is, the number of treatments)
- the interval between treatments, and milking out instructions
- disinfection of the teat
- sanitary handling of the product
- administration of the product
- massaging of quarter if necessary
- teat dipping
- conditions for storage of the product.

The milk withholding period for lactating cow products should be stated in both hours and milkings—for example:

Milk collected from cows within [...] hours ([..] milkings) following treatment MUST NOT BE USED or processed for human consumption or fed to bobby calves.

Part II: Guidelines for testing intramammary antibiotics formulated for use in non-lactating (dry) cows

The purpose of testing dry cow products is to establish the efficacy of the products in eliminating specified bacterial pathogens from infected quarters during the non-lactating period. Validation should be conducted in commercial herds using sufficient numbers of subclinically infected quarters to yield statistically significant results.

The principle for testing dry cow antibiotics is to compare the efficacy of the test product with that of an accepted and proven dry cow preparation. Trials incorporating an untreated control group of infected quarters are usually less precise because of the problems associated with spontaneous recovery in untreated quarters. Comparison of the test product with a reference product minimises the difficulties due to diagnostic errors and herd differences in response rate, and makes possible comparisons between trials. It also overcomes the reluctance of farmers to leave an infected quarter untreated.

The efficacy of the product in preventing acquisition of new infections during the dry period should be demonstrated if the applicant wishes to market the product with such a claim.

While Australian efficacy data are desirable, these are not mandatory. However, local trials may be relevant if overseas efficacy data do not address the Australian criteria, particularly in the area of trial design, bacterial strains, bacterial definition of infection and sampling protocols.

Selection of cows
Information guidelines and standards

Cows should be selected for inclusion in the trial on the basis of a high probability of their being subclinically infected. Individual cows included in the trial should be reliably identified (for example, by heel strap, ear tag or freeze brand).

Cows can be presumptively classified as subclinically infected in the two-week period before drying off using herd records (ICCC, rapid mastitis test, conductivity and/or enzyme analysis). The analysis should be made by the consulting veterinary surgeon in consultation with the farmer. Cows treated with dry cow therapy in the previous dry period for clinical or subclinical infection should be excluded. Cows treated in the current season for clinical mastitis, but not treated for infection in the previous dry period, may be included for consideration as candidates for bacteriological testing.

The infection status of cows should be evaluated by bacterial culture of quarter samples. Cows should be sampled by an experienced milk sampler, ideally at three consecutive milking or on three consecutive days, using the technique described in Experimental design—Sample collection and submission. Three samples collected over a five-day period would be acceptable although less desirable.

The last sample should be taken five clear working days before the prospective dry cow treatment is to be administered in order to allow final laboratory compilation of results, interpretation of findings, and allocation of cows to trial groups.

Milk samples submitted for bacteriological examination should be processed as described in Experimental design—Bacteriology and data recording. Cows should be classified as infected if two out of three bacteriological cultures of the aseptically collected milk prove positive for the same bacterial mastitis pathogen (Neave, 1975). This approach produces a 1 per cent false positive rate and should allow for optimal assessment of product efficiency.

Evaluation of antibiotic products for effectiveness in preventing new infections in the dry period is not indicated under most Australian conditions. However, if deemed necessary, selection of cows for this component of product performance should be undertaken by presumptive identification of a group of uninfected cows by reference to herd records and ICCC or enzyme analysis and made available for bacteriological examination. Half of the cows can be treated with the product and half can serve as untreated controls. Such a study should use a large sample size to detect significant differences between treated and untreated animals, since the incidence of new infections in the dry period is unlikely to be high.

Experimental design

The objective of testing is to assess the effectiveness of the product administered during the dry period in removing subclinical infections caused by specific bacterial pathogens. The efficacy of the product should be assessed by measuring the rate of intramammary infections in infected cows following treatment.

The product under test (the treatment) should be compared with a commercially available antibiotic product (the control), the efficacy of which has been demonstrated by extensive use in field trials under varied conditions. If possible, the trial should be conducted as a ‘blind’ trial, by having the tubes containing the treatment and control preparations unbranded and identified only by a code letter or number that is assigned and known only by an individual not involved in administering the product to the experimental animals. The tubes containing the treatment and control preparations should be of similar nozzle design, and both preparations should be administered similarly with respect to site of deposition within the teat canal, to minimise differences in the rate of acquisition of new infections associated with the treatment technique.

Treatment groups

Infected cows should be randomly assigned to two groups of equal size (treatment and control). Details of parity and quarter infection rate should be recorded for each animal. Since individual animals may have from one to four quarters classified as infected, the final number of infected quarters in the treatment and control groups may differ slightly.

Cows in the treatment group should receive a dose of the test compound in all four quarters, while cows in the control group should receive a dose of the reference product in all four quarters.

Sample size and statistical analysis

The experimental unit for the trial should be an individual quarter. Treatment and control preparations should be randomly allocated to infected cows. Data should be collected from a minimum of three herds.

A sufficient number of quarters should be tested overall to demonstrate that the efficacy of the test product is within 10 per cent of that of the control product, where the efficacy of the control product is at least 40 per cent (that is, the proportion of quarters that show a bacteriological cure following treatment with the control product should be no more than 10 per cent below the proportion of quarters showing a bacteriological cure following treatment with the control product).

As a guide, the z-test comparison of proportions (Snedecor & Cochran) is an appropriate statistical test to use to compare treatments, and the sample size should be established to ensure that the power of the test is at least 0.80, with α set at 0.05. There should be a table in the report representing the sample sizes (number of quarters per experimental group) recommended to compare treatment efficacy for different levels of efficacy expected for the control product.

Treatment method

Treatment should be supervised by the consulting veterinarian (or their delegate to the satisfaction of the consulting veterinarian). This step is critical to the success of the trial, as errors of identification and aseptic technique are most likely to occur at this point.

Before treatment can be instituted, the teats should be cleaned effectively. Washing should be restricted to the teats and the base of the teats only, to minimise contaminating run-off after the teats have been dried. Excess water should be dried off, using a separate paper towel for each cow.

The teat furthest from the operator should be wiped with an individual tissue soaked (not dripping) in 70 per cent alcohol. Laboratory bench wipes are most suitable because they contain little lint, are strong and do not hold excessive alcohol. A downward motion from the base of the teat to the end should be used.

The end of the teat should be turned towards the operator and, using a clean section of tissue, the teat orifice should be cleaned with at least 20 circular scrubbing motions. The cleaning of each teat and teat orifice should proceed accordingly, cleaning first the teat furthest from the operator, before moving to the nearest, to minimise the chance of contamination through accidental hand contact with disinfected teat orifices.

The contents of the appropriate tube or syringe should be inserted into the teat. The teat orifice should be held closed while the preparation is
massaged up into the streak canal and quarter to ensure adequate dispersion.

The teats should then be sprayed or dipped using a registered teat disinfectant.

All treated cows should be inspected 24 hours after treatment for signs of peracute intramammary infection, and then at least weekly for the duration of the trial to monitor for the presence of adverse effects associated with treatment.

Sample collection and submission

Resolution of infection should be assessed by measuring the infection status of treated cows in the early post-partum period. The arrangements for sample collection for the period immediately following calving should ensure that:

- cows are first sampled ideally at the first milking after calving, at least within two days of calving
- samples are collected at three consecutive milkings, or on three consecutive days
- samples are collected by a trained operator (veterinarian, laboratory technician or farmer)
- samples reach the laboratory no more than 24 hours after collection, following storage and transport at 1–6 °C.

It is best to involve professional collection teams (veterinary practitioners, government field staff or laboratory staff) in milk collection if large numbers of cows are to be sampled together, to minimise disruption to the milking schedule and to streamline the collection process.

Laboratory submission sheets should be designed that give details of farm, cow and quarter identification, date of calving, date and time of collection of the sample, and any abnormal findings. These sheets facilitate the collection process for the farmer, while ensuring adequate records for the evaluation of the product.

Careful planning of an identification system for collection tubes minimises the workload during collection and limit the likelihood of confusion of samples after collection.

To collect the samples, the teats should be cleaned as described in Treatment method.

Samples (of approximately 5 to 7 mL) should be collected from each quarter into a sterile 10 mL tube. The closest teat should be sampled first to prevent accidental contamination of the teat orifice by the milk collector’s hand.

The first two squirts of milk should be discarded in order to flush organisms from the teat canal. Then the sample should be drawn into the tube, which should be held nearly horizontal, about 2 cm from the tip of the teat. The stream should be directed against the wall of the sample tube to prevent frothing. Samples should be stored at 1–6 °C as soon as possible after collection.

Bacteriology and data recording

Standard aseptic technique should be observed in processing samples in the bacteriology laboratory.

The contents of each sample container should be resuspended immediately before sampling. One hundred microlitres (100 µl) of milk from each quarter sample should be inoculated onto a sheep blood agar plate (one sample per plate) and spread over the surface of the plate.

Plates should be incubated at 37 °C for a minimum of 18 hours. After incubation, bacterial colonies should be identified, and presumptive pathogens identified to the species level. The results of primary culture (number of colony types and approximate number of colonies) should be recorded. These results should be used early in the trial to identify and correct any problems in sample collection technique that may manifest in a high rate of contamination of milk samples.

The presence of one or more colonies of a mastitis pathogen (commonly *Staphylococcus* species or *Streptococcus* species—Blood & Radostits 1989) is considered indicative of infection. A quarter should be recorded as infected (non-cure) if at least two of the three milk samples collected immediately after calving prove positive on culture, with at least one colony of the same pathogen. A quarter should be recorded as uninfected (cure) if no more than one of the three samples proves positive on culture for a bacterial pathogen.

The antibiotic sensitivity of all bacterial isolates selected from pre-treatment samples should be evaluated and the results recorded. Standard minimum inhibitory concentration or disc diffusion methodology can be used for this purpose.

An individual cow and quarter record should be compiled for each cow in the trial, and should contain the following information:

- farm identification
- cow identification
- age
- production records
- incidence of clinical mastitis
- previous dry cow treatments (refer to Selection of cows)
- bacteriological results for the pre-treatment samples
- somatic cell count or enzyme analysis results for the pre-treatment samples
- antibiotic sensitivity profile (including with respect to the test product) for isolates of *Staphylococcus aureus*, or other nominated pathogen
- final classification of the results into cure or non-cure
- adverse effects associated with treatment.

Part III: Guidelines for testing intramammary antibiotics formulated for use in lactating cows

The purpose of testing lactating cow products is to evaluate the efficacy of the products in eliminating specified bacterial pathogens from clinically infected quarters during lactation. Testing should be conducted in commercial herds using sufficient numbers of clinically infected quarters to yield statistically significant results.

The principle for evaluating lactating cow antibiotics is to compare the efficacy of the test product with that of an accepted and proven lactating cow preparation. Trials incorporating an untreated control group of infected quarters are usually less precise because of the problems associated with spontaneous recovery in untreated quarters. Comparison of the test product with a reference product minimises the difficulties due to diagnostic
errors and herd differences in response rate, and makes possible comparisons between trials. It also overcomes the reluctance of farmers to leave an infected quarter untreated.

While Australian efficacy data are desirable, these are not mandatory. However, local trials may be relevant if overseas efficacy data does not address the Australian criteria, particularly in the area of trial design, bacterial strains, bacterial definition of infection and sampling protocols.

Selection of cows

Cows with clinical mastitis should be selected for inclusion in the trial, provided they have no history of treatment in the previous dry period for clinical or subclinical infection, or previously treated clinical mastitis. Individual cows included in the trial should be reliably identified (for example, by heel strap, ear tag or freeze brand).

The farmer’s assessment of clinical condition should be used to include animals in the trial. However, retention of all animals in the trial should be based on visual and microscopic assessment of milk, and test results including bacteriological culture and somatic cell count. The presence of pathogenic Staphylococcus species or Streptococcus species, or other mastitis pathogens, associated with high somatic cell count and/or abnormalities in the milk sample, should be used to classify a quarter with clinical mastitis. In cases of severe clinical mastitis, the farmer’s veterinarian should be consulted.

A sample of milk should be collected, before treatment, from each quarter of cows identified with clinical mastitis (see Experimental design —Sample collection and submission) and submitted for laboratory examination.

Experimental design

The efficacy of the product should be assessed by measuring the rate of intramammary infections in infected quarters treated during the lactation period.

The product under test (the treatment) should be compared with a commercially available antibiotic product (control), the efficacy of which has been demonstrated by extensive use in field trials under varied conditions. If practicable, the trial should be conducted as a ‘blind’ trial, by having the tubes containing the treatment and control preparations unbranded and identified only by a code letter or number that is assigned and known only by an individual not involved in administering the product to the experimental animals.

Treatment groups

Infected cows should be randomly assigned to two groups of equal size (treatment and control). Details of parity and quarter infection rate should be recorded for each animal. Since individual animals may have from one to four quarters classified as infected, the final number of infected quarters in the treatment and control groups may differ slightly. Cows in the treatment group should receive a dose of the test compound in all four quarters, while cows in the control group should receive a dose of the reference product in all four quarters.

Alternately, cows in the treatment group should receive a dose of the test compound in the infected quarters, while cows in the control group should receive a dose of the reference product in the infected quarter.

Note: Depending upon the experimental design, healthy quarters may be treated. Applicants may apply to the APVMA for technical assistance on which treatment regimen is the most appropriate.

Sample size

The experimental unit for the trial should be an individual quarter. Treatment and control preparations should be randomly allocated to infected cows. Data should be collected from a minimum of three herds.

A sufficient number of quarters should be tested overall to demonstrate that the efficacy of the test product is within 10 per cent of that of the control product where the efficacy of the control product is at least 40 per cent (that is, the proportion of quarters that show a bacteriological cure following treatment with the test product should be no more than 10 per cent below the proportion of quarters showing a bacteriological cure following treatment with the control product).

As a guide, the z-test comparison of proportions (Snedecor & Cochran) is an appropriate statistical test to use to compare treatment, and the sample size should be established to ensure that the power of the test is at least 0.80, with α set at 0.05. There should be a table in the report representing the sample sizes (number of quarters per experimental group) used to compare treatment efficacy for different levels of efficacy expected for the control product.

Treatment method

Treatment should be undertaken by the farmer, following directions provided by the manufacturer. A sample of milk should be collected before treatment (see Sample collection and submission) for laboratory examination to confirm the diagnosis of clinical mastitis. Treatment should normally follow milk collection, so the teat orifices should be sterile. If there is any doubt, the teats should be cleaned as described in Sample collection and submission.

The contents of the appropriate tube or syringe should be inserted into the teat. The teat orifice should be held closed while the preparation is massaged up into the teat canal and quarter to ensure good dispersion.

The teats should then be sprayed or dipped using a registered teat disinfectant.

Sample collection and submission

Resolution of infection should be assessed by measuring the infection status of quarters following treatment. The arrangements for sample collection from animals in the trial should ensure that:

- samples are collected at three consecutive milkings, or on three consecutive days, starting 14 days after the last treatment
- samples are collected by a trained operator (veterinarian, laboratory technician or farmer)
- samples reach the laboratory no more than 24 hours after collection, following storage and transport at 1–6 °C.
Information guidelines and standards

It is best to involve professional collection teams (veterinary practitioners, government field staff or laboratory technicians) in milk collection if large numbers of cows are to be sampled together, to minimise disruption to the milking schedule and to streamline the collection process.

Laboratory submission sheets should be designed that give details of farm, cow and quarter identification, date of calving, date and time of collection of the sample, and any abnormal findings. These sheets facilitate the collection process for the farmer, while ensuring adequate records for the evaluation of the product.

Careful planning of an identification system for collection tubes minimises the workload during collection and limits the likelihood of confusion of samples after collection.

Before samples are collected, the teats should be cleaned effectively. Washing should be restricted to the teats and the base of the teats only, to minimise contaminating run-off after the teats have been dried. Excess water should be dried off, using a separate paper towel for each cow.

The teat furthest from the operator should be wiped with an individual tissue soaked (not dripping) in 70 per cent alcohol. Laboratory bench wipes are most suitable because they contain little lint, are strong and do not hold excessive alcohol. A downward motion from the base of the teat to the end should be used.

The end of the teat should be turned towards the operator and, using a clean section of tissue, the teat orifice should be cleaned with at least 20 circular scrubbing motions. The cleaning of each teat and teat orifice should proceed accordingly, clearing first the teats furthest from the operator, before moving to the nearest, to minimise the chance of contamination through accidental hand contact with disinfected teat orifices.

Samples (of approximately 5 to 7 mL) should be collected from each quarter into a sterile 10 mL tube. The closest teat should be sampled first to prevent accidental contamination of the teat orifice by the milk collector’s hand.

The first two squirts of milk should be discarded in order to flush organisms from the teat canal. Then the sample should be drawn into the tube, which should be held nearly horizontal, about 2 cm from the tip of the teat. The stream should be directed against the wall of the sample tube to prevent frothing. Samples should be stored at 1–6 °C as soon as possible after collection.

Bacteriology and data recording

Standard aseptic technique should be observed in processing samples in the bacteriology laboratory.

The contents of each sample container should be resuspended immediately before sampling. One hundred microlitres (100 μl) of milk from each quarter sample should be inoculated onto a sheep blood agar plate (one sample per plate) and spread over the surface of the plate.

Plates should be incubated at 37 °C for a minimum of 18 hours. After incubation, bacterial colonies should be identified, and presumptive pathogens identified to the species level. The results of primary culture (number of colony types and approximate number of colonies) should be recorded. These results should be used early in the trial to identify and correct any problems in sample collection technique that may manifest in a high rate of contamination of milk samples.

The presence of one or more colonies of a mastitis pathogen (commonly *Staphylococcus* species or *Streptococcus* species—Blood & Radostitis 1989) is considered indicative of infection. A quarter should be recorded as infected (non-cure) if at least two of the three milk samples collected 21 days after treatment prove positive on culture with at least one colony of the same pathogen. A quarter should be recorded as uninfected (cure) if no more than one of the three samples proves positive on culture for a bacterial pathogen.

The antibiotic sensitivity of bacterial isolates selected from pre-treatment samples should be evaluated and the results recorded. Standard minimum inhibitory concentration or disc diffusion methodology can be used for this purpose.

An individual cow and quarter record should be compiled for each cow in the trial, and should contain the following information.

- farm identification
- cow identification
- age
- lactation
- production records
- clinical appearance of each quarter or each infected quarter
- bacteriological results for the pre-treatment samples
- somatic cell count/enzyme analysis results for the pre-treatment samples
- bacteriological results for three milk samples collected 21 days after treatment
- somatic cell count or enzyme analysis for the post-treatment samples
- antibiotic sensitivity profile (including with respect to the test product) for isolates of *Staphylococcus aureus*, or other nominated pathogen
- final classification of the results into cure or non-cure
- adverse effects associated with treatment.

Part IV: Determination of end point for antibiotic excretion in milk following intramammary treatment of lactating cows

Antibiotics in the milk from udders infused with intramammary preparations can be detected by direct and indirect methods. Direct methods are conventional microbiological assays where known amounts of test samples are applied to bacterial cultures with known antibiotic sensitivity patterns. Direct detection of antibiotics in milk should be carried out by trained laboratory personnel using appropriate equipped laboratory.

Indirect detection involves ‘marking’ such preparations with approved dyes and then infusing them into the mammary gland. The dye is excreted in milk with end points equal to those of the antibiotic (Novak et al. 1984). The potential advantage of dye marking is that it immediately alerts the farmer and the consumer to antibiotic contamination by visually discolouring the milk.

This section provides detailed guidelines for dye-marker techniques that should be used to assess the excretion of antibacterial agents administered to diseased lactating udders. Some manufacturers may already have such data, which can be submitted together with other data specified in previous sections of this document. However, the data should clearly indicate the procedure used to obtain the data from dye-marker trials.
Objective

The aim of providing this data is to demonstrate the dye marker – antibiotic relationship during excretion following treatment of the infected lactating udder.

Method

Cow numbers: Due to the considerable variations between different quarters of the udder of the same cow as well as between cows, the trial should be on a minimum of six cows.

Use of mastitic udder trials: At least some cows included in the trial should be selected on the basis of one or more quarters having high somatic cell counts.

Cows selected for use in the trial should have received no antibiotic treatment for four weeks prior to the trial.

Stage of lactation: Cows with average volume of milk production for the specified breed should be selected as far as possible. The submission should clearly indicate the stage of milk production and the actual yield to the nearest 0.02 kg of each treated quarter in each milking during the period of the trial.

Sampling technique:

- Efficient quarter milkers should be used, since the trial is to be conducted on a quarter basis, rather than a whole udder basis.
- The quarter milking equipment should be used with the cows for several days prior to the trial so they become accustomed to it.

The submission should give details of the milking procedures and sampling techniques used.

Analysis of samples

The laboratory performing the analyses may wish to freeze the samples before testing. Analysis should not be delayed more than a few days. Care should be taken to avoid contamination with penicillinase-producing organisms that may cause gross inaccuracy of the tests. If possible, the participating laboratory should be involved in bacteriological examination of milk samples.

Number of treatments

The manufacturer should make specific recommendations concerning the frequency and duration of treatment for each product. Each quarter used for the study should be treated according to those recommendations. In cases where the manufacturer does not make such recommendations, three tubes should be administered at 24-hour intervals. The first post-treatment sample should be taken at the first milking following the last treatment.

Three cows should be treated in one quarter and the following samples should be collected at all post-treatment samplings:

- milk from the treated quarter
- pooled milk from the three non-treated quarters
- a whole udder sample.

Three cows should be treated in two quarters and the following samples taken at all post-treatment samplings:

- milk from first treated quarter
- milk from the second treated quarter
- pooled milk from the two untreated quarters
- a whole udder sample.

Duration of trial

In the case of a product that the manufacturer wishes to put on open sale, the objective of the trial is to determine end points for excretion for both dye and antibiotic. The trial should therefore continue until these points have been reached.

In the case of a product that is intended for sale on a prescription basis and that is not to be dye-marked, the antibiotic end point should be determined so that an appropriate withholding time can be included on the label.

Since the trial may be concluded before analysis begins, manufacturers should draw upon previous experience and published reports to estimate the appropriate number of samples.

Measurement of dye concentration

A numerical concentration can be obtained from the number of serial dilutions with dye-free milk, which should match the sample with milk standards containing known concentrations of Brilliant Blue F.C.F. Dawson and Feagan (1960) recommended that four standards be set up (0.25, 0.5, 0.75 and 1.0 ppm). Care should be taken to compare milk from initial milkings with the standard having the highest concentration. All measurements should be made as accurately as possible.

All dye concentration measurements should be made under standard ‘daylight’ lighting conditions, and white containers should be used to hold the coloured milk samples.

For the purpose of the trial, a visual end point of 0.125 ppm should be adequate. There would, however, be no difficulty in carrying further observations with one of the simple anion exchange resin methods that have been developed for use by dairy factory personnel, which will permit detection of 0.016 ppm by untrained operators (0.005 ppm can be detected with refined versions of technique). An anion exchange technique that could be adopted as a standard is described by Feagan et al. (1965).

Measurement of antibiotic concentration in milk
Antibiotic measurements should be made by a quantitative assay technique capable of detecting the antibiotic in quarter milk samples at a concentration low enough to ensure that it would not be detectable in herd milk by the most sensitive assay technique. Ideally, these measurements should be made by the most sensitive technique available.

Manufacturers that are at all uncertain as to the acceptability of the proposed method to be used may wish to seek technical assistance from the APVMA before conducting the trials.

The following assay procedures could be employed in trials of products containing penicillin:

- The technique described in the document ‘Specification for the Identification and purity of some Antibiotics’, FAO Nutrition Meeting Reports Series No. 45A, WHO/Food Add./69:34. This is a quantitative plate technique and test organism in *Sarcina lutea* (ATCC 9341). The method has a sensitivity of 0.01 i.u./mL for benzylpenicillin-Na in milk.
- The Standard Association of Australia has described a filter paper disc method (AS 1095) and the test organism recommended in *Bacillus stereothermophilus*. It is a quantitative technique, which enables penicillin to be detected at or above 0.0025 i.u./mL in milk.

Any other technique that enables detection of 0.005 i.u./mL or lower concentrations of penicillin is likely to be acceptable.

**Submission of trial data**

Complete and impartial submission of results should be provided. The concentration of dye marker and antibiotic should be presented in tabular form, showing clearly the milking at which these two constituents become undetectable by the method employed.

**Formulation details**

Full information should be provided on the following:

- identity and concentration of all antibiotics and other active constituents
- identity and volume of base
- type of Brilliant Blue F.C.F. (micronised or crystalline)
- quantity of dye in each dose.

**References**


likely to have an unintended effect that is harmful to animals, plants, things or the environment.

For further information on the safety criteria, see Satisfying the statutory criteria.

Introduction

This section sets out the chemistry and manufacturing data that should be provided to the APVMA in support of an application for the approval of an active constituent. This guideline applies to active constituents of synthetic, semisynthetic or natural origin only and excludes immunobiological active constituents (see the specific guidelines page).

The APVMA has adopted the quality guidelines of International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH), with certain conditions to reflect particular Australian conditions. Where the VICH guideline specifies that it is for new veterinary drugs substances (active constituents) (such as VICH GL10(R) and GL39), we consider that it should be applicable to all veterinary active constituent applications. You should justify any deviation from the VICH guidelines, including from those indicated to apply only to new active constituents.

For further guidance on submitting chemistry and manufacturing data in support of active constituent approval you may also wish to view the guidance for industry documents for active constituent (drug substance) submissions available from the websites of:

- the US Food and Drug Administration, Center for Veterinary Medicine
- the veterinary medicines area of the European Medicines Agency
- the Veterinary Drugs Directorate of Health Canada.

Identification of the active constituent

You should provide details of the nomenclature, structure, identity and general properties of the active constituent.

Common name

You should nominate the common names for new active constituents. The preferred common name will be the name specified in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). If the active constituent is not listed in the SUSMP, the common name may be found in one of the following:

- World Health Organization—International non-proprietary names
- Therapeutic Goods Administration—Approved terminology for medicines—Chapter 1—Australian approved names for therapeutic substances
- British Pharmacopoeia (BP)
- British Pharmaceutical Codex
- Australian Pharmaceutical Formulary and Handbook
- British Pharmacopoeia (Veterinary) (BP (Vet))
- European Pharmacopoeia (Ph. Eur.)
- United States Pharmacopoeia (USP)
- Standards Australia (AS 1719-1994: Recommended common names for pesticides)
- International Organization for Standardization
- British Standards Institution
- Chemical Abstracts (CA)
- International Union of Pure and Applied Chemistry (IUPAC)
- the name descriptive of the true nature and origin of the constituent.

A trademark or trade name cannot be used as an approved name of an active constituent.

Chemical name

The full chemical name, in accordance with both the International Union of Pure and Applied Chemistry (IUPAC) and the Chemical Abstracts (CA) nomenclature, should be provided.

You should include all accepted and proposed non-proprietary names for the active constituent—for example, the International non-proprietary name (INN), United States adopted name (USAN), British approved name (BAN)—along with the names of the approving authorities.

Chemical Abstracts Service registry number

You should provide the Chemical Abstracts Service (CAS) number of the active constituent. If the CAS number has not been allocated, state ‘Not yet allocated’.

Manufacturer’s code numbers and synonyms

Manufacturer or laboratory code numbers and synonyms should be provided.

Molecular and structural formula and molecular mass

You should provide the molecular formula, molecular mass and structural formula of the active constituent. For active constituents existing as salts or hydrates, you should also provide the molecular mass of the free base/acid or anhydrous form. For polymeric compounds, you should provide the molar mass distribution in the form of the mass average molar mass (Mm) and number average molar mass (Mn).

Where relevant, the structural formula should include the stereochemical properties of the active constituent, such as the relative configuration (eg cis/trans, di) and absolute configuration (eg E/Z, R/S). Where possible, the structural formula should be given diagrammatically with all known stereochemistry.
Elucidation of structure and other characteristics

You should provide confirmation of the chemical structure of the active constituent. The elucidation of structure should be based on appropriate physical and chemical test results. This may include:

- a description of the synthetic route as evidence of structure
- an elemental analysis with theoretical values
- a discussion on ultraviolet (UV) characteristics, including pH dependence shifts
- infrared (IR) spectrometry
- $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectrometry
- $^{19}$F and $^{31}$P NMR spectrometry
- mass spectrometry (MS)
- any other relevant information to confirm the structure (for example, X-ray diffraction).

Physical and chemical properties

You should provide all relevant physical and chemical properties of the active constituent. The information should include the purity of the substance used to generate the data and the methods used for each test parameter. The information should include, as appropriate:

- a general description (for example, appearance, colour, odour and physical state)
- when a new active constituent contains one or more chiral centres, whether the active is a pure enantiomer, racemate or fixed combination of non-enantiomeric isomers
- specific optical rotation
- melting point (for solids)
- boiling point (for liquids)
- condensation point (for gases)
- refractive index (for liquids)
- density/specific gravity (for liquids)
- UV absorption maxima and molar absorptivity
- pH and/or pK_a values
- solubilities in common solvents
- n-octanol/water partition coefficient ($P_{ow}$ or log $P_{ow}$)
- dissociation constant, if appropriate
- if the active constituent can exist in more than one physical form (for example, polymorph, solvate or hydrate), information for the form (or forms) of the constituent that will be used in the manufacture of the product
- particle size distribution (including nanoscale particles).

A nanomaterial is any substance intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale—that is, in a size range typically between 1 nm (nanometre) and 100 nm—and that is either a nano-object (that is, confined in one, two, or three dimensions at the nanoscale) or a nanostructure (having an internal or surface structure at the nanoscale). Aggregates and agglomerates are considered to be nanostructured substances. Where size distribution shows that, by number of particles, 10 per cent or more of a substance is at the nanoscale, the substance will be considered a nanomaterial for risk assessment purposes.

To allow us to identify and assess the potential risks of nanomaterials, you should provide the following characteristics and physical chemical properties:

- composition
- identity
- purity
- morphology
- structural integrity
- catalytic or photocatalytic activity
- particle size/size distribution
- electrical/mechanical/optical properties
- surface-to-volume ratio
- chemical reactivity
- surface area/chemistry/charge/structure/shape
- water solubility/dispersibility
- agglomeration/aggregation (or other properties)
- descriptions of the methods used to assign these determinations.

Stability data

You should provide stability data to demonstrate the inherent stability of the active constituent. The content of the active constituent, any degradation products (especially toxicologically significant impurities), and other critical characteristics should be monitored initially and at sufficient sampling frequency during storage. The results of stability studies (long-term, accelerated, and under various conditions of stress such as heat, light, humidity, acid/base hydrolysis and oxidation) should be provided. You should propose a suitable re-test period based on the stability of the active constituent in an Australian climate. Australia has climatic conditions encompassing VICH zones I to IV. VICH GL3(R), GL5, GL10(R), GL18(R), GL39, GL45 and GL51 provide information on stability design and testing protocols and data evaluation.

You should also demonstrate the nanoscale stability properties of the active constituent, if relevant.

Method of manufacture of the active constituent

Manufacturer and site of manufacture

You should provide the name and business address of the manufacturer or manufacturers of the active constituent and the street address of the
Description of the manufacturing process

Active constituents produced by chemical synthesis

You should provide a detailed description of the manufacturing process to allow us to establish that the process is capable of consistently delivering quality active constituent in a process in which each step of the manufacturing is appropriately controlled and the active constituent meets all quality attributes, including specifications. The batch size (for example, in litres or kilograms) and scale (pilot or production) should be stated.

You should provide full details of the manufacturing process quality control procedures that ensure batch-to-batch consistency and reproducibility of the active constituent. You should describe the in-process quality control checks performed at various stages of the manufacture, purification and packaging of the active constituent; testing should include the specifications and tests for pivotal and key/critical intermediates.

An appropriate description of the manufacturing process will usually include:

- an introductory paragraph detailing the number of chemical steps, whether the process is a batch or continuous process, and significant purification steps
- a detailed description and flow diagram of the synthetic processes, including molecular formulae, chemical structures of starting materials, intermediates, reagents and chemical equations of the reactions involved, reflecting stereochemistry, and in-process quality control steps
- the relative amounts of each starting material and their order of addition
- reaction conditions (for example, temperature, pressure, pH and reaction times) and the duration and yield of each step of the process
- information on intermediates that are isolated and purified
- if a manufacturing concentrate is produced, details of the final concentration of the active constituent present, methods used to confirm the concentration, and details of the diluents and/or any additives used.

You should describe the nanoscale processes of the active constituent manufacturing process, if relevant.

Active constituents produced by fermentation

The information about an active constituent produced by fermentation should describe the fermentation process in detail, including:

- the source and strain of microorganism used in the fermentation process
- strain improvement procedures
- purity and stability checks
- cell banking arrangements
- storage
- propagation seeding procedures
- whether or not the microorganism has been deposited in a recognised culture collection, such as the American Type Culture Collection, the United States Department of Agriculture or the World Federation for Culture Collections
- the composition of the media and details of how the reaction conditions are controlled (for example, times, temperatures, pH, rates of aeration, and name and composition of preservatives)
- a detailed description of the isolation and purification procedure for the active constituent, including in-process controls used to ensure freedom from potentially pathogenic agents, such as viruses and prions.

Semisynthetic active constituents derived from fermentation

If the starting material for a semisynthetic antibiotic is obtained by fermentation, the description of the starting material should be provided as detailed under Active constituents produced by fermentation (above). The information for the synthesis of the final active constituent from the starting material should be provided as described under Active constituents produced by chemical synthesis (above).

Feed-grade active constituents

Feed-grade active constituents are permitted as components of feed – additive drug premixes, which are used in the manufacture of medicated feeds. The feed-grade active constituent is usually derived from fermentation and is marketed as an unpurified or partially purified product. It commonly contains a large percentage of carbohydrates, amino acids, fatty acids and nucleotides, but it may also contain small amounts of toxic components that are not readily isolated or identified.

For this reason, the microbial fermentation should be described in detail, including specifications for all components of the media and all procedures and precautions employed to prevent contamination or abnormal fermentation. You should include a description of all in-process tests used to determine quality and yield.

Active constituents of plant origin

For an active constituent of plant origin, you should give full details of the manufacturing procedure (such as extraction and purification) of the constituent. Your submission should also include:

- a description of the botanical species and the part of the plant used (such as leaf, flower or root)
- the geographical origin and, where relevant, the time of the year harvested.

If they are known, you should record the nature of chemical fertilisers, pesticides, fungicides and other agents used during cultivation. It may be appropriate to include limits for pesticide residues resulting from such treatments in the active constituent specifications. The absence of toxic heavy metals should also be confirmed.

Sterile active constituents

For sterile active constituents, the sterilisation process should be described in detail.
Quality control

You should provide the following information on the measures taken to assure the quality of the active constituent:

- control of all raw materials
- tests and acceptance criteria performed at critical steps of the manufacturing process to demonstrate that the process is controlled
- in-process quality control of intermediates and operations.

Animal-sourced material

For starting materials of animal origin used in the manufacture of the active constituent, you should provide information on:

- biological sources
- country of origin
- manufacturer
- specifications.

You should also provide evidence that the material is free of bovine spongiform encephalopathy (BSE) and transmissible spongiform encephalopathies (TSEs).

For information about importing biological agents, refer to the Department of Agriculture website.

Genetically modified organisms

For starting materials that consist of or contain genetically modified organisms (GMOs), the APVMA seeks advice from the Office of the Gene Technology Regulator (OGTR). For approval of a GMO, you should also refer to OGTR guidelines on data for a risk analysis relating to the use of the GMO.

Active constituent specification

A specification is a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an active constituent should conform. You should provide active constituent specifications to allow the APVMA to assess whether the constituent is of an acceptable quality for its intended use.

If a pharmacopoeial standard exists, the active constituent should comply with the recent monograph. If a pharmacopoeial standard is not available, you should provide a manufacturer’s specification. VICH GL39 and GL40 provide test procedures and acceptance criteria for active constituents, raw materials and excipients. The tests and limits in the manufacturer’s specification for an active constituent should include the universal and specific tests described in VICH GL39 (as appropriate). You should consider impurities according to VICH GL10(R) and GL40 and residual solvents according to VICH GL18(R).

The nanoscale properties of the active constituent, if relevant, should be incorporated into the active constituent specification.

Batch analysis data

You should provide batch analysis data to allow us to validate the processes (manufacturing and quality control) and determine whether the active constituent is manufactured consistently to meet the proposed quality standard. The data should include test results for all parameters listed in the specifications. The selection of batches to demonstrate routine compliance with the pharmacopoeial monograph or manufacturer’s specifications should be the same as that described in VICH GL3(R). You should consider the presence of impurities according to VICH GL10(R), GL39 and GL18(R).

The results should include:

- batch size, number, date of manufacture and date of analysis
- analytical determinations (for quantitative tests, such as of active constituent contents, individual and total impurities, provide the actual numerical results rather than vague statements such as ‘within limits’ or ‘conforms’)
- information on the analytical procedures used to generate the data, and validation of those procedures
- where applicable, chromatograms of the batches, showing the separation of impurities (chromatograms should be clearly labelled with batch numbers, peak identity and peak integration data)
- a copy of all raw data used to generate the final results.

The sum of the quantitative level of active constituent and impurities is often referred to as the mass balance. Mass balance is an important parameter in the batch analysis to ensure that all major impurities have been detected. The mass balance need not add up to exactly 100 per cent, because of the analytical error associated with each analytical procedure; however, the mass balance should be in the 98–102 per cent range.

You should demonstrate the nanoscale properties of the active constituent, if relevant.

Analytical methods and validation data

You should provide analytical methods and validation data to allow us to assess the quality and adequacy of the control processes. Harmonised methods, such as those found in the European, United States and Japanese pharmacopoeia, should be used where applicable. You should provide a full description of the analytical procedures used for the testing of the product, including:

- full details of the analytical methods (including method numbers)
- the purity of the reference standards
- where chromatographic (such as HPLC) and spectroscopic (such as NMR) techniques are used, representative chromatograms and spectra of the reference standard, veterinary chemical product and placebo (labelled with batch number, peak identity and peak integration data, if appropriate)
- worked examples of the calculations.
You should provide method validation data to allow us to assess the suitability of the method for its intended use. Typical analytical validation methodologies and characteristics are provided in VICH GL1 and GL2.

You should describe the nanoscale aspects of the active constituent analytical methods, if relevant.

### Analytical reference standards

If you are applying for approval of new active constituents, you should provide the following samples to the Australian Government National Measurement Institute (NMI):

- 1 gram of analytical reference standard of each pure active constituent or, if the active constituent is a mixture of major isomers that can be separated, 1 gram of each isomer
- 100 grams of the active constituent as manufactured (the percentage purity and the method used to determine purity should be provided)

You may provide justification that you should supply less than 1 gram analytical reference standard and/or less than 100 grams of active constituent as manufactured. We will consider your argument on its merits.

- 10 mg of analytical reference standards for the toxicologically significant impurities present in the active constituent
- 100 mg of analytical standard for all metabolites identified and for which a maximum residue limit (MRL) applies.

You should also submit storage instructions and information on the shelf life of the analytical reference standard and active constituent, especially if degradation is likely to occur during transport or storage.

The samples should be sent to:

National Measurement Institute
105 Delhi Road, North Ryde NSW 2113, Australia
PO Box 138, North Ryde NSW 1670, Australia
Phone: (02) 9449 0111
Fax: (02) 9449 1653
Email: info@measurement.gov.au

Samples should be accompanied by a letter stating:

- the reason for submitting the samples
- the purity of the materials supplied, with the certificate of analysis
- storage instructions
- acute oral and dermal toxicities of the materials, or the appropriate material safety data sheet (MSDS).

Take care to ensure that samples are properly packed. Samples that arrive leaking or otherwise damaged will be destroyed and replacement samples will be requested.

Samples should be provided to the NMI before approval of a new active constituent. When standards are supplied to the NMI, documentation to that effect should be forwarded to the APVMA.

From time to time, the APVMA may request replacements for some or all of the above samples to maintain the inventory.

### Packaging

The packaging or storage/shipping containers should be appropriate for the characteristics of the active constituent. You should provide a description of the packaging materials used for the active constituent and information about the corrosive effect, if any, of the active constituent on the packaging materials. This information is not required if the active constituent is formulated into a product at the site of manufacture.

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**Veterinary—Complementary animal health products: guidelines for veterinary herbal and marine-derived remedies**

### Introduction

This is a guideline on the sorts of information an applicant may choose to submit to address the safety and efficacy criteria for veterinary herbal and marine-derived remedies. It also provides guidance about how the information might be presented and analysed. The APVMA will consider each application on its merits. For further information on the safety and efficacy criteria, refer to the Make an application guideline.

### Registration of a veterinary product

The Agvet Code does not distinguish between naturally derived remedies and synthetic pharmaceutical medicines. Many ingredients derived from natural sources are pharmacologically active and may be capable of having an effect that can modify the health, productivity, performance or behaviour of animals.

The data that may be submitted to support the registration of a veterinary product can vary according to:

- the nature of the product
- the claims made for the product
- the intended use.
The difference between pharmaceutical or immunobiological medicines and complementary animal health products

Pharmaceutical and immunobiological medicines are products that contain well-characterised active constituents that have been subject to validated quantitative chemical or biological assays for purity and/or potency. Their labels usually make specific therapeutic claims. The medicines may be administered or applied internally or externally, including parenterally or topically to tissue other than skin.

Products in one or more of the following categories are pharmaceutical products, not complementary animal health products:

- products that are highly purified plant extracts (for example, where the extract is chemically or biologically well characterised and/or a quantitative test for purity or potency has been developed)
- products administered parenterally (that is, by injection)
- products applied topically to tissue other than the skin (for example, eye, nose or throat)
- products that make specific therapeutic claims for the prevention, cure or alleviation of a specific disease or condition.

Complementary animal health products (CAHPs) are products that:

- contain only natural ingredients as their active constituents
- make only general health claims, not specific therapeutic claims that refer to the prevention (or reduction), cure or alleviation of a specific disease or condition.
- are administered only orally or topically on the skin, not parenterally (for example, by injection) or applied topically to tissue other than skin (for example, eye, nose or throat).

'General health claims' refer to possible health, production or performance benefits for animals' organs or physiological systems without mentioning specific diseases or conditions; for example, 'May be of benefit for improving or promoting [organ or system] health.'

CAHPs include:

- herbal remedies
- probiotics (direct-fed microbials), prebiotics and enzyme products
- therapeutic diets
- homeopathic remedies
- oral vitamins, minerals, amino acids and fatty acids, and other nutrients or food-based derivatives, when used at concentrations higher than 100 per cent of the daily nutritional requirement in order to derive a health benefit (also known as nutraceutical products).
- other naturally derived remedies (for example, marine-derived ingredients such as green-lipped mussel or shark cartilage), but not products such as antimicrobials, hormones and vaccines.

Other than nutraceutical products, CAHPs are not highly processed or well characterised, and therefore do not have validated quantitative assays for purity or potency.

Nutraceutical products, because they are either highly purified and well-characterised ingredients or synthetic duplicates of those ingredients, normally have validated quantitative assays for purity or potency. Therefore, you should submit a complete chemistry package (as expected for a pharmaceutical product) for these types of products. You should discuss and justify the impact of this on other criteria, such as the product’s toxicity, where appropriate.

Veterinary herbal and marine-derived remedies

Herbal and marine-derived products that do not require registration

Plant or animal material that is an ingredient of the normal diet of an animal, and that is only represented as being suitable and used to help maintain normal (optimal) health, production or performance, is a food and not a veterinary chemical product.

Plant material that is an ingredient in a product for application to the normal healthy skin or coat of an animal, and that is only represented as being suitable and used to modify the appearance (not the physiology) of the skin or coat by cleaning, moisturising or changing the colour, is a cosmetic and not a veterinary chemical product.

Therefore, products that meet all of the following criteria do not usually require registration:

- products made from whole unprocessed plant or animal material and administered in feed or applied to the skin of animals
- products intended only for use as a food or cosmetic
- products that do not claim to contain biologically active constituents
- products that do not claim to modify the health, productivity, performance or behaviour of an animal.

Refer to the APVMA’s user guide: what is or isn’t a veterinary product for further information.

Criteria for reduced data submissions for herbal and marine-derived remedies

Herbal and marine-derived remedies may be eligible for evaluation for registration with reduced data submissions, compared with the data requirements for pharmaceutical or immunobiological products, if the products:

- make only general health claims
- are administered only by topical application to the skin, oral administration or consumption by an animal
- are for use only in non-food-producing species of animals (that is, companion animals).

The summary claim on the main panel of the label should clearly state:

- as the first statement: ‘This product is registered as a Complementary Animal Health Product’
- followed by a general health claim, such as: ‘May be of benefit for improving or promoting [organ/system] health or production or performance.’
Guidelines on data parts

You should provide data and/or valid scientific argument to address each data part when applying to register a CAHP.

Data should generally be submitted for Chemistry and manufacture, Toxicology, and Efficacy and target animal safety, as described below.

Data packages to support Metabolism and kinetics, Residues and trade, Occupational health and safety, Environment, Other trade aspects and Special data—antibiotic resistance, are not normally expected for herbal and marine-derived remedies used in companion animals. However, you should ensure that the omission of any data part is adequately justified in your submission.

Chemistry and manufacture (Part 2)

Validated quantitative assays for purity and potency are not generally expected, as quality will be determined by good manufacturing practice (GMP) controls on the raw materials, manufacturing processes, release and expiry specifications for testing physical and chemical properties other than assays and, when available, testing for marker substances. Where validated quantitative assays exist (such as for nutraceuticals), they should be provided.

You should provide:

- a description of the dose form or formulation type of the product
- the Australian approved name(s), botanical name(s) and descriptions of the plants or plant parts used as active constituents in the product
- a description of the extraction and/or purification process and quality controls for the active constituent(s)
- the results of identification and characterisation tests, including the analytical procedure(s) used to control the method of extraction (for example, fingerprint chromatogram, ultraviolet spectrum, biological test or other procedure for active constituents; refer to a pharmacopoeial monograph where relevant, or to details in a recognised herbal pharmacopoeial monograph such as the European or British herbal pharmacopoeias or Max Wichtl, Herbal drugs and phytopharmaceuticals)
- the specifications and analytical procedures for the analysis of purity and impurities, including tests for potential contamination by organic and inorganic impurities and residual solvents where they are likely to occur, such as microorganisms, products of microorganisms, pesticides, toxic metals and fumigants
- the complete formulation, composition and specification of each non-active constituent if the product contains such constituents
- a description of the physical and chemical properties of the product
- a description of the manufacturing process and quality controls for the product
- the specifications and details of any analytical procedures to ensure the batch-to-batch consistency and quality of the final product, such as assays of active constituents or relevant marker substances or acceptable bioassays
- where relevant, data used to support the proposed shelf life and stability of the product during storage and at the end of the proposed shelf life (if validated analytical methods are not available for stability testing, a product that has been stored for a period of time may be used in a repeat of the efficacy and safety trials to support the proposed shelf life).

You should ensure that the omission of any data part is adequately justified in your submission.

We may also consider applications for default shelf lives of 12 months for liquid and semi-solid products and 18 months for dry solid products if you provide valid scientific argument.

Toxicology (Part 3)

If the product is for use in only companion animals, you may choose to address the safety criteria related to the toxicology of the product by nominating an APVMA-registered reference product that contains the same active constituents in the same concentrations.

Alternatively, you may:

- provide evidence that the product’s active constituents are included in the Australian Register of Therapeutic Goods as a registered (AUST R) product, or are included in Part 2, 3 or 5 of Schedule 4 of the Therapeutic Goods Regulations (A) and are not included in Part 4 of the schedule, or have been gazetted to be thus included, which renders them eligible for listed registration (AUST L), and
- provide evidence that both the active and non-active ingredients have been approved by the APVMA or Therapeutic Goods Administration (TGA) for inclusion in the type of formulation and packaging proposed.

If the above scenarios do not apply, you should consider the following when preparing a submission to address toxicology:

- the purity and concentration of constituents
- whether they are manufactured in accordance with a pharmacopoeial monograph
- whether they are registered overseas.

You should submit copies of relevant material safety data sheets together with all available toxicity data.

For products containing more than one active constituent, we will consider any additional concerns about toxicology on a case-by-case basis.

We encourage you to review veterinary chemical products—Toxicology (Part 3) when preparing a submission. You should address the submission recommendations by providing data and/or valid scientific argument.

Efficacy and target animal safety (Part 8)

Australian or overseas efficacy and safety data for the use of the proposed product may be submitted for companion animal uses.

Products containing existing active constituents

For products containing existing active constituents, you may be able to provide scientific data or argument for the equivalence of your proposed product with a registered reference product, because these products are not considered to be highly formulation-dependent. Otherwise, you should refer to the guidance below for products containing new active constituents.

Products containing new active constituents

This section provides guidance on data packages for products containing new active constituents.
Efficacy

Although it is generally not appropriate to extrapolate between animal species or between different formulations, or to rely on non-clinical endpoints, we will consider a reduced efficacy data package for herbal and marine-derived remedies if any of the following cases apply:

- There are scientifically valid clinical data for a related formulation and/or in non-target species.
- There is relevant scientific information from recognised textbooks or other reputable sources that recognises the efficacy of the active constituent in the target species. This information may be derived from clinical veterinary practices and well-constructed client surveys.
- A physiological or pharmacological endpoint, rather than a clinical endpoint, is proven in the target species efficacy trials using the proposed formulation.

Otherwise, one or both of the following types of clinical studies, using the proposed formulation together with preclinical pharmacokinetic data and dose-determination studies, is desirable:

- a randomised controlled experimental trial using objective measurements of clinical endpoints in the target species.
- clinical case studies in the target species for which either the raw data are available or results are published in a peer-reviewed scientific journal.

Refer to the APVMA’s specific guidelines page for further information about efficacy trials.

Safety

You should refer to internationally acceptable guidelines, such as Target animal safety guidelines for new animal drugs, which is published on the website of the United States Food and Drug Administration (FDA). More information is available on the APVMA’s specific guidelines page.

The following are minimum requirements:

- Studies should be adequately designed, well controlled and conducted by a qualified investigator.
- Product formulation and use patterns used in studies should be identical to those being proposed for registration.
- The selection of study animals should consider the classes of the target species (age, sex, weight range) most at risk.
- Animals should be studied for at least three times the recommended maximum duration of use, up to a maximum of 3 months.
- A tolerance test should be conducted on five animals at five times the recommended maximum label dose, administered for the duration specified above. If the tolerance test indicates any sign of toxic effects, a margin of safety study as per the FDA guideline should be conducted.
- The evaluation for signs of toxicity should include:
  - feed and water consumption, clinical observation and physical examinations
  - changes to haematology and blood chemistry
  - urine and faecal analysis.
- Any abnormal finding or adverse reaction should be further investigated. A complete gross and histopathological examination should be carried out on all animals that die during, or as a result of, the study.

Two weeks or longer may be appropriate to acclimatise test animals. Baseline parameters should be established before the study begins. All prophylactic and therapeutic medications should be administered before the baseline study period so that they will not interfere with the study.

In the absence of reproductive studies, a standard label precautionary statement should be proposed; for example: ‘Use with caution in pregnant or lactating animals.’

Compatibility studies may be appropriate for some products if they are mixed with other products.

Irrespective of the results obtained during safety studies, any unanticipated reactions occurring during any other studies, or known or suspected in reports from users, in Australia or overseas should be reported at the time of application.

Examples

Example 1

An application is made to register a new herbal-extract tablet product for use in dogs and cats with a claim of ‘May help relieve symptoms associated with travel sickness.’

The product contains a new herbal active constituent that the TGA has approved for use in humans.

The following modules and data parts are expected to apply:

<table>
<thead>
<tr>
<th>Data part</th>
<th>Module</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>Module 1</td>
<td>Preliminary assessment</td>
</tr>
<tr>
<td>Part 2—Chemistry and manufacture</td>
<td>Module 2.2</td>
<td>Chemistry—Level 2</td>
</tr>
<tr>
<td>Part 8—Efficacy and target animal safety</td>
<td>Module 8.2</td>
<td>Efficacy and target animal safety—Level 2</td>
</tr>
<tr>
<td>Not applicable</td>
<td>Module 11.2</td>
<td>Finalisation—Level 2</td>
</tr>
<tr>
<td>Not applicable</td>
<td>Module 12</td>
<td>Data protection</td>
</tr>
</tbody>
</table>
The evaluation timeframe in this example is 11 months.

**Example 2**

- An application is made to register a new feed-additive powder product for use in dogs with a claim of ‘May aid in improving joint health.’
- The product contains a new active constituent derived from a marine animal. The TGA has not approved the constituent for use in humans, but it is likely to be of low toxicity.

The following modules and data parts are expected to apply:

<table>
<thead>
<tr>
<th>Data parts</th>
<th>Module</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>Module 1</td>
<td>Preliminary assessment</td>
</tr>
<tr>
<td>Part 2—Chemistry and manufacture</td>
<td>Module 2.2</td>
<td>Chemistry—Level 2</td>
</tr>
<tr>
<td>Part 3—Toxicology</td>
<td>Module 3.3</td>
<td>Toxicology—Level 3</td>
</tr>
<tr>
<td>Part 8—Efficacy and target animal safety</td>
<td>Module 8.2</td>
<td>Efficacy and target animal safety—Level 2</td>
</tr>
<tr>
<td>Not applicable</td>
<td>Module 11.1</td>
<td>Finalisation—Level 1</td>
</tr>
<tr>
<td>Not applicable</td>
<td>Module 12</td>
<td>Data protection</td>
</tr>
</tbody>
</table>

The evaluation timeframe in this example is 12 months.

Scheduling may be required in some instances. If so, an additional module 4.1 will apply.

**Example 3**

- An application is made to register a new product for companion animals that contains an existing active constituent. The product is not closely similar to any product already registered by the APVMA.
- The product contains a herbal active constituent that the TGA has approved for use in humans.

The following modules and data parts are expected to apply:

<table>
<thead>
<tr>
<th>Data parts</th>
<th>Module</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td>Module 1</td>
<td>Preliminary assessment</td>
</tr>
<tr>
<td>Part 2—Chemistry</td>
<td>Module 2.3</td>
<td>Chemistry—Level 3</td>
</tr>
<tr>
<td>Part 8—Efficacy and target animal safety</td>
<td>Module 8.3</td>
<td>Efficacy and target animal safety—Level 3</td>
</tr>
<tr>
<td>Not applicable</td>
<td>Module 11.2</td>
<td>Finalisation—Level 2</td>
</tr>
<tr>
<td>Not applicable</td>
<td>Module 12</td>
<td>Data protection</td>
</tr>
</tbody>
</table>

The evaluation timeframe in this example is 8 months.

The following content can be found at http://new.apvma.gov.au/node/904

If making a submission, please reference page number: 904

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**Veterinary—WAAVP guideline for ticks on ruminants**

The World Association for the Advancement of Veterinary Parasitology (WAAVP) is a not-for-profit organisation for scientists who study the parasites of non-human animals. The guidelines, developed by the international expert working groups of the WAAVP, assist in the international harmonisation of standards and procedures for the evaluation of veterinary parasiticides. The WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants aim to standardise the minimum set of data that should be submitted to demonstrate the efficacy of new ectoparasiticides for use on or in ruminants.

The APVMA has adopted the WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants to assist registration holders in the conduct of regulatory trials. The APVMA notes that in some instances the WAAVP guidelines advise consultation with the regulator. We also
recognise that because of Australia’s unique environmental and geographic parameters, parasite burdens and their population dynamics, farm management practices and animal breeds, there are some differences between the WAAVP guidelines and the APVMA’s recommendations for efficacy trials for products to be registered in Australia. Therefore, applicants should conduct efficacy trials within Australia under typical farm management practices covering relevant geographical regions and the following additional guidance is provided to assist you in conducting these trials. If you follow this additional guidance, your data should generally be sufficient for the APVMA to assess its confidence in the product’s efficacy given Australia’s unique conditions.

This preamble refers to the following World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline: Holdsworth, PA, Kemp, D, Green, P, Peter, RJ, De Bruin, C, Jonsson, NN, Letonja, T, Rehein, S & Vercruysse, J 2006, ‘World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of acaricides against ticks on ruminants’, Veterinary Parasitology, vol. 136, pp. 29–43.

**Tick species**

*Rhipicephalus (Boophilus) microplus* is the most important cattle tick in Australia, although *Haemaphysalis longicornis, Ixodes holocyclus* and *Rhipicephalus sanguineus* also occur. You should use *Rhipicephalus microplus* as the target species in your efficacy studies, as well as the other parasite species (e.g. *Ixodes holocyclus*) if you propose to claim efficacy against such parasites. If you make claims against specific resistant strains of cattle ticks, you should also demonstrate efficacy against those strains.

**Animals**

The World Association for the Advancement of Veterinary Parasitology guidelines are silent on which cattle breed should be used in these studies. The APVMA prefers that you use *Bos taurus* cattle which are naturally less resistant to cattle tick infestation than *Bos indicus* cattle.

**Field trials**

The World Association for the Advancement of Veterinary Parasitology guidelines recommend that you include at least two geographic locations in the overall study plan, with at least two study sites in each geographic location.

As additional guidance, the APVMA recommends the number, location and timing of field trials for *Rhipicephalus microplus* set out in Table 1.

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of trials</th>
<th>Area</th>
<th>Timing of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>South East Queensland</td>
<td>2</td>
<td>Tick-infested area from Gympie to New South Wales border</td>
<td>You should conduct trials between October and December</td>
</tr>
<tr>
<td>Central Queensland</td>
<td>2</td>
<td>Gympie north to Rockhampton</td>
<td>You should conduct trials between September and December</td>
</tr>
<tr>
<td>Tropical Queensland</td>
<td>2</td>
<td>from Rockhampton north</td>
<td>You should conduct trials from August to November or post-wet season from March to June</td>
</tr>
</tbody>
</table>

For *Ixodes holocyclus*, the WAAVP guidelines recommend two field trials in each geographic region. The two recommended geographic regions in Australia are coastal New South Wales and coastal Queensland.

**Acaricides for cleansing tick-infested cattle**

Given the importance of maintaining tick-free areas in Australia, if products claim efficacy for cleansing tick-infested cattle before cattle are introduced into a tick-infested area, then multiple treatments, commonly within a period of seven days, are used to ensure that cattle from infested or quarantined areas can be moved to tick-free country. Before moving these cattle, they are inspected by relevant authorities to ensure that there are no signs of tick life.

If you seek a claim for the cleansing of tick-infested cattle, you should conduct multiple treatments of infected cattle according to current movement control requirements and carry out efficacy assessments. However, examinations to support such a claim should include not only records of adult ticks collected or counted, but also detailed observations of the presence of other tick stages on the animals after they have been treated.

**Rainfastness**

The World Association for the Advancement of Veterinary Parasitology guidelines address rainfastness generally: ‘Where artificial rainfall is used to test the efficacy of a topically applied test product before or after heavy rain, the method of wetting used and the equivalent in terms of natural rainfall should be stated (for example, artificial rain applied by inverted sprinklers, equivalent to a rainfall of 20 millimetres in a storm lasting 30 minutes). The time of animal wetting before or after test product application should be recorded (for example 0, 2 hours, etc.).’

The APVMA recommends that for trials conducted for cattle tick, animals should be subjected to the equivalent of 12.5 millimetres of rainfall over a 10-minute period, immediately following treatment.

**Wool or hide damage**

Given the importance of the wool and cattle by-product industries to Australian commerce, it is recommended that you collect and submit data on wool staining or damage, hide or skin damage, or damage to animal products.
Veterinary chemical products—Overseas trade (Part 5B)

Introduction

The APVMA must be satisfied that a chemical product meets the trade criteria—that use of the chemical product according to the use pattern on the approved label would not unduly prejudice trade or commerce between Australia and places outside Australia. We therefore assess potential trade risks as part of our assessment of veterinary chemical products.

To enable an assessment of the use of veterinary chemicals in food commodities, and the related potential risks to overseas trade, we recommend a range of information that should be submitted with an application. For further assistance, refer to the guideline: Veterinary drug residues in food commodities and overseas trade. This information and data are part of the overall residues evaluation and assessment of the veterinary chemical product.

Trade can be adversely affected if the presence of residues of veterinary chemicals in export commodities is higher than the standards set for those commodities by an importing country. Australia has experienced a number of episodes of interrupted trade in commodities derived from livestock, following the detection of residues at levels above those allowed in the importing country.

Most of Australia’s trading partners have established maximum residue limits (MRLs). These are also known as ‘tolerances’ in some countries, if the chemicals have approved uses for residues of chemicals in food commodities in those countries. MRLs can vary from country to country due to different use patterns and other factors. Consequently, the legitimate use of a chemical in Australia according to the use pattern on the APVMA-approved label can result in residues in food that exceed the MRLs or tolerances of importing countries even though the residues are below the Australian MRL.

The purpose of providing information in the Part 5B (Overseas trade) submission is to enable us:

- to identify any potential risks to Australia’s export trade associated with the use of a veterinary chemical product
- to assess proposed strategies that may be used to mitigate any identified export trade risks
- to consult with relevant stakeholder groups (such as peak industry bodies and state departments of agriculture) prior to the public consultation phase of registration to explore any potential trade risks and the feasibility of any proposed risk-mitigation strategies
- to conduct a public consultation through either a notice in the APVMA Gazette or a Trade Advice Notice (TAN).

Types of data

Applicants should submit information to demonstrate that when the veterinary product is used as proposed and relevant residue-management strategies are followed, residues in food commodities will comply with the residue standards in relevant export markets.

If the proposed use of the veterinary product is expected to result in quantifiable residues in more than one food commodity and the information to be submitted is different for each affected commodity, applicants should provide separate trade information for each commodity, for example cattle meat and cattle milk.

We will consider a range of factors when assessing whether a product will cause undue prejudice to trade, including:

- whether a potential trade risk exists (for example, due to inconsistencies between Australian MRLs and the import tolerances of the trading partner)
- the applicant’s proposed strategies to minimise and manage an identified trade risk
- the capacity of affected industries to implement strategies to minimise and manage the risk to trade
- communication of trade advice to product users.

Strategies to manage identified trade risks include:

- the establishment and effective communication of export slaughter intervals (ESIs)
- the establishment of import tolerances
- making a maximum residue limit submission to Codex for the establishment of an appropriate Codex MRL
- industry-specific management strategies.

The ESI is the minimum period of time that should elapse between the last treatment of an animal with a veterinary chemical product and the slaughter of that animal. The ESI is included on the product label under the heading ‘Trade advice’. For further information on label statements refer to the Veterinary Labelling Code.

The trade advice statements are intended to alert the user of possible trade risks associated with their use of the product, and to provide sources of further information to identify and manage the trade risks. ESIs assist producers and exporters to comply with MRLs or import residue tolerances of trading partners when the MRLs or import tolerances are more stringent than the respective Australian MRLs.

ESIs are therefore important tools in the management of potential risks to trade arising from the use of a registered product. They are advisory periods which the applicant proposes, and are agreed to or amended by the APVMA in consultation with the affected producer industries. However, ESIs are non-statutory in that the Agvet Code does not specifically require that they be set.

The submission of overseas trade information may demonstrate that when the chemical product is used as proposed and relevant residue management strategies are followed, chemical residues in food commodities will comply with residue standards that currently apply in relevant export markets.

To assist in the assessment of trade risks, we consult with state and territory governments, stakeholder organisations, other interested parties and the general public. We conduct public consultation primarily by one or both of two processes:

- a notice in the APVMA Gazette
- a Trade Advice Notice.

Data submission and application layout
A checklist of data submitted for Part 5B (Trade) of an application for veterinary chemical products, and the way in which they should be set out, appears in Table 1. Each area should be addressed. If information is not provided, the subject heading should be retained with an explanation of why the information has not been provided (for example, ‘not relevant’ or ‘no information available’).

### Table 1: Data submission for Part 5B (Overseas trade)

<table>
<thead>
<tr>
<th>Submission</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table of contents</strong></td>
<td>List the sections included in the trade submission and their page numbers</td>
</tr>
</tbody>
</table>
| **Summary** | • You should briefly summarise all data and information supporting your proposal  
• Please provide general information that will assist the APVMA, and other authorities and stakeholders, to evaluate particular features of the product that might affect trade |
| **Export markets** | • The APVMA (June 2009) defined the major markets that are to be considered when establishing ESIs for cattle, pig and sheep tissues. Details of the markets appear in the operational notice located on the APVMA website  
• For all other species/commodities, you should identify the most important export markets by listing the top six to 10 importing countries ranked by Australian dollar value and volume |
| **Proposed Australian use pattern and label** | You should include a copy of the draft label which shows trade statements |
| **Overseas registration status** | • While this information may appear elsewhere in the application, you should repeat it in this section  
• Where possible, you should provide copies of the approved overseas label(s) |
| **Use patterns in overseas market countries** | • You should use attachments if necessary  
• Where possible, please provide copies of the approved overseas label(s) |
| **MRLs in overseas market countries** | • Where the product is registered, you should provide a copy of the notice of MRL from the competent authority  
• Where the product is not registered, but import tolerances have been established, you should provide a statement from the competent authority specifying the acceptable limits  
• You should indicate any action taken, or planned to be taken, to obtain or amend MRLs (including ‘import tolerances’) in overseas market countries |
| **Codex MRLs (CXLs)** | • You should include recommendations from the Codex Committee on Pesticide Residues (CCPR) or Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) that are currently under consideration  
• You should indicate when the applicant would be prepared to submit an application to Codex for the establishment of CXLs |
**Proposed Australian MRLs**  
List the proposed Australian MRL(s)  
You should provide a list of the proposed Australian MRLs.

**Potential prejudice to trade**  
Identify any potential prejudice to trade for the target commodity  
- If relevant, you should describe how any import tolerances affect other exporting countries and how those countries have dealt with such issues  
- You should consider any potential prejudice to trade for non-target commodities, i.e., the potential for collateral damage to Australia’s export trade in other animal commodities

**Export slaughter interval (ESI) proposal**  
The ESI proposal should identify the most sensitive export market in terms of its residue requirements

**Proposed strategies to minimise trade risk**  
You should provide details of any proposed trade risk-management strategies and associated communication strategies

**Other relevant trade information**  
Indicate results of any relevant trade-risk consultations with authorities and/or producer organisations  
Any other relevant information should be included in this section

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**Veterinary—Guideline on efficacy and target animal safety for products supplied for use in minor species or for minor use under permit**

**Introduction**

This is an outline of the APVMA’s target animal efficacy and safety data guidelines for veterinary chemical products intended for use in minor species or for minor use.

The Agvet Code Regulations defines minor use, in relation to a chemical product or an active constituent, as ‘a use of the product or constituent that would not produce sufficient economic return to an applicant for registration of the product to meet the cost of registration of the product, or the cost of registration of the product for that use, as the case requires (including, in particular, the cost of providing the data required for that purpose)’.

We regard minor species for a particular purpose as being defined by exclusion, as any species other than major species. We regard major species for a particular purpose as being generally defined as cattle, horses, sheep, pigs, chickens, horses, dogs, and cats.

Under state and territory prescribing laws, veterinarians may use APVMA-registered products ‘off label’, but take responsibility for product efficacy and safety to target animals, as well as health and safety of people consuming produce from treated animals, people using the product, and the environment.

Off-label use is prescribing, using, or authorising a client to use a registered drug or veterinary chemical in a manner outside the range of uses permitted by the approved label directions—including species of animal, dosage, treatment interval and so on. Veterinarians are permitted to exercise professional judgement in the off-label use or supply of most drugs or other veterinary medicines, but must not contravene a specific label restraint.

Where supply is to non-veterinarians, or for veterinarians intending to conduct an activity outside the scope of their state or territory prescribing rights, the information that may be submitted to the APVMA for the demonstration of efficacy and target animal safety will be influenced by whether the product is already registered by APVMA for use in another species or for another use in the registered species. The known pharmacological, toxicological and efficacy profile of an active constituent or a related active constituent may be used to support efficacy and target animal safety.

Where an active constituent has been approved by the APVMA or a product has been registered for a similar indication in another species, you may submit information relating to use in that species to support the application where scientifically justified. This approach may be used in lieu of conducting studies in the target species. For novel active constituents and for those where limited information is available relating to their use in any animal species, you should provide comprehensive information relating to use in the target species.

**Scope**

This guideline applies only to target animal efficacy and safety for pharmaceutical products. It excludes products for use in aquaculture and immunobiological products. When applying for minor use permits, applicants should also submit data or valid scientific argument to address the human health, environmental, and occupational health and safety aspects of the product as appropriate.

**Legal basis**

The statutory criteria that we must be satisfied of to issue a permit (with respect to safety, efficacy and trade) are the same as those required when
registering a product. In addition to these legislative requirements, we maintain a policy that a permit is unlikely to be issued where there is a suitably registered product available for that purpose, unless there is sufficient justification why a registered product cannot be used.

We may also consider advice from the APVMA Compliance section, holders, state and territory departments and the Adverse Experience Reporting Program on claims of ineffectiveness of or adverse reaction to a registered product or in situations where the registered product is unavailable. This procedure ensures that the permit system does not circumvent the normal registration processes. For extension of minor use permits, we will take into consideration use patterns and whether a suitable registered product has become available since the minor use permit was first issued.

**Minor use permit for supply of products to veterinarians for use outside of veterinary prescribing rights**

Permits for minor use may be issued where states or territories have limited such prescribing rights, for instance, to individual animals of a food-producing species. Where states or territories have limited such prescribing rights, we will, in consultation with those states or territories, consider granting a minor use permit for the treatment of a larger number of animals for a specified purpose.

A permit may be issued in instances where you can show that you are unable to provide comprehensive data on therapeutic effect because either:

- the indications for which the chemical product is intended are encountered so rarely that you cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided

The permit may be issued subject to the following conditions:

- the chemical product in question should only be used or dispensed by a registered veterinary surgeon and may be administered only under strict veterinary supervision
- the package leaflet and any other information should draw the attention of the veterinarian to the fact that in certain specified respects, the particulars available concerning the chemical product in question are as yet incomplete.

Before a permit is issued for a veterinary chemical product under the above conditions, you should provide information from scientific literature or pilot studies to justify the proposed dose rate and to support a reasonable expectation of efficacy. For example, studies conducted in another species where a comparable pharmacological profile can be shown may be sufficient to support a conditional dose and a reasonable expectation of efficacy.

You should also provide information demonstrating that the test product is safe when administered to the target species at, at least, the maximum recommended treatment dose and, where practicable, for the maximum duration of therapy.

**General guidelines for applications for use in minor species or for minor use**

You should provide efficacy and safety data of the product under evaluation in the target species to support your application. The means for demonstrating efficacy will be determined on a case-by-case basis. You should make an application to the APVMA for technical assessment early in the development process to ensure that all trials are appropriately designed and will be statistically valid; and that all other recommended guidance for submission of information has been addressed. We will take into consideration the practical limitations of generating data for an infrequently occurring disease. Published literature from acknowledged, ideally peer-reviewed, scientific journals may be used to support part of or the entire efficacy claim.

Veterinary chemical products intended for use under permit in minor species or for minor use must fall within the definition of ‘minor use’ permits (or some other available permit for use) and will be classified under five main categories:

- registered veterinary chemical product supplied for use in a minor species
- registered veterinary chemical product supplied for a minor use in a major species
- Therapeutics Goods Administration–registered human medicinal product supplied for use in a major or minor species
- unregistered product containing an approved active constituent supplied for use in a minor species or for a minor use
- unregistered product containing an unapproved active constituent supplied for use in a minor species or for a minor use.

Generally, in all five categories the following should be provided:

- data to characterise the mechanism of action and the known pharmacological (including toxicological) effects of the active substance.
- data to demonstrate the safety of the product in the target species to the test product following administration by the proposed route.
- data to support the efficacy of the product for all proposed indications in the target species.

If adequate information does not exist in the literature, you should demonstrate the efficacy of the product in appropriately designed studies. The type and number of studies to be conducted will depend on the deficiencies in available data. If you choose to conduct new studies to support the efficacy and safety of a product, you can obtain further information from the APVMA data guidelines.

**Registered veterinary chemical product supplied for use in a minor species (can be referred to as off-label use)**

Extrapolation of data from a major to a minor species will be considered where the product is approved for a similar indication in a major species, and where the pharmacology (both in terms of pharmacodynamics and pharmacokinetics) of the test product is likely to be comparable in both species.

Information should be provided to:

- show the practical use of the product in the minor species
- establish if accurate dosing of the product can be achieved
Registered veterinary chemical product supplied for a minor use (can be referred to as off-label use)

In the majority of cases where a registered product is used in a major species to treat a rare condition not listed on the label, the dose rate and route of administration for the proposed minor use indication will be unchanged, and therefore applicants may choose not to submit data. If the dose rate and/or route of administration proposed for the minor use are different to those already approved, similar sets of circumstances as indicated above in the General guidelines for applications for use in minor species or for minor use would likely apply and similar information should be submitted.

Therapeutic Goods Administration–registered human medicinal product supplied for use in a minor species or for a minor use

If a human medicine is already registered by Therapeutic Goods Administration, the product will have been assessed for chemistry and manufacture, toxicology and occupational health and safety. In this instance, you should submit information related to the use of the product in the minor species or for the minor use; that is, dosing accuracy, efficacy and safety information as well as residues as appropriate.

Unregistered product containing an approved active constituent supplied for use in a minor species or for a minor use

The information that may be submitted in addition to efficacy and safety on target species will depend on the information held by the APVMA on the active constituent. Under such circumstances, you may choose to apply to the APVMA for a technical assessment.

Unregistered product containing an unapproved active constituent supplied for use in a minor species or for a minor use

Due to the cost of developing an entirely new veterinary chemical product, it is likely that this category will be encountered rarely. In all such cases you should provide full efficacy and safety studies.

Target animal safety and efficacy studies

You should provide appropriate data to show the safety of the test product to the target species following administration by the proposed route. Whether you choose to submit specific target animal safety studies in minor species will depend on the information available on the safety of the active constituent or product in the minor species or another species (or both). This information may include data from toxicity studies in surrogate laboratory animals, literature reports, pharmacovigilance data, and safety information derived from efficacy studies. For example, if the test product is approved for another species and is known to have a wide margin of safety in that species, field study data demonstrating satisfactory tolerance in the target species following administration of the test product at the recommended treatment dose for the recommended duration of therapy may be considered adequate in lieu of a specific target animal safety study. The safety data should include a copy of scientific articles cited.

Where no data or limited data on the safety profile of the active substance in the target species are available, a basic controlled study demonstrating the safety of the (near-) final formulation in the target species should be provided. In order to demonstrate a margin of safety in the target species, the study should be designed to investigate the safety of the product when it is administered at doses in excess of the recommended treatment dose (for example, three times and five times the proposed dose rate). The applicant should justify the study design proposed. Where safety in breeding animals of another species is demonstrated, applicants may provide valid scientific data in lieu of additional safety data in breeding animals of the target species. However, in the absence of adequate data, a restriction on use in breeding animals (for example, use in accordance with the risk/benefit assessment of a veterinary surgeon) may apply.

Interspecies extrapolation of pre-clinical data to support applications for minor species can be supportive if scientifically justified. You should provide a rationale for the selected treatment regime and duration of therapy. The proposed treatment regime may be justified using one or more of the following:

- specific dose determination studies
- pharmacokinetic and pharmacodynamic (for example, minimal inhibitory concentration) data
- literature data or results of pilot studies or clinical experience reports
- extrapolation from another species for which the product is registered.

You should provide a dose confirmation study and a field trial. Clinical studies should be conducted using the final formulation. In the absence of specific dose determination studies, the efficacy of the product at the recommended dose regime should be demonstrated in an adequate and controlled dose confirmation study in the target species. Dose confirmation studies may not be needed if a field study has been provided and the selected dose is justified.

Applying for a minor use permit

Applicants should apply for a minor use permit online through the APVMA portal.

The following content can be found at http://new.apvma.gov.au/node/723
If making a submission, please reference page number: 723
Issues to consider during method development are outlined in the below section.

VICH GL49 is one of a series developed to facilitate the mutual acceptance by national or regional regulators of residue information for veterinary drugs used in food-producing animals. It was originally prepared after consideration of the current national or regional requirements and recommendations for evaluating veterinary drug residues in the European Union, Japan, the United States, Australia, New Zealand, and Canada.

While VICH GL 49 covers most of the Australian recommended considerations in terms of analytical methodology used to quantify veterinary drug residues, there are some additional considerations that are unique to Australia. These additional methodological considerations are detailed in this document.

**Guidance on residue analytical methodology**

This guideline is only intended to apply to analytical procedures that have been developed for the evaluation of veterinary drug residue methods (assays developed to determine residues in marker residue depletion studies). It is not intended to define the criteria needed for validation of regulatory monitoring assay procedures.

**Introduction**

Residues data are used to establish maximum residue limits, demonstrate compliance with existing maximum residue limits, determine appropriate withholding periods and determine export slaughter intervals. In addition to the residues data that support registration of veterinary products that are used in or on food-producing species, you should provide a description of the analytical methods used to generate the residues data.

When developing analytical methods for a veterinary drug substance, the method(s) should:

- have the ability to determine (identify, quantify and confirm) all the components included in the residue definition or marker residue
- be specific enough that interfering substances never exceed 30 per cent of the limit of analytical quantitation
- have demonstrated repeatability
- cover all tissues or commodities that may be obtained from treated animals
- where possible, identify which multi-residue methods have the capacity to measure the residues.

**Types of analytical methods**

Analytical methods currently available for determining residues of veterinary drugs are as follows:

- **Bioassays**: Broad-spectrum bioassays are used extensively in Australia to routinely screen urine, milk and kidney for the presence of antimicrobial agents. They continue to be important in the screening of large numbers of samples for the presence of inhibitory substances. These methods are generally not suitable for generating quantitative data for registration purposes. Specific bioassays or immunoassays are used for quantifying residues of veterinary drugs, especially antibiotics.
- **Instrumental methods**: Methods such as gas liquid chromatography or high-performance liquid chromatography, in conjunction with various detectors, can be used both for the routine analyses of most veterinary drugs and to confirm and quantify their residues. Instrumental quantitation of new antimicrobial drugs is preferred to quantitation by bioassay or immunoassay, provided the specificity and sensitivity of the instrumental method are adequate.
- **Other instrumental methods**: Methods including scanning thin layer chromatography and spectroscopic methods are less commonly used to quantify residues of veterinary drugs.

The choice between bioassays, immunological tests and instrumental methods will depend on the suitability of the respective methodologies for the task at hand. Circumstances will dictate which of the method types is appropriate. The APVMA’s preference is for an instrumental method that is specific and quantitative.

**Objectives of analytical methods**

When developing instrumental analytical methods for veterinary drugs, it is important the method(s) should:

- have a substantiated and acceptable extraction efficiency
- have the ability to determine (identify and quantify) all the components included in the residue definition or marker residue
- be specific so that interfering substances never exceed 30 per cent of the limit of quantitation
- have acceptable precision and accuracy
- cover all animal species that are proposed to be the subject of the registration application
- apply to tissues and commodities (such as muscle, liver, kidney, fat, injection sites, eggs, milk, and honey) that are relevant to the registration application.

In the case of bioassays and immunoassays, you only have to meet those objectives listed above that are relevant.

**Development of analytical methods**

In cases where standard methods are not available, or where an existing method requires modification to meet specific requirements, you should provide details of the method development. In all cases, whether the method to be employed is a standard procedure, a modification of an existing method, or an entirely new method, the laboratory should demonstrate that the performance characteristics of the analytical method meet the criteria outlined in the below section Guidance on validation of residue analytical methodology.

**Issues to consider during method development** are:

- The method should cover all relevant tissues (such as muscle, liver, kidney and fat) and animal commodities (such as eggs, milk and honey) in accordance with the registration proposal. When milk is involved, the analytical method should apply to whole milk. When use of the drug involves administration to laying hens, eggs should be included in the method development. While partitioning of the residue between the yolk and the white of eggs should be determined, the method development should occur using the whole egg (minus shell).
- The analytical method should address the residue definition or marker residue and be able to determine (identify and quantify) all the...
components included in the residue definition. If the analytical method does not address the residue definition, it may not be suitable for generating residue data.

- Whereas bioassays are acceptable for screening large numbers of samples for residues, they are generally unacceptable for maximum residue limit-setting purposes. When using instrumental methods, you should base the residue definition or marker residue on the moiety or moiety measured; that is, the parent compound and/or one or more metabolites. In certain circumstances, the residue definition or marker residue will require the chemical conversion of parent and/or metabolites to another derivative that is measured.

- The method should be fully validated. You should provide validation data for all matrices for which the method is to be used. In addition, you should provide data for control and fortified samples. Method validation is discussed in detail in the below section Guidance on validation of residue analytical methodology.

- Extraction efficiency of the method should be determined with incurred residues, as it is a critical component for measuring the true analyte concentration. The method should adopt an extraction procedure that has been proven by analysis of samples for radiolabelled studies or by an exhaustive series of extractions that utilise different solvent and/or buffer combinations for the successive extractions of incurred residues. Linking method development to metabolism studies that utilised radiolabelled drug is one means of achieving the former.

- The extraction efficiency of methods used in submissions pertaining to generic veterinary drugs should also be considered and demonstrated. You can accomplish this by demonstrating equivalence to the existing method through proficiency testing programs such as the National Residue Survey programs. If you need to develop methods for generic veterinary drugs, we advise you to use, where possible, the same extraction procedure and solvents as you used for establishing the maximum residue limits in the first instance. Alternatively, you could use a method published by the Codex Alimentarius Commission, or other published methods as guidance. These may involve exhaustive extractions and/or comparisons of extraction efficiencies when different solvents are used. You should also consider using other means to release residues from the matrix (for example, the use of perchloric acid releases neomycin from tissues; the use of glucuronidase for freeing residue conjugates; and the use of protease for releasing protein bound residues).

- The method should also demonstrate stability of the residue in the extracts, especially where the method cannot be completed within one work session or where extraction or clean-up occurs overnight. This is more critical with some classes of compounds than others.

- The sensitivity of the method should be acceptable for the intended purpose. It is noted that liquid chromatography with tandem mass spectrometry detection methods are routinely used in monitoring and surveillance laboratories these days, so contemporary analytical methods need to have comparable selectivity and sensitivity. Where the data are being used to support a change in either the maximum residue limit or the withholding period, or for the establishment of an export slaughter interval, the method should be able to detect residues to levels at the method’s limit of quantitation/limit of detection. Further, laboratories are asked to quantify and report values between the limit of detection and limit of quantitation of the method, to assist in the statistical analyses of the residues data.

- You should generate recovery data across the range of residue concentrations that occur in the trial samples, and should, as a minimum, include recoveries at the limit of quantitation and the proposed maximum residue limit. Single-point recovery data are not sufficient when validating a method. For assays that utilise an internal standard, you should provide recovery data for both the analyte and the internal standard.

- You should compare bioassays and immunoassays with an instrumental method to determine specificity and to demonstrate comparable quantitation of the residue definition. If bioassays or immunoassays are not able to quantify the residue definition, they are unsuitable for generating residues data for registration purposes.

You should perform all residue studies that are conducted in Australia, including both the animal and laboratory phases, in accordance with good laboratory practice (GLP) standards. For studies conducted in Australia, only those undertaken by facilities that are accredited under the Australian GLP compliance monitoring program can claim to be GLP compliant. For overseas studies to claim GLP compliance they must be conducted by facilities accredited in accordance with that country’s GLP compliance monitoring program.

Reporting of analytical methods

You should provide complete details of the validated analytical method(s) used:

- in pharmacokinetic and residue kinetic studies
- for the determination of marker residue(s) in the trials conducted for the estimation of withholding periods.

The following is a list of information that you should typically include in support of the adequacy of the analytical procedures you are using:

- a full description of the analytical method, including:
  - purpose and scope
  - reagents
  - equipment and instrumentation
  - collection of samples
  - storage of samples
  - stability of residues during storage
  - preparation of the laboratory sample
  - preparation and clean-up of tissue extracts
  - procedure for the determination of the residues
  - calculation of results, for example method of standardisation, use of calibration curves (mathematical model, parameters, working range)
  - quality control (internal)
  - documentation confirming the purity of the reference materials.

- full details of the validation results, including raw data (refer to the below section Guidance on validation of residue analytical methodology)
- details of studies into extraction efficiency, including the systems examined and/or solvents used, and the results
- representative chromatograms—the minimum information that should be submitted includes a standard, an untreated sample, a fortified untreated sample and a sample for each matrix from a treated animal.

Guidance on validation of residue analytical methodology

The objective of validation of an analytical method is to demonstrate that the procedure, when correctly applied, produces results that are fit for purpose. The purpose of this document is to describe the procedures to be carried out to validate the analytical procedures used to conduct residues analysis and metabolism studies. These procedures are not intended to apply to analytical methods applied to the chemistry and manufacture of veterinary drugs or products containing veterinary drugs.

Performance characteristics
In general, there are specific performance characteristics of a method validation. Those performance characteristics are defined as follows:

- standard calibration
- linearity
- accuracy
- precision
- limit of detection
- limit of quantitation
- selectivity or specificity
- stability in matrix
- conduct of storage stability trials
- process sample stability
- robustness.

Each of these characteristics will be described below as they apply to the validation of methods intended for use in veterinary drug residue depletion studies.

**Standard calibration**

Reference compounds should be of known purity. You should determine the stability of reference. For some antimicrobial compounds fresh dilutions should be prepared daily. You should assess linearity using at least five standard concentrations ranging from the limit of quantitation to the maximum concentration expected to be found in the sample extract, or the proposed maximum residue limit, whichever is higher.

**Linearity**

A calibration curve should be generated in which the linear relationship is evaluated across the range of the expected matrix (tissue, milk, egg or honey) concentrations. Calibration standard curves can be generated in three formats, depending upon the methodology: standards in solvent or buffer, standards fortified into control matrix extract and standards fortified into a control matrix and processed through the extraction procedure. You should describe linearity by a linear, polynomial or other (as appropriate) regression plot of known concentration versus response, using a minimum of five different concentrations. Acceptability of weighting factors should be determined by evaluation of the residuals across three runs to determine if the residuals are randomly distributed. You should evaluate the residuals across at least three separate runs.

The recommended acceptance criterion for a standard curve is dependent upon the format of the standard curve. Calibration standard curves generated by fortification of a control matrix and processed through the procedure are subject to the same acceptance criteria as the samples (see Precision). Calibration standard curves generated by standards in solvent/buffer or by fortification of control matrix extract would require more stringent acceptance criteria (repeatability of 15 per cent or less at all concentrations, except at or below the limit of quantitation, where it can be less than or equal to 20 per cent).

Some assays (for example, microbiological assays) could require log transformations to achieve linearity where other assays (for example enzyme-linked immunosorbent assays (ELISA) and radioimmunoassays) could require a more complicated mathematical function to establish the relationship between concentration and response. Again, you should verify acceptability of the function selected by evaluating the residuals generated when that function is used.

**Accuracy**

Accuracy refers to the closeness of agreement between the true value of the analyte concentration and the mean result that is obtained by applying the experimental procedure a very large number of times. Accuracy can also be determined by recovery experiments using fortified blank matrices (mutually independent replicates). For example, 18 blank test portions could be selected and six fortified at each analyte level. Accuracy is closely related to systematic error (analytical method bias) and analyte recovery (measured as per cent recovery). The recommended accuracy for residue methods will vary depending upon the concentration of the analyte. The accuracy should meet the range listed in Table 1.

<table>
<thead>
<tr>
<th>Analyte concentration (µg/kg)*</th>
<th>Acceptable range for accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 µg/kg</td>
<td>–30% to +20% (70–120%)</td>
</tr>
<tr>
<td>≥1 µg/kg</td>
<td>–30% to +10% (70–110%)</td>
</tr>
<tr>
<td>≥10 µg/kg &lt; 100 µg/kg</td>
<td>–30% to +10% (70–110%)</td>
</tr>
<tr>
<td>≥100 µg/kg</td>
<td>–20% to +10% (80–110%)</td>
</tr>
</tbody>
</table>

*µg/kg = ng/g = ppb (micrograms per kilogram = nanograms per gram = parts per billion)

**Precision**

The precision of a method is the closeness of agreement between mutually independent test results obtained from homogenous test material under stipulated conditions of use. Results are typically expressed as the percentage-relative standard deviation of replicate analyses (n = 6) at various concentrations of analyte. Analytical variability between different laboratories is defined as reproducibility, and variability from repeated analyses within a laboratory is defined as repeatability. Single-laboratory validation precision should include a within-run (repeatability) and a between-run component.

The within- and between-run precision of the analytical method can be determined as part of the validation procedure. There is generally not a need to determine reproducibility (between-laboratory precision) in order to conduct a residue depletion study, because the laboratory that is developing the method is often the same laboratory assaying the samples from the residue study. Instead of establishing reproducibility of the assay, a within-run precision can be determined. Within- and between-run precision should be determined by the evaluation of a minimum of three replicates at three different concentrations representative of the intended validation range (which should include the limit of quantitation) across three days of analysis.

For the purposes of the residue method validation, acceptable variability is dependent upon the concentration of the analyte. The precision should meet the range listed in Table 2.
Limit of detection

The limit of detection (LOD) is the smallest measured concentration of an analyte from which it is possible to deduce the presence of the analyte in the test sample with acceptable certainty. There are several scientifically valid ways to determine LOD. The APVMA’s preferred approach to determining the limit of detection is the definition used by the International Union of Pure and Applied Chemistry (IUPAC), where the LOD is estimated as the mean of 20 control sample (from at least six separate sources) assay results plus three times the standard deviation of the mean.

Limit of quantitation

The limit of quantitation (LOQ) is the smallest measured content of an analyte above which the determination can be made with the specified degree of accuracy and precision. As with the LOD, there are several scientifically valid ways to determine LOQ.

The APVMA’s preferred approach to determining the LOQ is also the IUPAC definition, where the LOQ is estimated as the mean of 20 control sample (from at least six separate sources) assay results plus 10 times the standard deviation of the mean.

Testing of the accuracy and precision at the estimated LOQ provides the final evidence for determination of the LOQ. If the coefficient of variation for the repeatability measurement at that concentration is less than or equal to the accuracy and precision acceptance criteria (see above), then the estimated LOQ is acceptable.

Particular emphasis is placed on determining the ‘true’ LOD and LOQ for the analytical method as, in many instances, the LOQ becomes the target endpoint for export slaughter interval determinations when a major importing country has not set any import standards or tolerances for the veterinary drug. In instances where a veterinary drug is classified as a ‘banned substance’, any detection may be classed as a violation, so surveillance testing may be conducted down to LOD concentrations.

Selectivity or specificity

Selectivity is the ability of a method to distinguish between the analyte being measured and other substances that might be present in the sample being analysed. Details concerning selectivity should relate to any substances that are likely to be present and give rise to a signal when the measuring principle described is used, for example homologues, analogues and metabolic products of the residues of interest. For the methods used in residue depletion studies, selectivity is primarily defined relative to endogenous substances in the samples being measured. Because the residue depletion studies are well controlled, exogenously administered components (that is, other veterinary drugs or vaccines) could either be known or not be allowed during the study. If it is your intent to submit the validated method as a regulatory method, it might be prudent to test known products used in the animals being tested for possible interference. From the details concerning specificity it should be possible to determine the extent to which the method can distinguish between the analyte and the other substances under the experimental conditions.

Stability in matrix

Samples (tissue, milk, eggs or honey) collected from residue depletion studies are generally frozen and stored until assayed. It is important to determine how long these samples can be stored conditions without excessive degradation prior to analysis. You should, as part of the validation procedure or as a separate study, conduct a stability study to determine the appropriate storage conditions (for example 4 °C, –20 °C, or –70 °C) and length of time the samples can be stored prior to analysis.

Samples should be fortified with known quantities of analyte and stored under the appropriate conditions. You should periodically assay the samples at specified intervals (for example, initially, one week, one month, three months). If the samples are frozen, you should conduct freeze or thaw studies (three freeze or thaw cycles—one cycle per day at a minimum). Alternatively, you can use incurred samples with initial assays conducted to determine the starting concentrations. The recommended protocol for assessing stability in matrix is the analysis of two different concentrations in triplicate near the high and low end of the validation range. Stability in matrix is considered acceptable if the mean concentration obtained at the specified stability time point agrees with the initial assay results or freshly fortified control sample assay results within the accuracy acceptance criteria established in Accuracy.

Conduct of storage stability trials

You should analyse the samples taken for residue analysis as quickly as possible after collection, before physical and chemical changes take place. If samples are going to be stored for a significant period of time (six months or longer), you should provide either argument or data on the stability of residues during storage conditions you are using.

Studies on the stability of residues in samples, over the time and at the temperature of storage, should be carried out with representative substrates. You should conduct a stability study with sample material subjected to similar sample preparation procedures and storage conditions as those for the proposed magnitude of residue studies. However, you may store the samples being subjected to a storage stability study as homogenates rather than in a whole state. The homogenate represents a worst case, as the homogenisation process can release enzymes, acids and other chemicals that can react with the veterinary drug or its metabolites. This may lead to unacceptable results if the residue degrades under these conditions.

You may conduct experiments on prepared samples with incurred residues. Alternatively, you may spike aliquots of prepared control samples with a known amount of drug before they undergo normal storage conditions.

Where degradation to a metabolite (contained in the residue definition) is likely during storage, it is desirable to conduct stability studies on samples spiked with the metabolite in addition to those for the parent compound.

Table 2: Analyte concentrations and acceptable within- and between-run precision

<table>
<thead>
<tr>
<th>Analyte concentration</th>
<th>Acceptable within-run precision (repeatability) coefficient of variation (CV)</th>
<th>Acceptable between-run precision CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 μg/kg</td>
<td>20%</td>
<td>32%</td>
</tr>
<tr>
<td>≥1 μg/kg and &lt;10 μg/kg</td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
<td>≥10 μg/kg and &lt;100 μg/kg</td>
<td>10%</td>
<td>16%</td>
</tr>
<tr>
<td>≥100 μg/kg</td>
<td>10%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Process sample stability

Often, test samples are processed one day and assayed on a second day or, because of an instrument failure, they may be stored for additional days, for example over a weekend. The stability of the analyte in the process sample extract might be examined as necessary to determine stability under processed sample storage conditions. Examples of storage conditions would be 4 to 24 hours at room temperature and 48 hours at 4 °C. Other storage conditions might be investigated consistent with the method requirements. The recommended protocol for assessing processed sample stability is the analysis of two different concentrations in triplicate near the high and low end of the validation range. Processed sample stability is considered adequate if the mean concentration obtained at the specified stability time point agrees with the initial assay results or with freshly fortified and processed control sample assay results within the accuracy acceptance criteria established in Accuracy.

Robustness

Evaluation of the robustness of regulatory methods is of major importance. Evaluation of robustness for residue methodology is less of a concern for residue methods, as these are usually conducted within a single laboratory using the same instrument. However, you should still evaluate robustness, particularly for areas of the method that could undergo changes or modifications over time. These might include reagent lots, incubation temperatures, extraction-solvent composition and volume, extraction time and number of extractions, solid phase extraction cartridge brand and lots, analytical column brand and lots and high-performance liquid chromatography elution solvent composition. During the development, validation or use of the assay, method sensitivity to any or all of these conditions can become apparent and you should evaluate the variations in the ones most likely to affect the method performance.

The following content can be found at http://new.apvma.gov.au/node/743

If making a submission, please reference page number: 743

Veterinary chemical products—Metabolism and kinetics (Part 4)

Introduction

Metabolism studies are used to assess the fate of the chemical in target animals and to assess the character of chemical residues in food-producing animals. The composition of a residue (parent and metabolites) and the target organs or food commodities in which it is present (ie muscle, fat, liver, kidney, milk, eggs and honey) should be known, so that residue-depletion trials and analytical methods deal with the relevant residue components. These studies are also used to facilitate the development of analytical methods for determining residue levels.

Metabolism and kinetics studies in both target animals and laboratory animals help assess:

- user safety (as in Toxicology and Occupational health and safety)
- consumer safety (as in Residues).

Types of data

Metabolism and toxicokinetic or pharmacokinetic studies are submitted to facilitate the human-food-safety evaluation of veterinary drug residues that help to ensure that food derived from animals that have been treated with a veterinary product is safe for human consumption.

- Metabolism studies are used to assess the fate of the chemical once it has been administered to an animal and, for food producing animals, to identify the nature of the residue and its target tissues.
- Toxicokinetic or pharmacokinetic studies allow quantitation and determination of the time course of absorption, distribution, biotransformation and excretion of the parent compound and its metabolites.

Studies should be performed in both target animals and laboratory animals, and are generally conducted using radiolabelled substances. The recommended considerations when performing metabolism and pharmacokinetic studies are described in the guideline: Veterinary drug residues—comparative metabolism studies, selection of marker residue(s), and ratios of marker residues to total residues.

Metabolism and toxicokinetic studies in laboratory animals should characterise the metabolites to which laboratory animals are auto-exposed during the toxicological testing of the veterinary drug. This helps to determine whether the metabolites that people will consume from tissues of target food-producing animals are also present in the laboratory animals used for the safety testing.

If the laboratory animals produce similar metabolites to those produced by the food-producing animal, the laboratory animals will have been auto-exposed to the same metabolites that humans will consume from tissues of treated food-producing animals. Auto-exposure of metabolites is taken as evidence that the safety of metabolites has been adequately assessed in the toxicity studies.

Metabolism and pharmacokinetic studies in the target animal(s) should permit an assessment of the quantity and nature of residues in food derived from animals treated with a veterinary drug, and should provide data on:

- the depletion of residues of concern from edible tissues of treated animals at varying times after drug administration
- the individual components, or residues, that comprise the residues of concern in edible tissues
- the residue(s) that can serve as a marker for analytical methods intended for compliance purposes (that is the monitoring of appropriate drug use)
- the ratio of marker residue to total radioactive residues
- the identification of a target tissue or tissues.

Kinetics data that are obtained during toxicity studies should be submitted in the toxicology section of the application.

Metabolism data submission and application layout

Table 1 shows a checklist of data to be submitted for Part 4 (Metabolism and kinetics) of an application to register veterinary chemical products, and the way in which you should set them out.

Table 1: Data submission for Part 4 (Metabolism and kinetics)
### Table 1: Data submission for Part 4 (Metabolism and kinetics)

<table>
<thead>
<tr>
<th>Submission</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of contents</td>
<td>List the sections included in the trade submission and their page numbers</td>
</tr>
</tbody>
</table>

#### Laboratory animals
- Metabolic and toxicokinetic studies in laboratory animals (to characterise the metabolites)
- Summary of studies
- Characterisation and structural identification of major metabolites
- Distribution and storage in the tissues including bioaccumulation, if applicable
- Biotransformation and a description of any metabolites produced
- The mode and extent of excretion or elimination of the parent compound, and/or its degradation products

- You should provide a single summary of all the metabolism and pharmacokinetic studies in laboratory animals, reviewing the absorption, distribution, metabolism and excretion of the drug
- The metabolic pathway should be proposed
- Full copies of each of the studies should be provided in the appendixes

#### Target animals
- Metabolism and pharmacokinetic studies in target animals (for the determination of marker residue, marker residue to total residue, proposed target tissue and the appropriate analytical method)
- Summary of studies
- Characterisation and structural identification of major metabolites
- Proposed marker residue
- Proposed marker to total residues ratio
- Proposed target tissue
- The total residue concentration for each tissue for each collection time point
- The components of the total residues for each collection time point for comparison to the total residue concentrations
- The amounts of total residue radioactivity extracted (percentage extractable) using various treatments (enzyme, acid)
- A complete description of the procedures used for chromatographic and chemical characterization of the drug residues components

- You should provide a single summary of all the metabolism and pharmacokinetic studies in target animals, along with a review of the absorption, distribution, metabolism and excretion of the drug
- The metabolic pathway should be proposed
- A clear outline of the reasons for the proposed marker residue, the marker residue to total residue ratio, and the target tissue should be submitted
- The components of the total residues should be examined to support the proposed marker residue
- If original detailed studies are performed using laboratory animals, similar metabolic pathways should be shown to occur in target animals exposed to the product
- Similarities and differences in the degradation of the chemical should be discussed in light of the residues that may be present in food commodities for human consumption
- Full copies of each of the studies should be provided in the appendixes

#### Metabolism database
You should include a metabolism database similar in format to the toxicological database described in the toxicology section

#### Appendixes
Copies of the full reports for metabolic and toxicokinetic studies in laboratory animals, and metabolism and pharmacokinetic studies in target animals along with complete details of the analytical method(s) and validation reports

The following content can be found at http://new.apvma.gov.au/node/434
If making a submission, please reference page number: 434

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**Veterinary chemical products—Chemistry and manufacture of products (Part 2)**

This is a guideline about the types of information you can submit to address the safety criteria for veterinary chemical products and active constituents. It also provides guidance on how the information might be presented and analysed, and should be considered in conjunction with any guidelines the APVMA has made or adopted that are specific to the type of product for which you intend to demonstrate safety.

This guideline applies to non-immunobiological veterinary chemical products only. The chemistry and manufacturing data that should be provided for immunobiological products can be found on the APVMA’s specific guidelines page.

The information submitted with an application for a veterinary chemical product must satisfy us that the use of the product in accordance with the APVMA-approved instructions is not, or would not be:

- an undue hazard to the safety of people exposed to it during its handling or to people using anything containing its residues
- likely to have an effect that is harmful to human beings
- likely to have an unintended effect that is harmful to animals, plants, things or the environment.

For further information on the safety criteria, see Satisfying the statutory criteria.

### Introduction

This section sets out the chemistry and manufacturing data that should be provided to the APVMA in support of an application for the registration of a veterinary chemical product.

Different chemistry and manufacturing data, as included in separate guidelines, may be provided for certain product types.
The APVMA has adopted the quality guidelines of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH), subject to certain changes to reflect particular Australian conditions.

Where the VICH guideline specifies that it is for new veterinary drugs substances (active constituents) and new medicinal products (for example, VICH GL11(R) and GL39), we consider that it should be applicable to all veterinary product applications (such as generic veterinary chemical products). You should justify any deviation from the VICH guidelines, including those that are indicated to apply only to new active constituents and veterinary products.

For further guidance on submitting chemistry and manufacture data in support of veterinary chemical product registration you may also wish to view the ‘guidance for industry documents for veterinary chemical product (drug product) submissions’ available from the websites of:

- the US Food and Drug Administration, Center for Veterinary Medicine
- the veterinary medicines area of the European Medicines Agency
- the Veterinary Drugs Directorate of Health Canada.

**Formulation type/pharmaceutical dosage form**

The formulation type/pharmaceutical dosage form is the form in which the product is presented for veterinary use. You should indicate the type of formulation to be registered.

If the product formulation is to be reconstituted before use, the formulation type or pharmaceutical dosage form of the end-use formulation should be indicated.

A nanomaterial is any substance intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale—that is, a size range typically between 1 nm (nanometre) and 100 nm. It is either a nano-object (that is, confined in one, two or three dimensions at the nanoscale) or has a nanostructure (having an internal or surface structure at the nanoscale). Aggregates and agglomerates are considered to be nanostructured substances. Where size distribution shows that, by number of particles, 10 per cent or more of a substance is at the nanoscale, the substance will be considered a nanomaterial for risk assessment purposes.

If the product has nanoscale properties, they should be indicated.

**Formulation composition**

The formulation composition describes the qualitative and quantitative formulation of the product. You should provide:

- the constituent name, which is the common name, the complete chemical name (IUPAC, CA name) if a common name does not exist, or the proprietary name for components that are complex mixtures
- the CAS registry number, if available
- the constituent standard, which allows us to assess the purity, quality and risk associated with each constituent present in the product
- the concentration (including stability overages), which is the amount of each constituent in the formulation
- the purpose in the formulation, which is the function of each constituent.

Batch analyses or certificates of analysis from the manufacturer or supplier of each constituent should be included to allow us to assess compliance with the nominated standard.

If a pharmacopoeial standard exists, the constituent should comply with the recent monograph. The pharmacopoeial standard should be European Pharmacopoeia (Ph. Eur.), British Pharmacopoeia (BP or BP (Vet)), United States Pharmacopoeia (USP), or any other pharmacopoeia recognised by the APVMA. Where a pharmacopoeial standard does not exist, you should provide details of the manufacturer’s specifications.

VICH GL39 and GL40 provide test procedures and acceptance criteria for active constituents, raw materials and excipients. The tests and limits in the manufacturer’s specification for an active constituent should include the universal and specific tests described in VICH GL39 (as appropriate). You should consider impurities according to GL10(R) and residual solvents according to VICH GL18(R).

If any constituent used in the product has nanoscale properties, they should be indicated.

Where an active constituent is formed in situ (for example, by chemical reaction), both the starting material(s) and the active constituent should be described.

If materials (active and non-active constituents) of animal origin are used, you should provide evidence that they are free of bovine spongiform encephalopathy (BSE) and transmissible spongiform encephalopathies (TSEs). You should provide the biological source, country of origin, manufacturer details and Department of Agriculture import permit. The Department of Agriculture guidelines for managing the risk of transmitting BSE and TSEs are available from the department’s website.

The formulation composition should not include raw materials used in the manufacture that are not present in the final product formulation. For example, if a solvent is used as an aid in the process and removed in the final stages, that solvent should not be included in the formulation composition details.

Desiccants and inert gases should not be included in the formulation composition details.

Overages of constituents should only be included in the formulation composition details if they are included for storage stability purposes. Manufacturing loss overages should be noted in the manufacturing process details only.

**Manufacturing process**

You should provide a detailed description of the production-scale manufacturing process to allow us to establish that the process is capable of consistently delivering high-quality product, that each step of the manufacturing process is appropriately controlled and that the finished product meets all quality attributes including specifications.

The production scale batch size (for example, in litres or kilograms) should be stated. For sterile products, you should describe the sterilisation process in detail. If applicable, you should describe nanoscale processes in the product manufacturing process.
You should provide details of the quality control procedures that ensure the batch-to-batch consistency and reproducibility of the product. This includes the in-process quality control checks performed at various stages of the manufacture, processing and packaging of the product. Testing should include the specifications and tests for pivotal and key/critical intermediates.

**Product specifications**

A specification is a list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which a product should conform. You should provide product specifications to allow us to assess whether the product is of an acceptable quality for its intended use.

The tests (parameters) for product specifications should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. The tests and limits generally applicable to all products and for particular formulation type/dosage forms are given in VICH GL11(R), GL19 and GL40.

Limits of acceptance should relate to the release limits, and shelf-life specifications should allow acceptable and justifiable deviations from the release specification based on the stability evaluation and the changes observed in storage. The acceptance criteria should include suitable upper and lower limits for the active constituent content (assay), and descriptive, lower–upper or maximum limits of other test parameters as appropriate. The specification limits should take into account the use of any overages in the formulation. A clear distinction should be made between the release specification (the limits for each batch at the time of manufacture) and the expiry specification (the limits with which any sample should comply during its shelf life).

You should include the nanoscale properties of the product, if applicable, in the specification.

You may also wish to view the guidance for industry documents for veterinary chemical products (drug) available from the websites of the US Food and Drug Administration, Centre for Veterinary Medicine and the Veterinary Drugs Directorate of Health Canada for further information on specifications for veterinary chemical product registration.

**Batch analysis**

You should provide batch analysis data to allow us to validate the manufacturing and quality control processes and determine whether the product is manufactured consistently to meet the product release specifications at each of the proposed sites of manufacture. Results for a minimum of three pilot or production scale batches of the product should be provided. The data should include test results for all parameters listed in the product specifications.

If applicable, the nanoscale properties of the product should be demonstrated.

**Stability data**

You should provide stability data to allow us to assess how the product varies over time under a variety of conditions, such as temperature, humidity, light and heat. VICH GL3(R), GL4, GL5, GL8, GL17 and GL45 provide information on stability design and testing protocols. Because veterinary chemical products are date controlled, a suitable shelf life should be proposed based on the stability of the product in an Australian climate. Australia has climatic conditions encompassing VICH zones I to IV.

Data from stability studies should be provided on a minimum of three pilot or production scale batches of the product. The batches should be manufactured at the nominated site of manufacture. The product should be tested in the same containers (packaging material) and with the same closure system as proposed for registration.

The product label storage instructions relevant to an Australian climate and the recommended temperature and relative humidity design for stability tests are as shown in Table 1.

<table>
<thead>
<tr>
<th>Storage instruction on the product label</th>
<th>Real-time stability test protocol</th>
<th>Accelerated stability test protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store below –18 °C (Deep freeze)</td>
<td>–20 °C ± 5 °C</td>
<td>Not appropriate</td>
</tr>
<tr>
<td>Store below –5 °C (Freeze)</td>
<td>–20 °C to –5 °C ± 5 °C</td>
<td>Not appropriate</td>
</tr>
<tr>
<td>Store between 2 °C and 8 °C (Refrigerate. Do not freeze)</td>
<td>5 °C ± 3 °C</td>
<td>25 °C ± 2°C/60% RH ± 5% RH</td>
</tr>
<tr>
<td>Store below 8 °C (Refrigerate)</td>
<td>5 °C ± 3 °C</td>
<td>25 °C ± 2°C/60% RH ± 5% RH</td>
</tr>
<tr>
<td>Store below 25 °C (Air conditioning)</td>
<td>25 °C ± 2°C/60% RH ± 5% RH</td>
<td>40 °C ± 2°C/75% RH ± 5% RH</td>
</tr>
<tr>
<td>Store below 30 ºC (Room temperature)</td>
<td>30 °C ± 2°C/65% RH ± 5% RH</td>
<td>40 °C ± 2°C/75% RH ± 5% RH</td>
</tr>
</tbody>
</table>

You should provide a statistical analysis of the stability data in accordance with VICH GL51. The guideline provides recommendations on establishing the shelf life for products intended for storage in climate zones I and II only. You should ensure that the stability data provided are appropriate to support the shelf life of the product under Australian climate conditions (I–IV).

The need for stability overages of constituents in the product should be supported by the statistical analysis of the storage stability data.

You should provide cold temperature stability data for liquid formulations to allow us to assess any adverse impact. You may, as an alternative, consider a label statement warning against exposure to storage at low temperature (for example, freezing).

You should provide stability data after the first opening of the container for parenteral and other sterile products in multi-dose containers to allow us to assess the in-use stability of the product/packaging. You may, as an alternative, consider a label statement that instructs the user to discard any unused product within 24 hours of first broaching the container or in the case of eye and ear preparations four weeks after first opening the container.

You should provide stability data for products that are reconstituted or diluted before use and are claimed or implied to be stable when stored for a certain period.

**You should provide stability data for products that are reconstituted or diluted before use and are claimed or implied to be stable when stored for a certain period.**

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A shelf life can be approved for certain product types under certain circumstances without stability data being provided. The situations in Table 2 may be applicable.

<table>
<thead>
<tr>
<th>Product type</th>
<th>Formulation type</th>
<th>Storage condition</th>
<th>Shelf life (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minerals (excluding parenteral products)</td>
<td>Liquid</td>
<td>Below 30 °C (Room temperature)</td>
<td>18</td>
</tr>
<tr>
<td>Minerals (excluding parenteral products)</td>
<td>Solid</td>
<td>Below 30 °C (Room temperature)</td>
<td>24</td>
</tr>
<tr>
<td>Vitamins (excluding parenteral products)</td>
<td>Liquid</td>
<td>Below 25 °C (Air conditioning) and protected from light</td>
<td>12</td>
</tr>
<tr>
<td>Vitamins (excluding parenteral products)</td>
<td>Solid</td>
<td>Below 25 °C (Air conditioning) and protected from light</td>
<td>12</td>
</tr>
<tr>
<td>Vitamins and minerals (excluding parenteral products)</td>
<td>Liquid</td>
<td>Below 25 °C (Air conditioning) and protected from light</td>
<td>12</td>
</tr>
<tr>
<td>Vitamins and minerals (excluding parenteral products)</td>
<td>Solid</td>
<td>Below 25 °C (Air conditioning) and protected from light</td>
<td>12</td>
</tr>
<tr>
<td>Existing active constituent already used in a registered product of non-food producing species—ornamental fish, aviary birds and rodents</td>
<td>Liquid</td>
<td>Below 30 °C (Room temperature)</td>
<td>18</td>
</tr>
<tr>
<td>Existing active constituent already used in a registered product of non-food producing species—ornamental fish, aviary birds and rodents</td>
<td>Solid</td>
<td>Below 30 °C (Room temperature)</td>
<td>18</td>
</tr>
<tr>
<td>Therapeutic pet food</td>
<td>Dry</td>
<td>Below 30 °C (Room temperature)</td>
<td>12</td>
</tr>
<tr>
<td>Therapeutic pet food</td>
<td>Canned</td>
<td>Below 30 °C (Room temperature)</td>
<td>24</td>
</tr>
<tr>
<td>Herbal and marine-derived complementary animal health product</td>
<td>Liquid</td>
<td>Below 30 °C (Room temperature)</td>
<td>12</td>
</tr>
<tr>
<td>Herbal and marine-derived complementary animal health product</td>
<td>Solid</td>
<td>Below 30 °C (Room temperature)</td>
<td>18</td>
</tr>
<tr>
<td>Equine oral electrolyte</td>
<td>Solid</td>
<td>Below 30 °C (Room temperature)</td>
<td>36</td>
</tr>
</tbody>
</table>

You should demonstrate the nanoscale stability of the product, if applicable.

You should note that the approved shelf life for the product will only be based on the stability data provided at the time of the application. A commitment to continue the stability studies is not sufficient to support a longer shelf life.

### Analytical method and validation data

You should provide analytical method and validation data to allow us to assess the quality and adequacy of the control processes. Harmonised methods, such as those found in the European, United States and Japanese pharmacopoeia, should be used where applicable. A full description of the analytical procedures used for testing of the product should be provided, including:

- full details of the analytical methods (including method numbers)
- the purity of the reference standards
- where chromatographic and spectroscopic techniques are used, representative chromatograms and spectra of the reference standard, veterinary chemical product and placebo, labelled with batch number, peak identity and peak integration data (if appropriate)
- worked examples of the calculations.
Method validation data should be provided to allow us to assess the suitability of the method for its intended use. Details of the validation of analytical procedures are provided in VICH GL1 and GL2. Typical validation characteristics that should be considered for validation are in VICH GL1.

If we have assessed the analytical methods in a previous application, you may reference the data provided in that application. However, if the formulations are not identical, you should provide specificity and recovery (accuracy) data to demonstrate that the analytical method is appropriate for use on the new formulation.

You should provide the nanoscale aspects of the product analytical methods if they are relevant.

Packaging

You should provide a description of the primary container and closure system, including the composition of the construction materials of each primary packaging component and its specification. The pack size(s) should be provided. Any desiccant or inert gas added to the container for stability purposes should be identified. You should discuss the integrity of the container in terms of its compatibility with the product (including sorption to container and leaching) and its performance in protecting the product physically and in protecting it from moisture and light.

The integrity of the container should not be impaired by the product it contains, nor should the product be adversely affected by the packaging material.

The following content can be found at http://new.apvma.gov.au/node/903
If making a submission, please reference page number: 903

Veterinary—WAAVP guideline for myiasis-causing parasites on ruminants

The World Association for the Advancement of Veterinary Parasitology (WAAVP) is a not-for-profit organisation for scientists who study the parasites of non-human animals. The guidelines, developed by the international expert working groups of the WAAVP, assist in the international harmonisation of standards and procedures for the evaluation of veterinary parasiticides. The WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants aim to standardise the minimum set of data that should be submitted to demonstrate the efficacy of new ectoparasiticides for use on or in ruminants.

The APVMA has adopted the WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants to assist registration holders in the conduct of regulatory trials. The APVMA notes that in some instances the WAAVP guidelines advise consultation with the regulator. We also recognise that because of Australia’s unique environmental and geographic parameters, parasite burdens and their population dynamics, farm management practices and animal breeds, there are some differences between the WAAVP guidelines and the APVMA’s recommendations for efficacy trials for products to be registered in Australia. Therefore, applicants should conduct efficacy trials within Australia under typical farm management practices covering relevant geographical regions and the following additional guidance is provided to assist you in conducting these trials. If you follow this additional guidance, your data should generally be sufficient for the APVMA to assess its confidence in the product’s efficacy given Australia’s unique conditions.


Blowfly species

You should use *Lucilia cuprina* as the target parasite species for a claim for blowfly strike in your efficacy studies.

Field trials

The World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines provide a general recommendation in section 1.3.3.1 that you should select a minimum of two studies in two distinct geographic locations. In section 3.3.2, the WAAVP guidelines provide specific recommendations for field trials with strike flies. The WAAVP guidelines specify that the sponsor must demonstrate that the test product, when used as directed, will be effective for fly strike in a range of geographic environments as well as in animals of different ages, breeds, sexes, wool lengths and so on. The guidelines advise that this will normally involve a minimum of five to 10 well-conducted and strategically located regional field studies where adequate fly challenge is demonstrated. The APVMA clarifies and confirms that you should refer to section 3.3.2 for guidance on the numbers of trials, locations and types of animals when you conduct field studies for blowfly strike.

The WAAVP guidelines recommend that you include a negative control group in field trials to demonstrate adequate fly-strike pressure. We consider that as an alternative to including a negative control group in field trials, you may provide daily rainfall data, temperature data and fly-trap records of catches of *Lucilia cuprina*, or whatever data demonstrate adequate fly pressure. You should also include at least one positive control group (sheep treated with an appropriate registered product) in the field trials in that case. Hearsay by farmers or local advisory people would not be considered acceptable evidence of fly pressure.

Fly-strike dressings

When assessing fly-strike dressings as treatments against existing strikes, the World Association for the Advancement of Veterinary Parasitology guidelines recommend that the test product should preferably demonstrate efficacy in killing active, advanced third instar field-derived larvae on sheep, as this is the stage most likely to be detected by farmers.

We recommend that the test product *should* demonstrate efficacy in killing active, advanced third instar field-derived larvae on sheep, as this is the stage most likely to be detected by farmers.
Wool or hide damage

Given the importance of the wool and cattle by-product industries to Australian commerce, it is recommended that you collect and submit data on wool staining or damage, hide or skin damage, or damage to animal products.

Veterinary—Guideline for registration of allergenic substances

The “EU guideline on Allergen products: Production and quality issues” lays down the quality recommendations for allergen products of biological origin, including allergen extracts derived from natural source material and allergens produced through recombinant DNA technology, used for specific immunotherapy or in vivo diagnosis of immunoglobulin E (IgE)-mediated allergic.

This guideline is adopted by the APVMA as a guidance for registration of veterinary allergenic products and to be used in conjunction with the APVMA’s Part 8 Efficacy and Safety Guidelines.

Import permit

A copy of the current Department of Agriculture import permit should be included with applications involving imported biological components.

Label

Label warnings relating to concurrent immunosuppressive therapy should be included in the Restraint section of the leaflet. You should review the Veterinary Labelling Code for further guidance on labels.

Veterinary drug residues in food commodities and overseas trade

The Agvet Code provides that before granting an application for a veterinary chemical product, the APVMA must be satisfied that the chemical product meets the trade criteria. This means that if a product is used in accordance with the use pattern on the approved label, it would not unduly prejudice trade or commerce between Australia and places outside Australia.

The legislative requirement to consider the overseas trade aspects of veterinary residues in food commodities is unique to Australia.

Scope

This guidance document is intended to provide recommendations on the type of information that should be provided to enable the APVMA to:

- identify any potential risks to Australia’s export trade associated with the use of a veterinary product
- assess proposed strategies that may be used to mitigate any identified export trade risks
- consult with relevant stakeholder groups (such as peak industry bodies, state departments of agriculture), prior to the public consultation phase of registration, to explore any potential trade risks and the feasibility of any proposed risk mitigation strategies
- conduct a public consultation through either a notice in the APVMA Gazette or a Trade Advice Notice (TAN).

Identification of potential risks to Australia’s export trade

Most of Australia’s trading partners have established maximum residue limits (MRLs). These are also known as ‘tolerances’ in some countries if the drugs have approved uses for veterinary drug residues in food commodities in those countries. MRLs can vary from country to country due to different use patterns and other factors. In some countries, particular veterinary medicines may not be registered and MRLs may not have been established; these countries may have a zero tolerance for residues of these chemicals. Consequently, the legitimate use of a drug in Australia according to the use pattern on the APVMA-approved label can result in residues in food that exceed the MRLs or tolerances of importing countries, even though the residues are below the Australian MRL.

Commodities considered in the trade assessment

The food-producing animals listed in Table 1 are animals from which major export food commodities are derived. They have been selected on the basis of both the dollar value of trade (more than A$100 million per annum) and the potential impact that the presence of residues in a food commodity could have on Australia’s total export trade. Where an application is made for a veterinary product to be used on or on any of the food-producing animals listed in Table 1, and an MRL is required to be established or amended, a trade assessment will be performed.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Food commodity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquatic species</td>
<td>Crustaceans: crabs, prawns, lobsters etc. Fin fish Molluscs: clams, mussels, oysters, squid, scallops, abalone</td>
</tr>
<tr>
<td>Bees</td>
<td>Honey</td>
</tr>
<tr>
<td>Cattle</td>
<td>Meat, milk, processed dairy commodities</td>
</tr>
<tr>
<td>Goats</td>
<td>Meat, milk</td>
</tr>
</tbody>
</table>
Overseas trade information data package

You should submit information to demonstrate that when the veterinary product is used as proposed and relevant residue-management strategies are followed, residues in food commodities will comply with residue standards that currently apply in relevant export markets.

Each area in this guideline should be addressed. If information is not provided, an explanation of why it has not been provided should be included (for example, ‘not relevant’ or ‘no information available’).

If the proposed use of the veterinary product is expected to result in quantifiable residues in more than one food commodity, and the information to be submitted is different for each affected commodity, you should provide separate trade information for each commodity; for example, cattle meat and cattle milk.

The trade assessment

The potential risks to Australia’s export trade in commodities from animals treated with the veterinary drugs are assessed as part of the residues assessment.

The purpose of the trade assessment is to:

- consider any potential risks to Australia’s export trade associated with the use of a veterinary chemical product
- assess proposed strategies that may be used to mitigate any identified export trade risks
- consult with relevant stakeholder groups (such as peak industry bodies, state departments of agriculture) prior to the public consultation phase of registration, to explore any potential trade risks and the feasibility of any proposed risk mitigation strategies.

The timeline for the trade assessment depends on whether you have authorised us to release trade information at a relatively early stage of the assessment process. If you authorise early release of trade information, we are able to consult with relevant stakeholders before completing the residues evaluation report.

In this case, the trade component of the evaluation report is more advanced than when consultation is restricted to the post-assessment period. We still conduct a public consultation phase post assessment, but the extent of feedback is more informed, due to early engagement of stakeholders. For these reasons, early release of trade information facilitates the resolution of any identified trade risks.

If you do not authorise early release of trade information, we can only undertake consultation with stakeholders after completion of the residues assessment. After the consultation period, we consider submissions we have received as a result of public consultation, and prepare a supplementary assessment taking into account the comments of stakeholders.

Early release of trade information

We can release trade information for consideration by authorities and stakeholders during the assessment of the application (ie before public release) to facilitate the public consultation process. However, you must give your consent for us to do this. You should clearly state whether you give permission for early release of trade information.

Strategies to mitigate identified trade risks

There is a range of strategies you may propose to mitigate the potential trade risks identified. In considering proposals to minimise and manage identified trade risk you should take into account:

- inconsistencies between Australian MRLs and the import tolerances of overseas trading partners
- the capacity of affected industries to implement strategies to minimise and manage the risk to trade
- methods for communicating trade advice to product users.

Strategies to manage these matters can include:

- the establishment and effective communication of export slaughter intervals (ESIs)
- the establishment of import tolerances
- making a maximum residue limit submission to Codex for the establishment of an appropriate Codex MRL
- industry-specific management strategies.

When developing proposed strategies for communicating trade advice, you should consult with the user industry and any other affected industries. We will take particular note of how the applicant’s proposed communication strategy integrates with industry measures to manage trade risks. A statement on the veterinary chemical product’s label may be the only means of alerting the user to the possibility of trade risks arising from use of the product.

Export intervals and export slaughter intervals

The ESI is the primary tool used to mitigate trade risks for food commodities derived from livestock that are slaughtered. The ESI is the minimum period of time that should elapse between the last treatment of an animal with a veterinary product and the slaughter of that animal for export.

The export slaughter interval is not the same as the Australian withholding period

The Australian withholding period (WHP) is the minimum period that needs to elapse between the last administration of a veterinary product to an animal, and the slaughtering of the animal or the collection of milk, eggs or honey from the animal for human consumption. The withholding period

<table>
<thead>
<tr>
<th>Pigs</th>
<th>Meat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poultry</td>
<td>Meat, eggs</td>
</tr>
<tr>
<td>Sheep</td>
<td>Meat, milk</td>
</tr>
</tbody>
</table>
ensures that edible commodities from treated animals contain residue levels below the MRL. WHPs are intrinsically linked to food safety.

In contrast, ESIs are an important component of the APVMA being satisfied that use of the product would not result in undue prejudice to trade. The ESI is the minimum period that must elapse between last administration of the veterinary product to an animal (including medicated feed), and slaughter for export. ESIs are used to manage trade risks, ensuring that exported food commodities meet the most sensitive MRL, import tolerance or other requirement set by a major trading partner. For any one product, the ESI may be the same as, or longer than, the product WHP.

**Establishing export slaughter intervals**

ESIs for veterinary drugs are established on the basis of residue-depletion data. Studies should be conducted with the formulation that is to be marketed in Australia, and animals should be treated in accordance with the critical use pattern specified on the product’s label.

Residues data should support the establishment of an ESI. The data should show depletion of the veterinary drug down to the lowest MRL, import tolerance or other requirement of the major trading partners for the relevant food commodity. Where it is identified that some of the major trading partners have not set an MRL for a particular veterinary drug, the ESI will be based on the time required for residues to deplete to the limit of quantification of an appropriately validated analytical method. We do not accept the use of extrapolation of residues data beyond the sampling points when determining an ESI.

**Communication of trade advice to users**

A trade submission should show how communication of trade advice will be provided for all stakeholders in all relevant food commodity production chains. The communication of trade advice can include ESIs or generic export statements on labels, supported by any or all of the following:

- an entry in the APVMA’s ESI website databases for:
  - cattle and/or
  - sheep.
- ESI information records associated with:
  - Livestock Production Assurance National Vendor Declaration forms
  - PigPass National Vendor Declaration forms
  - The National Livestock Identification System database
- information in a brochure supplied by the registration holder
- information obtained through the registration holder company’s information phone line or website.

**Trade advice on product labels**

Trade-advice statements are intended to alert the user to possible trade risks associated with their use of the product, and to provide sources of further information to identify and manage the trade risks.

The APVMA and commodity industries support the free availability of information on ESIs. All methods of promoting and communicating ESIs are encouraged, including:

- information on the product’s label
- education campaigns
- website listings
- publication of lists
- point-of-sale material
- quality assurance programs
- vendor declarations.

Strategies for the communication of ESIs should achieve the following:

- integration with strategies already implemented by users which minimise trade risk measures
- integration with strategies already implemented by commodity industries which minimise trade risk measures
- facilitation of an effective whole-of-chain communication of trade information.

Trade-advice statements are established for all products used in or on cattle, sheep and pigs. Products for use in or on other food-producing (meat) species (such as aquatic species, goats etc.) may also have trade advice and ESIs assigned to them.

In consultation with industry stakeholders, we have developed a number of ESI statements for inclusion on veterinary product labels. For further information on the label statements, refer to the Veterinary Labelling Code.

**Maximum residue limits in overseas countries**

For assistance in ascertaining the MRLs that apply in overseas countries or the Codex MRLs, you should visit the following websites:

- European Medicines Agency—European Public MRL Assessment report (EPMAR)
- Japan’s Ministry of Health, Labour and Welfare
- US Food and Drug Administration—Code of Federal Regulations Title 21
- FAO/WHO Food Standards Codex Alimentarius Commission—Veterinary Drug Residues in Food

The following content can be found at http://new.apvma.gov.au/node/746

If making a submission, please reference page number: 746

**Veterinary—Food safety studies for veterinary drugs used in food-producing animals**
Information guidelines and standards

This guideline is based on the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products guideline (VICH GL48), one of a series of guidelines developed to facilitate the mutual acceptance of food-safety (residue) data for veterinary drugs used in food-producing animals. This guideline was prepared after consideration of the current national and regional requirements and recommendations for evaluating veterinary drug residues in the European Union, Japan, the United States, Australia, New Zealand and Canada.

While VICH GL48 covers many of the Australian recommended considerations in terms of food-safety studies performed to determine the maximum residue limit and the withholding period, there are some additional considerations that are unique to Australia. These additional food-safety considerations are detailed in this document.

Objective of this guideline

As part of the approval process for veterinary chemical products in food-producing animals, food-safety (marker-residue depletion) data are used to establish maximum residue limits, demonstrate compliance with existing maximum residue limits, determine appropriate withholding periods and determine export slaughter intervals. The food-safety studies submitted to support registration or approval of a new veterinary medicine product in the intended species should:

- demonstrate the depletion of the marker residue upon cessation of drug treatment to the regulatory safe level (that is, the maximum residue limit) in edible tissues including meat, milk and eggs
- generate data suitable to determine appropriate withdrawal periods to address consumer safety concerns in edible tissues including meat, milk, eggs and honey.

This guideline provides study-design recommendations to help you generate food-safety data to satisfy the data recommendations for establishing maximum residue limits and recommending appropriate withdrawal periods for a specific product.

Scope of this guideline

When you conduct food-safety studies according to the recommendations described in this guideline, you should generate adequate data to determine maximum residue limits and establish withholding periods. The guideline encompasses the most common food species, namely cattle, pig, sheep and poultry, as well as bees and fish. The principles in this guideline can also be applied to other less common or novel food-producing animals.

Food-safety studies

Test product

The test product used for the study should be representative of the commercial formulation. Test product manufactured in accordance with good manufacturing practice (pilot scale or commercial scale) is the preferred source of test article.

The test product should be formulated to the top of its specified range of active constituent content and should be applied according to the proposed label directions. If there is more than one application method, separate trials or valid scientific argument may be necessary.

Trial design

General guidance

You should conduct food-safety studies in conformity with the Organisation for Economic Co-operation and Development’s principles of good laboratory practice, and follow internationally-recognised and regularly updated test protocols. In addition, you should provide the following detailed information where applicable:

- the species, breeds, strains or source of the test animals used
- the number, age, sex, body weight and production status of the dosed animals, including growth rate and milk, egg or honey yield
- the animal husbandry conditions; namely the water and food consumption of individual animals (especially for veterinary chemical products administered via drinking water and/or feed)
- details of the formulation of the administered veterinary chemical product and method of dose preparation
- details of the mode of dose administration—dose (in milligrams per kilogram of body weight), frequency of dosing, and duration.

The food-safety study should be conducted with previously unmedicated animals that are representative of the proposed target populations. Animals of both sexes should be used if a product is intended for use in both female and male animals. After animals have been treated with the veterinary chemical, edible tissues and biological fluids should be collected at appropriate times for residue analysis. The groups of animals used should be large enough to allow statistical assessment of the residues data.

Treatment regimens can be broadly classed as:

- Single treatments, where a veterinary chemical product is given once to an animal for a specific therapeutic effect. In this case, a single dose of veterinary chemical product (at the maximum dose rate) is the appropriate exposure regimen during residues trials.
- Repeat treatments, such as endo- or ecto-parasiticide treatments, where a single treatment is repeated. If a repeat dosage regimen can be reasonably anticipated in practice, then repeat treatments should be considered.
- Short-term treatments, where animals are dosed for a number of days, on one or more occasions. In this case, test animals should be dosed for the maximum period permitted on the label. Where the re-treatment interval is short, or the veterinary chemical has a propensity to remain in edible tissues, residue trials may need to incorporate multiple treatment periods at the shortest proposed re-treatment interval.
- Long-term treatments, where animals are treated for prolonged periods, for example medicated feed or water treatments, and where a zero day withholding period is desired. In this case, animals should be treated at the maximum proposed rate for a period that is sufficient to enable the residue concentrations in edible commodities to reach a steady-state equilibrium (that is, for the residue concentrations in tissues to reach a plateau).

Food-safety studies should characterise enough of the decline profile to enable the necessary withholding periods to be recommended with confidence. Australia does not subscribe to the concept of a ‘practical zero withdrawal period’. So, if a zero-day withholding period is being sought,
Information guidelines and standards

one of the sampling times should be at zero hours after withdrawal, and the residues data should demonstrate compliance with the relevant maximum residue limits at all times after treatment.

Residues data from a well-designed residues decline trial are also likely to be used to determine an export slaughter interval for the product. To establish the export slaughter interval, it may be necessary for you to monitor the residues decline profile until it reaches concentrations below the maximum residue limit or the limit of quantification.

Dairy Animals

In any submission for registration, you should address three aspects unique to dairy cows:

- the possibility of a treated dry cow re-joining the milking herd prematurely, soon after dosing, and her milk entering the farm milk supply
- the occurrence of residues in calves as a result of access to milk from treated cows, either from suckling during the first few days post-partum or being fed discarded milk
- the occurrence of in utero drug transfer resulting in tissue residues in calves.

These principles also apply to studies involving goats and sheep.

Food-safety studies should establish the minimum recommended treatment-to-calving interval during which application or administration of a product is appropriate. Normal animal husbandry practices should be considered. Pre-calving intervals that approximate the period between drying off and calving increase the risk of violative milk residues, should cows calve early.

When milk is destined for human consumption or for feeding to calves destined for human consumption, the study should also establish the maximum period post-partum when milk could contain residues greater than the maximum residue limit. As most calves destined for human consumption are allowed to suckle their dams or consume milk taken from treated cows, tissue residues in calves should be addressed by residues data or valid scientific argument.

When determining maximum residue limits in milk, the potential effects of antimicrobial substances on microorganisms used in the manufacture of dairy products are also considered. Therefore, you should consider the effect of antimicrobial substances on the activity of dairy starter cultures when performing trials for antimicrobial products for use in dairy cows. The determination of the maximum concentration without effect for an antimicrobial substance on a starter culture is based on the guidelines established by the European Agency for the Evaluation of Medicinal Products—Committee for Veterinary Medicinal Products (2000).

Sheep ectoparasiticides

Food-safety studies for sheep ectoparasiticides involve many variables, including application technique, wool length at the time of treatment, animal type and environmental conditions. However, the studies should result in tissue residues as high as could be expected when the product is used according to label directions (the maximum residue scenario). Residues in wool may also need to be considered. For further information refer to the residues in wool guideline.

For plunge and shower dips, you should:

- use fine- or medium-wool merinos in store condition to achieve a maximum residue scenario
- dip sheep four to six weeks after shearing
- thoroughly mix plunge dips and spray dip tanks prior to use
- make sure the trial sheep are the first animals to pass through the dip
- take samples of the dip wash from the dip tanks immediately before and after treatment of the trial animals; determine and report the pesticide concentration
- make sure the dip concentration used during the trial approximates the maximum concentration expected under any top-up or reinforcement system of dip solution replenishment
- achieve 100 per cent wetting of the sheep to the skin. Common dry spots include behind the ears, around the neck and along the backbone for plunge dips and under the neck and along the flanks from the shoulder to the hip for shower dips. Report wetting at the common dry spots for 10 sheep from each treatment
- report dip design and dipping procedure.

For jetting trials, you should:

- use fine- or medium-wool merinos in store condition to achieve a maximum residue scenario
- aim to achieve complete wetting to the skin over the target area
- describe the equipment and procedure used
- only use hand jetting
- report wetting to skin level under the treated area for 10 sheep from each treatment.

For off-shears treatments, short-wool and long-wool pour-ons, backliners and spray-ons, you should:

- use both a combination of fine- to medium-wool merinos (in store condition) and second-cross lambs
- calibrate the application equipment just before use in the trial
- unless otherwise recommended by label directions, apply off-shears treatments within 48 hours of shearing
- perform trials using sheep with six months' wool growth to demonstrate the worst case for residues.

For wound dressings, treatment of fly strike commonly involves the application of the product to open wounds, increasing the likelihood of systemic absorption. In this circumstance, dosing of healthy sheep is not appropriate and there are significant animal welfare issues associated with the use of fly-struck sheep. Consequently, if the product is also to be registered for use as a jetting or dipping solution, specific data relating to its use as a wound dressing may not be necessary. If use as a wound dressing is the only use proposed for the product, you should conduct residues trials with the proposed product.

Poultry

Within Australia, poultry may be farmed using a cage system, a free range system, or a barn or deep-litter system. The management and husbandry practices employed in each system will influence the way chemicals and drugs are administered, and the way any resulting residues are managed. The design of food-safety studies for veterinary chemicals used in the production of poultry should consider the type of poultry farm, the intended
function of the birds, the developmental stage of the birds at the time of treatment and the route of treatment or medication.

The question of whether poultry are to be used as broilers, breeders or layers is fundamental to the design of residue trials, as it will determine the samples collected for residues analysis. Current industry practices should also be considered. For instance, both tissue and residues data should be generated from treated breeder birds if birds or eggs that are culled from the breeding programs are to enter the food chain. Residues data from the first eggs collected for human consumption should be provided for products used to treat pre-lay replacement pullets after sexual maturity (more than 12 weeks of age). Similarly, residues-decline data in eggs should be provided for treatment of pullets at the point of lay (that is, around 17 weeks), or for treatment of adult layers.

The method of administration, formulation type and extent of activity of a product will determine the design for food-safety studies. However, studies should endeavour to address the worst-case residue scenario, that is to say the maximum consumption or dose of medication. The following paragraphs detail some factors to be considered for specific routes of treatment or medication.

- Medicated drinking water: Administration via the drinking water is often preferable because domestic poultry will drink when they will not eat. However, fluid intake by the birds may vary due to the weather, to the ease of access or hygiene of drinking water dispensers, or to the unpalatability of the medicated water. Consequently, you should report the quantity of medicated water consumed by birds during residue trials, to determine the actual dosage received. You should also give consideration to the composition of the watering system or containers and the quality of the actual water. Galvanised metal may result in chelation of the drug with metal ions. Other materials may lead to adsorption of the drug onto the container surface. Chelation of the drug may also occur when ‘hard’ water is used to prepare the medication, and the use of chlorinated or otherwise sanitised water may destroy the medication. Each of these factors may result in a reduction of the intended dose delivered to the birds. Therefore, when the drug is to be administered in the water, samples of the medicated water should be collected and analysed to confirm the drug concentration.

- Feed additives: Feed additives, incorporated into pellets, crumble or mash, are commonly used in the mass medication of poultry, particularly when the physicochemical properties of the drug make it insoluble in water. Variations in feed consumption are associated with hot or cold weather; housing changes; breed, type, strain and age of bird; body weight; rate of lay; energy and fibre content of feed, and particle size of feed ingredients. These factors may alter the level of feed consumption by 10–20 per cent, thereby altering the effective dose rate (in the feed) by an equivalent percentage. Therefore, it is important that the quantity of medicated feed consumed by birds during residue trials be reported, to enable determination of the actual dosage received. It should also be noted that absorption of the drug by treated birds may be unpredictable because it may bind to feed ingredients. Also, the milling process may affect the stability of the drug, as pelleted feeds may be subjected to high temperatures, which may cause breakdown of the active constituents. Therefore, it is important to conduct residue studies using the predominant feed form (pellet, crumble or mash), and to analyse samples of the medicated feed for their drug content before and after milling or processing.

Bees

When designing a food-safety study for determining residues in honey, one trial involving a representative floral type should be conducted under conditions of good honey flow.

You should collect pre-treatment samples of honey from all hives from the brood nest and the super, and store and analyse them individually to determine if the test chemical is present. You should conduct and report cleaning validation. For example, after use, the extractor, uncapping knife, honey tank, bucket and the pipe from the extractor should be thoroughly cleaned using a high-pressure water cleaner, then washed with hot water, and finally dried. The honey from eight frames of an untreated control hive should then be extracted and the honey that drains from the extractor collected and poured over the internal walls of the previously-cleaned holding tank. A sample of this honey should be collected for assay to confirm that the equipment is free of any residual chemicals.

Aquatic animals

Within the aquaculture industry, withholding periods are typically expressed in terms of ‘degree days’—for example, a withholding period of 500 degree days is equivalent to 50 days at 10 °C or 25 days at 20 °C. This approach is used because water temperature may affect the rates of growth and residue depletion in the treated species. Consequently, you should record water temperature throughout all residue-decline trials conducted with aquatic species.

Animals and animal husbandry

General guideline

Generally, one food-safety study should be performed in pigs, sheep and poultry. For cattle, a single study in beef cattle could be applied to dairy cattle (or vice versa). However, because of differences in ruminant and pre-ruminant physiology, separate studies are recommended when the target species encompasses both adult and pre-ruminating animals. You should also do a separate study to demonstrate the residue-depletion profile in milk of dairy animals or in eggs produced by laying hens.

The food-safety study should take into account all factors that may contribute to the variability of residue levels in animal commodities. Factors such as animal breeds and physical maturity should be considered within the pool of animals included in the study without warranting an increase in the number of animals.

Animals should be healthy, identified individually and should not have been previously medicated. However, it is recognised that animals might have received biological vaccinations or prior treatment; for example, with anthelmintics. In the latter case, an appropriate wash-out time should be observed for the animals prior to enrolment in the actual study. Study animals should be representative of the commercial breeds and representative of the target animal population that will be treated. You should report on the sources of the animals, their weights, breeds, health statuses, ages and sexes.

Animals should be selected such that their age and body condition will not cause underestimation of residues. For example, residues of a fat-soluble compound could be diluted by applying the product to fat animals, or unduly concentrated by application to very lean animals. Coat length and body surface area to body-mass ratios are other factors that may require consideration depending on the product. Store condition animals are preferred.

Animals should be allowed adequate time to acclimatised and normal husbandry practices should be applied where possible. The feed and water supplied to the animals should be free from other drugs or contaminants and you should ensure adequate environmental conditions that are consistent with animal welfare requirements.
Food-safety studies for dairy commodities

After treatment, all dairy animals should be kept together according to the normal husbandry practices on the farm, except where the test treatment is externally applied to only part of the herd. In this case, the treated animals should be physically separated from the remainder of the herd. This is to ensure that licking and other direct contact does not affect absorption and subsequent excretion into the milk, and to prevent contamination of the remainder of the herd.

For studies using intra-mammary products, all animals should have visibly healthy udders, free from the effects of chronic mastitis. For dry-cow studies, pregnant animals with a predicted parturition date should be introduced into the study facility well in advance of study enrolment.

Food-safety studies for poultry commodities

The birds used in food-safety studies should be healthy, and sourced from contemporary, commercial genotypes. No concomitant drug therapy should be used on any bird or pen during the study. Animal housing, feeding and care should follow recommendations for welfare, including vaccination according to industry practices. The housing conditions for birds (that is, pen areas, stocking densities) should reflect commercial practices in the geographical location of the study, and take into consideration seasonal variations in temperature and the weight of the birds. Likewise, the number of birds per feeder or waterer should reflect commercial practices.

Food-safety studies in bees

The colonies used in food-safety trials should be standardised in terms of adult bee populations and brood. The hives should be uniquely identified and allocated to a treatment group; untreated control hives are not necessary. The hives are typically arranged in a row-column configuration and should be located to mimic the conditions found at the time of the year when apiarists would normally treat hives with the particular chemical.

Food-safety studies in aquatic species

Animals should be representative of the commercial species and of the target animal population that will be treated. You should report on the sources of the animals, their weights, health statuses, and their ages or developmental stages. The body-weight ranges should be consistent with the product label and appropriate for the proposed use. For example, if the product is intended for market-sized fish then you should use market-sized fish.

The table below classifies fish into groups based on taxonomic order. An "all fish" claim could be obtained by conducting one study in each of the groups.

<table>
<thead>
<tr>
<th>Order</th>
<th>Representative species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmoniformes*</td>
<td>Coho salmon (Oncorhynchus kisutch); Rainbow trout (Oncorhynchus mykiss)</td>
</tr>
<tr>
<td>Cypriniformes</td>
<td>Carp (Cyprinus carpio)</td>
</tr>
<tr>
<td>Perciformes</td>
<td>Yellowtail (Seriola quinqueradiata)</td>
</tr>
<tr>
<td>Scorpaeniformes</td>
<td>Mebaru or rockfish (Sebastes inermis, Sebastes cheni, Sebastes ventricosus)</td>
</tr>
<tr>
<td>Siluriformes</td>
<td>Channel catfish (Ictalurus punctatus)</td>
</tr>
<tr>
<td>Osmeriformes</td>
<td>Ayu or sweet fish (Plecoglossus altivelis)</td>
</tr>
<tr>
<td>Anguilliformes</td>
<td>Eel (Anguilla japonica)</td>
</tr>
<tr>
<td>Pleuronectiformes</td>
<td>Bastard halibut (Paralichthys olivaceus); Summer flounder (Paralichthys dentatus)</td>
</tr>
<tr>
<td>Tetraodontiformes</td>
<td>Japanese pufferfish (Takifugu rubripes)</td>
</tr>
</tbody>
</table>

* Salmoniformes provide the worst-case scenario, as rearing conditions are the minimum water temperature across this group of fish. Therefore, you should conduct one residue depletion study performed at the minimum water temperature in Salmoniformes to gain approval for all the fish orders in this group.

You should conduct studies in an environment that mimics commercial conditions such as water flow and exchange rates, water temperature, water quality and light. The water quality should be the same quality and quantity that is appropriate for the animal’s developmental stage, and the water temperature should be recorded daily. The housing should be representative of commercial growing conditions. If more than one housing condition is used commercially, you should select the housing condition that results in maximum tissue residues for the study. Animals should be fed both the quality and quantity of food appropriate for their stage of development and to ensure adequate nutrition and growth, as seen in commercial conditions.

Number of animals

General guidance

You should use a large enough number of animals to allow a meaningful assessment of the data. From a statistical point of view, residue data from a minimum of 16 animals, with four animals being sacrificed at four appropriately distributed time intervals, are recommended. Larger numbers of animals should be considered if the biological variability is anticipated to be substantial, as the increased numbers may result in a better-defined withdrawal period. Control (non-treated) animals are not necessary as part of the actual study; however, sufficient amounts of control matrices should be available to test related analytical methods. Generally, for food-safety studies, at least four animals evenly mixed as per sex, for each sacrifice time, are recommended. These animals should be representative of the animals to be treated. Typical bodyweight ranges are around 40 to 80 kilograms for pigs, around 40 to 60 kilograms for sheep and around 250 to 500 kilograms for beef cattle. Non-lactating dairy cows could also be used for food-safety (tissue) studies.

Food-safety studies for dairy commodities—milk

For lactating animal studies, at least 20 animals, randomly selected from a herd where all lactation stages are represented, are recommended. High-yielding animals at an early lactation stage and low-yielding animals at a late lactation stage should be included in the group. The trial should
Information guidelines and standards

Dosing and route of administration

General guidance

You should administer the highest intended treatment dose for the maximum intended duration. It is advised that you consider repeat treatments at the highest application rate, with the shortest interval and maximum number of treatments. Separate studies are appropriate for each formulation type and for each mode of treatment.

If an extended drug administration period is intended, duration of treatment sufficient to reach a steady state in target tissue(s) can be used instead of the full length of the treatment. However, a steady state in all tissues should be confirmed. The time-to-steady-state data are often obtained as part of the total residue study. Where daily or continuous exposure are involved, sampling should show when residues plateau in tissues and milk. You should take samples at an adequate number of time points (3 or 4 generally) at the plateau concentration. This allows the maximum concentration in tissues and milk to be established prior to the commencement of depletion.

Injectable products

Animal treatment should be consistent with the maximum treatment regime specified on the product label, including the volume, location and injection method. For example, if the label specifies 4–6 treatments and a maximum injection volume of 20 millilitres, you should conduct the study using six treatments and administer the maximum volume at the injection site that will be sampled. If the label specifies a dosage range, you should conduct the study using the highest dosage level. For multiple treatments, you should give the injections alternately between left and right sides of the animal. As the maximum injection volume needs to be considered, trials designed specifically for determination of injection site residue depletion are advisable.

Where the withdrawal period will be clearly determined by residue depletion at the site of injection, you generally have the option of collecting data from two injection sites per animal (and using the data from both sites to determine the withdrawal time). This practice can have a positive impact on study design with respect to animal welfare by reducing animal numbers.

An example of this approach is as follows: For a product that utilises only a single injection, treatment can be given on the right side of the neck on day zero and then on the left side of the neck on day four. Euthanasia on day 7 following the final treatment would provide depletion data at seven days’ (left injection site) and 11 days’ (right injection site) withdrawal. In this case, however, collection and assay of the other tissues would not be necessary, as the drug product is intended for administration via a single parenteral route. If the drug product is intended to be administered via more than one parenteral route, you should provide a separate marker-residue depletion study for each route of administration. If the withdrawal period is clearly defined by depletion of residues from the injection site following subcutaneous or intramuscular dosing, a separate intravenous residue study (at the same dose) is not recommended provided the same withdrawal period (for subcutaneous or intramuscular dosing) can be applied to the intravenous route.

Intramammary products

Drug products intended for intra-mammary administration either for lactating animals or for pre-parturition (that is, dry-cow treatment) studies should be given to all quarters (that is, normally four quarters in bovines). It is unlikely that all quarters will be treated with an intra-mammary product during commercial practice; for residue studies this study design represents a worst-case scenario.

For dry-cow (pre-parturition) studies, a minimum of 20 animals is recommended. The study should include randomly selected cows representative of commercial dairy practices. The veterinary chemical should be administered after the last milking (dry-off) and at a time consistent with the proposed treatment-to-calving interval. To reduce variability in the residues data, the pre-calfing period should be tightly controlled and the study should be designed so that enough animals give birth in a limited time interval. This can be accomplished by treating animals with the veterinary chemical based on the expected calving date. For example, for a treatment-to-calving interval of 49 days, residues data should be collected from at least 20 cows calving between 33–49 days after treatment. For a pre-calfing treatment interval of 56 days, residues data should be collected for at least 20 cows calving between 37–56 days after treatment.

Food-safety studies for poultry commodities—edible tissues and eggs

For food-safety (tissue) studies, a sufficient number of birds should be used to obtain at least six tissue samples at each sampling time. The actual numbers of birds used in each trial will depend on the type of residue trial being undertaken and whether pooling tissues from a number of birds (to form composite samples) is necessary to obtain adequate material for analysis (due to the immaturity of the bird, or small organ size). Usually, birds are sacrificed at zero day withdrawal and at three or more later points in time.

For food-safety (egg) studies, a sufficient number of birds should be used to collect ten or more eggs at each sampling time. Eggs from birds within a dosage group may be pooled, if necessary, to form composite samples so that adequate sample weight is available for analysis and retained samples. For composite egg samples, ten groups of laying birds should be treated (each group should contain sufficient birds for at least three eggs per group per day). You should record the numbers and weights of eggs per group per day.

Food-safety studies for bee commodities—honey

It is recommended that a minimum of five hives are used for each treatment at each sampling time. This will facilitate the extraction of honey from an entire super at each sampling point, thereby overcoming difficulties that would otherwise be associated with the variation within a super of honey and chemical residues that may occur in the individual combs. Harvesting honey in this manner also mimics commercial practice.

Food-safety studies for commodities from aquatic animals

Residue data from a minimum of 10 aquatic animals per time point is recommended. Small fish, crustaceans and Mollusca may require a composite sample of multiple animals. In cases where a composite is necessary, sufficient numbers of animals should be collected in order to facilitate assessment of the marker residue. It is recommended that animals should be sacrificed at four appropriately distributed time intervals.

Animal treatment should be consistent with the maximum treatment regime specified on the product label, including the volume, location and injection method. For example, if the label specifies 4–6 treatments and a maximum injection volume of 20 millilitres, you should conduct the study using six treatments and administer the maximum volume at the injection site that will be sampled. If the label specifies a dosage range, you should conduct the study using the highest dosage level. For multiple treatments, you should give the injections alternately between left and right sides of the animal. As the maximum injection volume needs to be considered, trials designed specifically for determination of injection site residue depletion are advisable.

Where the withdrawal period will be clearly determined by residue depletion at the site of injection, you generally have the option of collecting data from two injection sites per animal (and using the data from both sites to determine the withdrawal time). This practice can have a positive impact on study design with respect to animal welfare by reducing animal numbers.

An example of this approach is as follows: For a product that utilise only a single injection, treatment can be given on the right side of the neck on day zero and then on the left side of the neck on day four. Euthanasia on day 7 following the final treatment would provide depletion data at seven days’ (left injection site) and 11 days’ (right injection site) withdrawal. In this case, however, collection and assay of the other tissues would not be warranted since the product was administered contrary to the label (two injections rather than one injection) and as a result residues could be excessively elevated. Such a dosing regimen is designed specifically to determine injection site residue depletion.

If the drug product is intended to be administered via one parenteral route, you should provide a separate marker-residue depletion study for each route of administration. If the withdrawal period is clearly defined by depletion of residues from the injection site following subcutaneous or intramuscular dosing, a separate intravenous residue study (at the same dose) is not recommended provided the same withdrawal period (for subcutaneous or intramuscular dosing) can be applied to the intravenous route.

Intramammary products

Drug products intended for intra-mammary administration either for lactating animals or for pre-parturition (that is, dry-cow treatment) studies should be given to all quarters (that is, normally four quarters in bovines). It is unlikely that all quarters will be treated with an intra-mammary product during commercial practice; for residue studies this study design represents a worst-case scenario.
For pre-parturition (that is, dry-cow treatment) studies, the test article should be administered after the last milking (dry-off) and should be consistent with the desired pre-calving interval.

Ectoparasiticide products intended for cattle

Animals should receive the highest exposure to the pesticide allowed by the proposed label. This means the longest exposure time (maximum time in the dip or spray, ‘thorough coverage’); the maximum amount of material per animal (pour-ons, back-line treatments, dusts); or free access of animals to the material, plus correct placement and recharging (back-rubbers and dust-bags).

The dosing should consider:

- the shortest recommended interval between treatments
- the maximum number of re-treatments in the season per year
- the highest rates of application based on the body weights of the animals.

Products applied without dilution should have an active concentration at or near the top end of product specification. Concentrations in dips should be at the maximum permissible concentration in relation to directions for use on the label. This concentration should be maintained for the trial. The stirrer group should be retained for re-dipping, and animals should be analysed as part of the trial. Due account needs to be taken, on recharging dips and sprays, nozzle types, and pressure and delivery rate of sprays.

You should make an effort to ensure that climatic conditions (for example, rain periods) do not compromise the maximum treatment regime. Rainfall occurring throughout the trial should be reported, as it may confound trial results.

Ectoparasiticide products intended for sheep

Animals should be dosed at the highest milligram per kilogram rate on the label (the highest label rate) regardless of individual animal body weight, with the maximum number of treatments applied at the minimum treatment interval in accordance with label directions. If you use a table specifying doses for defined live-weight groupings, the highest label rate is usually the rate applicable to the animal with the lightest body weight identified in the table. In some instances, the highest rate may be the rate applicable to suckling lambs. Trial sheep should be dosed with the quantity of product required for the heaviest sheep in the group. For dose rates based on time since shearing, the highest dose rate allowed on the label (usually that for the longest wool) should be used.

Application of these treatments should accurately address label directions using the prescribed application equipment and should follow recommended industry practice. The application equipment should be calibrated just prior to use in the trial and, unless otherwise recommended by label directions, off-shears treatments should be applied within 24 hours of shearing.

Bee products

The residue trial design should address the maximum treatment regimen (that is, the maximum dose rate and the maximum number of treatments at the minimum re-treatment interval). The method of applying the chemical in the trial should be identical to the intended commercial use. Chemicals are typically applied to beehives in sugar syrup (wet treatment), caster sugar (dry treatment), or as pest strips suspended in the brood nest. You may need to apply the chemical prior to the commencement of the main honey flow.

Products intended for aquatic species

Studies should address all modes of application and dosing of the veterinary chemical. These may include adding a solution of chemical directly to the water or in feed. You should use the highest dose per application rate that is likely to be used commercially and that is to be listed on the product label. The animals should consume the medicated feed within a short period of feeding so that the product does not leach into the water. To minimise the possibility of under dosing, all the medicated feed should be eaten. Where several treatments are likely, you should use the highest number of applications, with the shortest interval between successive applications.

Animal sacrifice

Animals should be euthanised using commercially applicable procedures and observing appropriate exsanguination times. Chemical euthanasia can be used unless it will interfere with the analysis of the marker residue.

Sampling

General considerations

Following euthanasia, tissue samples in sufficient amounts should be collected, trimmed of extraneous tissue, weighed and divided into aliquots. If the analysis cannot be completed immediately, the samples should be stored under frozen conditions pending analysis. If samples are stored after collection, you bear the responsibility for demonstrating residue stability through the time of assay.

The normal tissues collected for analysis are muscle, fat, liver and kidney. If metabolism studies show that the chemical has a predisposition for another edible tissue, that tissue should also be sampled. Table 2 indicates the recommended samples for collection.

<table>
<thead>
<tr>
<th>Edible tissue</th>
<th>Sample description by species</th>
<th>Edible tissue</th>
<th>Sample description by species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Loin</td>
<td>Muscle</td>
<td>Loin</td>
</tr>
<tr>
<td>Injection site muscle</td>
<td>Core of muscle tissue ~500 g 10 cm diameter × 6 cm deep for intramuscular 15 cm diameter × 2.5 cm deep for subcutaneous</td>
<td>Injection site muscle</td>
<td>Core of muscle tissue ~500 g 10 cm diameter × 6 cm deep for intramuscular 15 cm diameter × 2.5 cm deep for subcutaneous</td>
</tr>
<tr>
<td>Liver</td>
<td>Cross-section of lobes</td>
<td>Liver</td>
<td>Cross-section of lobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For formulations that are able to leave local residues such as dermal pour-on products, samples of relevant tissues (for example, muscle, subcutaneous fat or skin or fat from the application site) should be collected for analysis in addition to those specified in Table 2.

One additional tissue from Table 3 should be selected for residue assay based on the results of the total-residue study. This would typically be the additional tissue with the highest residues or the slowest depletion rate. Only one additional tissue is recommended. For example, if the total-residue study indicates that cattle heart has the slowest depletion rate, heart should be selected for assay in the marker-residue depletion study, but cattle small-intestine marker-residue data are not recommended.

### Table 3: Additional tissues that may need to be collected

<table>
<thead>
<tr>
<th>Edible tissue</th>
<th>Sample description by species</th>
<th>Cattle or sheep</th>
<th>Pigs</th>
<th>Poultry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gizzard</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Entire</td>
</tr>
<tr>
<td>Heart</td>
<td>Cross-section</td>
<td>Cross-section</td>
<td>Entire</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>Composite, rinsed of content</td>
<td>Composite, rinsed of content</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Other tissues</td>
<td>Composite</td>
<td>Composite</td>
<td>Composite</td>
<td></td>
</tr>
</tbody>
</table>

### Injection sites

For parenteral preparations, residue-depletion data from the injection site(s) should be included. Injection site residues are local residues that may or may not remain localised at the site of administration. As such, it is important for you to develop appropriate quality-control sampling procedures that ensure the collected tissue actually encompasses the injection site. Any approach you take should be justified on a case-by-case basis, taking into account the data available and the formulation characteristics. The following methodologies may be considered (regardless of the option selected, the primary core sample should target 500 grams plus or minus 20 per cent):

- Collection of an additional ring sample (300 grams plus or minus 20 per cent) around the primary core sample (500 grams plus or minus 20 per cent). These tissue amounts would generally not apply to small animals that do not allow sampling of 500 grams. For these situations, the optimum sampling strategy should be defined on a case-by-case basis and should be justified. However, collection of two samples (a core and surrounding sample) remains appropriate.
- Collection of an elliptical (or other appropriate shape) sample along the injection track and/or the site of irritation. You should provide evidence that this method correctly targets the injection site residues, such as with accompanying photographs of the site(s) of sampling.

Samples should be collected from the last injection site (or sites), as appropriate. In the case of products requiring multiple injections, the study design should be such that the last injection site will occur on the side of the animal receiving the higher number of injections. When a circular core sample is indicated, collection of the injection site muscle tissue (from large animals) should be centered on the point of injection and consistent with the recommendations shown in Table 2. For injections placed into the base (bottom third) of the ear, collection of neck muscle on the side of the injection, plus cheek muscle and tongue, should be considered.

### Milk

When sampling, all four udder quarters should be milked out, the whole sample mixed thoroughly, and a sub-sample taken. You should determine the fat content of all milk samples analysed to demonstrate the validity of sampling. The time points for sample collection can be suggested by metabolism data. The morning and afternoon samples taken on the same day should be handled and analysed separately (that is, not combined). Milk samples from different animals should not be pooled. Residue analysis should be conducted and reported on whole milk. Records of milk volume and butterfat should be submitted with trial data for the individual cows for the period before and during the collection period.

For multiple-dosed products used in dairy animals, samples should be taken after the last treatment. For products that might qualify for zero-day withdrawal, samples should also be collected during treatment. Duplicate milk samples (200 millilitres each for residue and fat determinations, respectively) should be collected from individual animals:

- at the morning or afternoon milking on the day before treatment, and
- at the morning and afternoon milking on sufficient days after treatment to show the peak and decline of the residues below the appropriate reference point (for example, maximum residue limit or limit of quantitation) as determined by the chemical properties of the drug product.

The partitioning of parasiticides and other veterinary drugs between the aqueous phase and milk fat of whole milk should be considered as the degree of partitioning will determine the importance of the residue concentration in processed milk products such as butter, ice cream and cheese. A partitioning study, involving a minimum of two samples, is best accomplished on samples where residues in milk are at a maximum.

### Eggs

Egg samples should be obtained from 10 or more laying hens at every laying time point during the medication period and after the final medication. Egg samples should be collected after the period necessary to complete egg yolk development, which is usually up to 12 days. Egg white and yolk should be combined for analysis.

### Honey

Information guidelines and standards
Honey from different hives in the same treatment group should be bulked for analysis to reflect the fact that honey is a bulked commodity. All samples of honey should be at least 100 grams. When honey is removed from hives, supers of honey combs from each treatment should be kept together, extracted and bulked in one batch. A portion of the honey from each treatment group should be collected in a uniquely identified pail for future sampling and analysis.

Cross-contamination of honey samples from different treatment groups should not occur and will invalidate the trial results. To prevent contamination from occurring during the extraction process, the extraction plant can be modified to allow honey to be bucketed from the extractor outlet rather than have it run through the pumps and lines.

Aquatic species

Separate samples should be collected from individual animals. If the amount of sample collected from one animal is not sufficient for the assay of marker residue, composite samples from multiple animals may be acceptable.

<table>
<thead>
<tr>
<th>Aquaculture species</th>
<th>Edible tissue type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>Muscle including skin in natural proportions (that is the entire fillet with the overlying skin, without scales, in natural proportions from one side of the fish). The entire sample should be collected, homogenised and subsamples collected from the homogenate.</td>
</tr>
<tr>
<td>Crustaceans</td>
<td>Muscle excluding shell. For species marketed as ‘soft shell’, the entire animal including the unhardened shell is considered as edible tissue. The edible tissue for shrimp includes the mid-intestinal gland.</td>
</tr>
<tr>
<td>Mollusca</td>
<td>Whole animal after removal of the shell</td>
</tr>
</tbody>
</table>

Analytical method for assay of marker residue

You should submit a validated analytical method to determine the marker residue in samples generated from the residue-depletion studies in the edible tissues and where applicable, in milk and eggs. The method(s) should be capable of reliably determining concentrations of marker residue which encompass the appropriate reference point (that is, maximum residue limit) for the respective tissues or products.

For further information on method validation refer to the guideline Analytical methodology.

Reporting of data—outcomes of the food-safety studies assessment

Assessment will involve review of the residue-decline data in the target animal species. Where maximum residue limits need to be determined, these limits should to be set using the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives maximum-residue-limit-setting approach (as adopted by the APVMA on 1 July 2006).

Maximum residue limit determination

The residues-decline data for each edible tissue will be subjected to a regression analysis and the maximum residue limit is determined as a point on the curve describing the upper side 95 per cent confidence limit of the 95th percentile. However, the determination of the maximum residue limit is an iterative process. It involves calculation of the daily dietary exposure levels using the theoretical maximum daily intake except in cases where the use of the estimated daily intake has been shown to be the appropriate approach. This is then reconciled with the health standard (acceptable daily intake). Where the total amount of residues consumed exceeds the acceptable daily intake, further iterations are performed with lower maximum residue limit proposals.

Withholding period determination

The residue-decline data should enable an appropriate withholding period to be determined that will ensure that the concentration of residues will be well below the recommended or established maximum residue limits. The APVMA endeavours to use evidenced-based statistical analyses to establish withholding periods wherever possible. Therefore, the withholding period is determined to be the time point when the residues observed in the food-safety study, using the upper side 95 per cent confidence limit of the 95th percentile, are below the established maximum residue limits in all edible tissues.

Veterinary—WAAVP guideline for biting and nuisance flies on ruminants

The World Association for the Advancement of Veterinary Parasitology (WAAVP) is a not-for-profit organisation for scientists who study the parasites of non-human animals. The guidelines, developed by the international expert working groups of the WAAVP, assist in the international harmonisation of standards and procedures for the evaluation of veterinary parasiticides. The WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants aim to standardise the minimum set of data that should be submitted to demonstrate the efficacy of new ectoparasiticides for use on or in ruminants.

The APVMA has adopted the WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants to assist registration holders in the conduct of regulatory trials. The APVMA notes that in some instances the WAAVP guidelines advise consultation with the regulator. We also recognise that because of Australia’s unique environmental and geographic parameters, parasite burdens and their population dynamics, farm management practices and animal breeds, there are some differences between the WAAVP guidelines and the APVMA’s recommendations for efficacy trials for products to be registered in Australia. Therefore, applicants should conduct efficacy trials within Australia under typical farm management practices.
management practices covering relevant geographical regions and the following additional guidance is provided to assist you in conducting these trials. If you follow this additional guidance, your data should generally be sufficient for the APVMA to assess its confidence in the product’s efficacy given Australia’s unique conditions.


Field trials for buffalo fly

The WAAVP guidelines recommend that you carry out studies in several locations; and that you select a minimum of two studies in each geographic location.

As additional guidance, the APVMA recommends a minimum of four trial sites to be selected from Table 1, which sets out the number, location and timing of field trials for buffalo fly. At least two of these trial sites should be situated in Tropical Queensland, and one in Central Queensland. The fourth site can be located in the South East, or in one of the other areas mentioned. Where the intention is to register the product for use on dairy cattle, a fifth site, located on a dairy farm in one of the regions listed, should also be chosen for an efficacy trial.

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of trials</th>
<th>Area</th>
<th>Timing of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropical Queensland</td>
<td>2</td>
<td>High-rainfall area north of Townsville</td>
<td>November to April</td>
</tr>
<tr>
<td>Central Queensland</td>
<td>1</td>
<td>Bundaberg north to Mackay</td>
<td>December to April</td>
</tr>
<tr>
<td>South East Queensland</td>
<td>1</td>
<td>Buffalo-fly-infested area south of Bundaberg</td>
<td>January to April</td>
</tr>
</tbody>
</table>

Rainfastness

The World Association for the Advancement of Veterinary Parasitology guidelines address rainfastness generally: ‘Where artificial rainfall is used in dose confirmatory studies to test the efficacy of a topically applied test product after heavy rain, the method of wetting used and the equivalent in terms of natural rainfall should be stated (eg artificial rain applied by sprinklers, equivalent to a rainfall of 20 millimetres in a storm lasting 30 minutes). The time of animal wetting before or after test product application should be recorded (eg 0, 2 hours, etc.).’

The APVMA recommends that for trials conducted for buffalo fly, animals should be subjected to the equivalent of 12.5 millimetres over a 10 minute period within two hours of treatment.

Wool or hide damage

Given the importance of the wool and cattle by-product industries to Australian commerce, it is recommended that you collect and submit data on wool staining or damage, hide or skin damage, or damage to animal products.

Veterinary chemical products—Toxicology (Part 3)

Introduction

This chapter sets out the guidelines for submitting toxicology data—or scientific argument in the absence of data—as part of applications for approval of new active constituents, registration of veterinary chemical products, variation of registered veterinary chemical products, or application for permits to use veterinary chemical products.

Toxicology data and/or scientific argument are evaluated by the Office of Chemical Safety (OCS) within the Department of Health. The data and/or scientific argument provide information on the potential human health hazards arising from proposed uses of veterinary chemical products. This information is important in establishing relevant health recommendations for safe use of veterinary chemical products, including:

- acceptable daily intakes
- acute reference doses
- poison scheduling
- first aid instructions
- safety directions
- warning statements
- re-handling statements
- other limitations on use (for example, restraints, restrictions).

Reference materials

We have provided details of documents referred to in this chapter (including codes and standards) in the ‘References’ section, including bibliographic details and, where appropriate, ISBN and purchase information. You should be aware that many of these documents are updated regularly and for this reason we have not supplied dates in the text. Therefore, it is important to ensure that you use the latest edition of reference materials.

VICH guidelines
We have adopted the following relevant guidelines published by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH). These VICH guidelines, which refer to Organisation for Economic Co-operation and Development (OECD) Guidelines for the Testing of Chemicals (see ‘Conduct of studies’), may be useful when you are generating data in support of your application.

The VICH studies to evaluate the safety of residues of veterinary drugs in human food are:

- Reproduction testing: VICH Guideline no. 22
- Genotoxicity testing: VICH Guideline no. 23
- Carcinogenicity testing: VICH Guideline no. 28
- Repeat-dose toxicity (90 days) testing: VICH Guideline no. 31
- Developmental toxicity testing: VICH Guideline no. 32
- General approach to testing: VICH Guideline no. 33

Types of applications

The toxicology data elements that you should address in your application depend on the nature of the application. The nature of the application determines which toxicology data module is appropriate.

Each module has a number of toxicology data elements, which are described in detail in the legislative instrument. A comprehensive assessment comprises a full toxicology data package, containing all of the data elements are listed in ‘Data elements for a comprehensive toxicology submission’. A reduced assessment or limited assessment comprises a subset of the data elements contained in a comprehensive assessment.

Data elements and guidelines

The APVMA assesses the data you generate and submit for evaluation to identify the immediate hazards to the user, and to enable the classification for poison scheduling or to ensure that the poison scheduling remains appropriate, and to set directions for the safe use of the product.

General recommendations

Submission

You should submit toxicology data packages according to the procedures outlined in the regulatory guidelines. Submissions that deviate significantly from the procedures outlined in the regulatory guidelines may be of reduced or no regulatory value.

A template for submission of data for comprehensive assessment of toxicology data or scientific argument in the absence of data is provided below. You may also use this template for reduced assessment and limited assessment by deleting the headings of data elements that are not listed in the relevant module.

The documentation you submit to us should be complete and well organised. It should be presented in sufficient detail to allow independent scientific assessment (for example, you should provide individual animal data when available). You should supply copies of original reports. Summaries, abstracts and published material alone usually do not contain adequate detail for independent scientific evaluation. Data submitted that do not enable independent evaluation may be of reduced or limited regulatory value, or determined to be inappropriate for regulatory purposes.

Your application for approval of a veterinary active constituent or registration of a veterinary chemical product should include all the available toxicological data and address all data elements. The submission should be sufficiently complete to allow a detailed assessment. In certain cases, you may provide scientific argument based on accepted scientific principles or data published in peer-reviewed journals in lieu of submission of toxicology studies.

If you do not believe that a particular data element is necessary, you may request a data waiver. In such cases, you should maintain the data headings and provide a valid scientific argument as to why the data element should not be included. The OCS will determine the regulatory value of scientific arguments for waiver requests based on their merits.

For some applications, certain studies may not be relevant because of the type of active constituent or product being proposed for registration, or because of the specific veterinary situation where the product is intended for use. For example, carcinogenicity testing may not be relevant for an active constituent that is not intended for food-producing use (see ‘Data elements’ for further information).

You should not omit any report that could influence the toxicology assessment of the substance.

Applications and/or assessment involving other regulatory authorities

You should include details of any applications for the same active constituent or product lodged with other regulatory agencies, either in Australia or overseas. Where available, you should provide the same data relied on by the other regulatory agency (noting the general recommendations and guidance outlined in previous sections of this guideline) in determining the results of these applications and coming to subsequent regulatory decisions. Where available, you should also provide any other reports or documentation related to the chemical or product. If use of the chemical or product has been considered unfavourably by an overseas regulatory body, you should provide all details and submit a scientific argument discussing this information in the context of the Australian approval of the active constituent or registration of the veterinary chemical product.

The regulatory agencies across the different chemical sectors in Australia and overseas often operate under differing risk paradigms, and data generated for the purpose of one regulator may not be applicable within other regulatory sectors. You should provide data generated for non-veterinary products such as human medicine. The OCS will evaluate such data on their merits and they may be of reduced or no regulatory value, as data guidelines differ between prescription and over-the-counter human medicines.

Conduct of studies

All toxicity studies should be conducted in accordance with the adopted OECD Guidelines for the Testing of Chemicals or other recognised test guidelines—for example the US Environmental Protection Agency’s Office of Chemical Safety and Pollution Prevention health effects test guidelines, the European Union’s guidelines or the Japanese Ministry of Fisheries and Food guidelines—and in accordance with an acceptable
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n\non-active constituents. However, it is always preferable that you provide studies conducted with the product to be registered.

Similar physicochemical and toxicological properties to the formulation for which registration is sought. Estimates of the potential hazard by (for example, a simple dilution in water, or a tablet formulation in an inert material), or by read-across from a reference product formulation that has similar physicochemical and toxicological properties to the formulation for which registration is sought. These similarities between the two formulations may be due to:

- a common active constituent functional group
- common breakdown products via physical and/or biological processes that result in structurally similar chemicals
- a constant pattern in physicochemical and/or biological properties.

The OCS will determine the regulatory value of scientific arguments for read-across based on their merits and reliability.

Details of studies should follow relevant recognised testing guidelines and data reporting should include, but not be restricted to:

- selection of animal species, housing and feeding conditions, and preparation and randomisation of animals
- a description of study procedure including route of administration, number and characteristics of animals in the main and any interim, satellite or recovery groups; dose selection rationale and dose preparation
- all parameters studied
- the frequency at which parameters were studied
- the duration and frequency of dosing and any recovery period
- the time of administration in relation to the observations and effects observed.

Reports should include detailed results for the individual animals in the studies, together with statistical analyses of results. You should include summary tables or diagrams where these will assist in reviewing data (for example, body weight, haematology, metabolite profile) or where they will permit sets of data to be compared on the same page (for example, those for control and treated animals). Studies should also include summarised reports of histopathological examinations, in tabular form, so that the incidence of observations can be studied in relation to dosage, sex and duration of treatment. You should also provide historical control data, if available.

When undertaking toxicity studies, guidance in toxicology study design can be obtained from the adopted OECD Guidelines for the testing of chemicals, or equivalent recognised test guidelines.

You should include additional toxicological studies on individual metabolites or degradation products in situations where the metabolites or degradation products formed through animal metabolism, photodegradation or other mechanism differ from those identified in mammalian metabolism studies. These studies are used to judge which compounds should be included in the residue definition, and may also be used to assess the risk to humans from a toxic degradation product during application.

**Animal testing**

Experiments involving animals should be conducted using the minimum number of animals necessary to allow statistically valid conclusions to be made. Where available, and according to the ‘3Rs’ principle (replacement, refinement, reduction), we encourage you to submit data that are compliant with adopted OECD test guidelines (or other recognised test guidelines) and were obtained from in vitro assay systems.

Each application should contain complete reports of all animal investigations and in vitro studies. These data should cover each of the elements listed in ‘Data elements for a comprehensive toxicology submission’ that are relevant to the application. You should also provide any available human data.

**Chemistry and manufacture**

Applications that include toxicological data should be accompanied by chemistry and manufacture data. This is because details of the chemical and physical properties of the active constituent, the profile of impurities and the constituents of formulations are important in carrying out a complete toxicological evaluation of the product.

Impurities present in an active constituent used in the formulation of a veterinary product may be important both toxicologically and environmentally. Consequently, you should identify any impurity present at a concentration that may be toxicologically significant, and identify all impurities present in the active constituent at a concentration of one gram per kilogram or more.

Formulation constituents should be clearly identified by name and Chemical Abstracts Service registry number. The use of trade names or proprietary names alone is not acceptable. You should provide all available information relevant to the hazard assessment of non-active constituents used in the product. This information should include, but is not limited to, a safety data sheet for each of the constituents.

For further details, refer to Veterinary chemical products—Chemistry and manufacture (Part 2).

**Extrapolation of data**

In certain cases, it may be possible to estimate the acute toxicity of a formulation by extrapolation from acute toxicity data on the active constituent (for example, a simple dilution in water, or a tablet formulation in an inert material), or by read-across from a reference product formulation that has similar physicochemical and toxicological properties to the formulation for which registration is sought. Estimates of the potential hazard by extrapolation and read-across should take into consideration the acute toxicity of the active constituent as well as the acute toxicity of the individual non-active constituents. However, it is always preferable that you provide studies conducted with the product to be registered.
Where you do not provide acute toxicity studies on the proposed product formulation, you should submit a valid scientific argument outlining why you have not provided the data. You should note that if the scientific argument is accepted by the OCS, the minimum recommendation for evaluation is a safety data sheet for each constituent in the product formulation.

Further, where two or more active constituents are formulated together in a novel combination as determined by the OCS (that is, a hazard profile has not been previously established), toxicity studies should be performed with the formulated product as outlined in ‘Toxicity of mixtures’, to investigate the possibility of synergism or potentiation. Alternatively, in the absence of data, you should provide a scientific argument so that the OCS may determine its regulatory value.

Approval of an alternative source of an approved veterinary active constituent

Registration holders may apply for approval of a new source of an approved active constituent. If we consider that the active constituent from the new source may not be equivalent to an approved source in terms of its impurity profile, you should provide toxicological data—or a scientific argument in the absence of data—for assessment by the OCS.

The data elements that you should provide where we refer to the OCS for toxicity assessment are:

- acute oral and dermal toxicity studies
- two in vitro genotoxicity studies (as outlined in ‘Genotoxicity studies’).

These studies should be conducted on the new source of active constituent containing the listed impurities or on the newly identified and/or toxicologically significant impurities. If the OCS determines that these studies do not demonstrate equivalence, further testing may be appropriate.

The OCS will consider a scientific argument for not undertaking studies on a new source of technical-grade active constituent. The argument should follow a tiered approach:

1. determination of the hazard profile of the newly identified or toxicologically significant impurities; that is, whether the impurities are classified for human health effects on Safe Work Australia’s Hazardous Substances Information System
2. consideration of information from acceptable toxicology databases and literature searches providing information on the hazard profile of the impurities, or data on both the impurity and the structurally similar chemical if read-across is proposed
3. supportive quantitative structure–activity relationship evidence derived using Deductive Estimation of Risk from Existing Knowledge software (only) as a prediction of the toxicity of the impurity and structurally similar chemical if read-across is proposed.

Information from this stepwise approach should support the proposed scientific argument that equivalence is demonstrated and testing is not relevant. The OCS will determine the regulatory value of scientific arguments based on their merits and reliability.

Guideline for veterinary products intended for domestic animals

Domestic animal products should be relatively harmless or capable of causing only mild illness if accidental poisoning occurs. Poisoning by veterinary products can, and does, occur from products sold for use with domestic animals. Unfortunately, young children are often the group most at risk of such poisoning.

Appropriate consideration of inherent toxicity, formulation, packaging and labelling can reduce the hazard to domestic users and especially to young children. The following guidelines, when applied to experimental animal data, should reduce the hazard of veterinary products.

Acute oral toxicity

Any domestic veterinary product that may be ingested should not be expected to be acutely toxic to a child at doses up to 1500 milligram per kilogram (mg/kg) body weight. Recognising that acute toxicity may reflect a range of adverse effects, the use of the term ‘acutely toxic’ here is intended to mean life-threatening.

The OCS will (as appropriate) consider the following aspects of acute oral toxicity to determine whether a domestic veterinary product is considered acutely toxic to a child:

- where acute toxicity data on the formulation is available, it would be used to determine whether the value of 1500 milligram per kilogram body weight is not appropriate and may be increased
- whether one or two swallows (approximately 10 gram or 10 millilitre) of the product presents an acutely toxic dose to an infant or small child.

Acute dermal toxicity

Any formulation designed for use in domestic animals should not be acutely toxic at dermal doses up to 2000 milligram per kilogram body weight.

Acute inhalational toxicity

Any formulation designed for use in domestic animals should not be acutely toxic at inhalational concentrations up to 2000 milligram per cubic metre (four-hour exposure) for a gas, 20 milligram per litre (four-hour exposure) for a vapour and 5 milligram per litre (four-hour exposure) for dusts and mists.

Irritancy potential

The irritancy to skin and eyes of domestic veterinary products should be low. The OCS will take into consideration the formulation and application methods of a product on a case-by-case basis. You should provide relevant information regarding any risk mitigation measures available for the proposed product.

Repeated exposure

Domestic veterinary products should present a low risk from repeated use. This should be considered in the context of a deterministic risk assessment approach.
Directions for safe use

Safe use of domestic veterinary products should not require safety equipment that is not readily available to the householder. Safety equipment other than gloves is not considered an appropriate mitigation option for domestic veterinary product handlers, because users are not trained in handling hazardous substances and compliance is not expected. Domestic veterinary products may not be supported for domestic use if safety equipment other than gloves is required for their safe use.

First aid directions

The product should carry appropriate first aid directions in the event of poisoning. Formulations designed for use with domestic animals should not require specific antidotes or aggressive first aid measures.

Data elements

The data elements for a comprehensive assessment of toxicology data are shown in ‘Data elements for a comprehensive toxicology submission’. Unless specified, all studies should be conducted with the active constituent for which approval is sought.

If you believe that a specific data element is not relevant to your application, you should justify the absence of studies by providing a valid scientific argument under the heading for the data element(s) in question. Similarly, a valid scientific argument to justify the absence of acute toxicity studies should be provided under the heading of the data element when read-across is proposed from a formulation that has similar physicochemical and toxicological properties to the product formulation for which registration is sought.

Data elements for a comprehensive toxicology submission

The data elements for a comprehensive assessment of toxicology data are:

- contents
- data summary
- toxicokinetics and metabolism
- acute toxicity studies:
  - studies on the active constituent
  - studies on the product
- short-term toxicity studies (repeat dose)
- sub-chronic toxicity studies (repeat dose)
- long-term (chronic) toxicity studies (repeat dose):
  - chronic toxicity studies
  - carcinogenicity studies
  - combined chronic toxicity and carcinogenicity studies
- reproduction studies
- developmental studies (including developmental neurotoxicity)
- genotoxicity studies
- neurotoxicity studies
- additional studies:
  - toxicity of metabolites and impurities
  - other adverse effects
  - toxicity of mixtures
  - mechanistic studies and mode of action
  - immunotoxicity
- human toxicological data
- no-observed-effect level
- acceptable daily intake
- acute reference dose
- first aid instructions and safety directions
- toxicological database/bibliography.

Contents

A table of contents greatly assists the assessment process.

Data summary

Your application should include an overall summary of the toxicological information provided in relation to the active constituent or product, as well as rationale for any conclusions made. The summary should contain:

- a brief description of the active constituent or product (including hazard classification and packaging)
- a brief description of the pattern of use of the product. A detailed description of the data elements that you should provide is given in Veterinary chemical products—Occupational health and safety (Part 6).

All principal treatment-related changes, such as biochemical and morphological changes observed in the studies should be identified in the data summary, with proper cross-referencing to the detailed data. Where your application claims that:

- findings are not toxicologically significant, you should provide evidence of their reversibility and a scientific argument in support of the proposal. By anticipating such possibilities from early tests, it may be possible to include subgroups for recovery trials in later studies
- findings are not treatment related, you should provide a scientific argument supporting the claim, supported by historical control data if available, preferably from the testing laboratory and by the route of administration tested
- findings are considered to be of low relevance to humans, you should provide a scientific argument based on mechanistic data identifying the mode of action and using a weight-of-evidence approach for the relevance of the identified mode of action to human health based on the Bradford Hill criteria. This approach is contained within the International Programme on Chemical Safety framework for analysing the relevance of a cancer mode of action for humans.
Information guidelines and standards

The OCS will determine the regulatory value of scientific argument that findings were not toxicologically significant, not treatment related or of low relevance to humans, based on their merits and reliability.

You may use tables as a means of summarising the information. Where studies are cited, they should be cross-referenced in the main body of the application.

If you have submitted metabolism and kinetics (Part 4) data, you should summarise these data with argument as to how they relate to relevant aspects of toxicology.

In most cases, the data summary need not exceed two to three pages.

Toxicokinetics and metabolism

You should provide studies examining the absorption, distribution, metabolism and elimination of active constituents in laboratory animals (see Veterinary chemical products—Metabolism and kinetics (Part 4) for further details). The route of administration for these studies should be carefully considered, and take into account routes of likely exposure to the active constituent in question.

An investigation of the extent of dermal absorption of the active constituent or product is desirable for risk assessment. In the absence of dermal absorption data, a default position of 100 per cent of substance applied to the skin will be considered absorbable. This default may be reduced under specific physicochemical properties; that is, if a substance has a molecular weight of greater than 500 and a partition coefficient (log Pow) less than -1 or greater than 4, the default will be reduced to 10 per cent dermal absorption.

For dermal absorption studies provided in support of an application, the tested formulation should be identical to, or closely resemble, the product under consideration. The adequacy of this similarity will be determined on a case-by-case basis. Tested concentrations should represent expected human exposure concentrations; for example, the concentration of chemical in the product and the proposed end-use concentration(s) should be tested. Submission of in vitro dermal absorption studies using (1) rat and (2) human skin in conjunction with (3) an in vivo rat dermal study (a ‘triple pack’) is recommended to enable likely human dermal absorption to be estimated. The adequacy of dermal absorption data that does not follow the triple-pack approach will be assessed on a case-by-case basis and may be of reduced value for risk assessment purposes.

You can find further guidance on conducting and interpreting dermal absorption studies in the OECD Guidance notes on dermal absorption.

Acute toxicity studies (active constituent)

Acute toxicity studies examine the adverse effects arising from administration of a single oral dose or a single dermal or inhalation exposure of a substance over a specified period or multiple doses given within 24 hours.

To allow assessment of the acute toxicity of a substance, studies in animals should examine the most likely routes and forms of exposure in humans.

Acute oral toxicity studies should be performed in at least one mammalian species. Rats are the preferred rodent species for oral studies unless a species more representative of human toxicity is known. You should also provide acute dermal and inhalation studies in at least one species. For skin and eye irritation studies, rabbits are an acceptable species, but alternatives from adopted OECD guidelines for the testing of chemicals (or other recognised guidelines) to the usual in vivo test may be suitable. In vivo eye irritation tests may not be appropriate due to animal welfare considerations in certain circumstances. If you do not believe an eye irritation study is appropriate, you should provide a valid scientific argument as to why these studies should not be included. For example, if the results from a skin irritation study or validated in vitro study demonstrated corrosivity or severe irritation, it is acceptable not to test the product in an eye irritation study, as it is presumed that the product will be corrosive to the eye. Similarly, products with pH extremes of 2 or less, or 11.5 or more are considered corrosive to the eye, unless the acid or alkaline reserve (buffering capacity) of the product suggests otherwise.

A skin sensitisation study is performed to test for possible hypersensitivity reactions to the substance. Guinea pigs are normally used for sensitisation studies. Internationally validated alternative methods, such as the murine local lymph node assay, are also acceptable.

Acute toxicity studies (formulated product)

For each new veterinary product, you should submit a ‘six-pack’ of acute toxicological data. This consists of the following studies on the product:

- acute oral toxicity
- acute dermal toxicity
- acute inhalation toxicity
- eye irritation
- skin irritation
- skin sensitisation.

If such data is not available, you should provide valid scientific argument as to why you have not submitted data. In certain circumstances, a toxicological evaluation of the product may be conducted by taking the known toxicological properties of the active constituents and excipients in the formulation and extrapolating these to estimate the acute toxicity of the product. We recommend that you adequately address the reasoning for not providing toxicity studies.

Short-term toxicity studies (repeat-dose studies of less than 90 days duration)

Short-term toxicity studies involve multiple administration of a substance for periods of less than 90 days. Such studies provide information on the possible health hazards likely to arise from repeated exposures over a limited period of time.

For classes of chemicals that cause cholinesterase inhibition, short-term oral (gavage) studies in animals, incorporating frequent monitoring of cholinesterase levels, are desirable.

Sub-chronic toxicity studies (90 days to less than 12 months)

Sub-chronic toxicity studies are performed to assess possible effects observed in short-term repeated exposure and as preliminary dose range-finding studies before chronic studies are started. They should demonstrate a range of activity, from the no-observed-effect level through to a clear
Information guidelines and standards

toxic effect level. Often this range can be encompassed in a single study using one control and three test groups.

Sub-chronic toxicity studies should be performed in two species, a rodent and a non-rodent species. Dogs are the commonly used non-rodent species, and should be of a defined breed (the beagle is frequently used). Rabbits are not considered an acceptable non-rodent species unless available data suggest that they are more relevant for the prediction of health effects in humans.

Long-term (chronic) toxicity studies (12 months or longer)

Chronic toxicity studies

You should provide long-term (chronic) studies to assess long-term toxic effects (chronic toxicity) that may not be demonstrable in sub-chronic studies (for example, from cumulative toxicity).

Chronic toxicity studies normally consist of long-term, continuous, daily oral administration of the test compound to two species. The use of both a rodent and non-rodent species is desirable to provide an adequate assessment of interspecies variation. Rats and dogs are the preferred species.

In chronic toxicity studies, it is desirable to have a dose–response relationship as well as a no-observed-effect level. To this end, normally one control and at least three test groups should be used. The highest dosage should induce a recognisable toxic response without eliciting excessive lethality. At least one dosage level should result in no observed toxic effects. Where a no-observed-effect level is not achieved and the study is identified as the key study for risk assessment purposes and/or establishing an acceptable daily intake value, an additional safety factor may be implemented to account for the uncertainty regarding a lower limit of toxicity.

Carcinogenicity studies

Carcinogenicity studies are normally performed in two species. Such studies should be regarded as relevant whenever biologically significant residues of the compound or its metabolites occur, or when human exposure to the compound results from the normal use pattern of the compound.

Carcinogenicity testing may not be relevant for an active constituent that is not intended for food-producing use, has a restricted use pattern, and is not an in vivo somatic cell genotoxicant, and where findings in available systemic toxicity data do not raise concerns for carcinogenicity (for example, absence of pre-neoplastic lesions).

Carcinogenicity studies involve administration of the test material, usually in the feed, throughout the major portion of the life span of the species. An adequate number of animals should be included at each dose level to enable suitable statistical evaluation of the results (that is, most of the animals should survive for the duration of the study). It is recommended that rodent species such as rats and mice be used. The use of non-rodent species may be considered when available data suggest that they are more relevant for the prediction of health effects in humans.

You should present historical data describing the normal occurrence of a finding in the particular species and strain of animal in the testing laboratory for the route of administration tested. This assists in deciding whether or not a tumour or lesion is compound related. The submission of historical control data not from the testing laboratory, and/or not by the route of administration that the test used, may be of reduced or no regulatory value.

Where a tumour is considered to be of low relevance to humans, you should provide a supporting scientific argument, based on mechanistic data identifying the mode of action and using a weight-of-evidence approach for the identified mode of action to human health based on the Bradford Hill criteria.

The OCS will determine the regulatory value of scientific arguments that tumour findings were of low relevance to humans, based on their merits and reliability.

Combined chronic toxicity and carcinogenicity studies

A combined chronic toxicity and carcinogenicity study may provide information on the possible chronic and carcinogenic effects likely to arise for a period lasting up to the entire life span of the species. However, careful design is suggested because information for each objective may differ.

You should present historical data describing the normal occurrence of a finding in the particular species and strain of animal in the testing laboratory for the route of administration tested. This assists in deciding whether or not a tumour or lesion is compound related. The submission of historical control data not from the testing laboratory, and/or not by the route of administration that the test used, may be of reduced or no regulatory value.

Where a tumour is considered to be of low relevance to humans, you should provide a supporting scientific argument, based on mechanistic data identifying the mode of action and using a weight-of-evidence approach for the identified mode of action to human health based on the Bradford Hill criteria.

The OCS will determine the regulatory value of scientific arguments that tumour findings were of low relevance to humans, based on their merits and reliability.

Reproduction studies

Reproduction studies involve the administration of a substance over one or more generations (multi-generation studies) to provide information on the effects of the substance on male and female reproductive systems, including gonadal function, the estrus cycle, mating behaviour, conception, gestation, parturition, lactation, and weaning, and the growth and development of the offspring.

Such studies may also provide information about the effects of the test substance on neonatal morbidity, mortality, and preliminary data on prenatal and postnatal developmental toxicity, and serve as a guide for subsequent tests. These studies should be conducted with at least three dose groups and a concurrent control group, and would normally be conducted using rodents, preferably rats.

If other species are used, justification should be given and the test parameters should be modified as appropriate.

Developmental studies

Developmental studies involve administration of a substance to pregnant animals over a specified period of gestation (organogenesis) to provide
information on prenatal exposure on the pregnant test animal and on the developing foetus, and may include assessment of maternal effects as well as death, structural anomalies and abnormalities, or altered growth in the foetus. Functional deficits, although an important part of development, are generally assessed in reproduction and developmental neurotoxicity studies.

Developmental toxicity studies should be performed in a rodent and non-rodent species. Rats are the preferred rodent species and rabbits are the preferred non-rodent species. You should provide justification if another species is used.

Genotoxicity studies

It is now known that some substances can cause changes to the genetic material. These changes may involve a single gene, or whole chromosomes (structural and/or numerical), and damage to DNA via effects such as unscheduled DNA synthesis, DNA strand breaks, DNA adduct formation or mitotic recombination. A set of well-validated tests able to detect different classes of genetic toxicants will demonstrate the potential of a compound to induce genetic damage in humans. Tests (i) and (ii) described below should be conducted in the first instance:

1. a test designed to demonstrate the induction of point mutations (base-pair substitution and frameshift) in a microbial assay (for example, salmonella reverse mutation test), with and without the use of appropriate metabolic activation systems
2. a test designed to demonstrate the production of chromosome damage in an in vitro mammalian cell assay (for example, Chinese hamster ovary assay), with and without the use of appropriate metabolic activation systems.

An in vivo test is also recommended.

If (1) or (2) are positive, two of three tests described below under (3), (4) and (5) should be carried out in rodents (rats or mice) in order to characterise the genotoxic potential in vivo in somatic cells:

3. a test designed to demonstrate the production of cytogenetic damage (for example, micronuclei) in the bone marrow or other proliferative cells of intact animals
4. a test designed to demonstrate genotoxic damage, involving other than cytogenetic endpoints (for example, unscheduled DNA synthesis or P32-post-labelling adduct formation) and preferably in a suspect or known target tissue for the substance
5. a test designed to demonstrate mutations in transgenic rats or mice that have transgenes containing reported genes for the detection of various types of mutations in somatic tissues.

If (3), (4) or (5) are positive, a test described below under (6), (7) or (8) should be carried out in rodents (rats, mice or Chinese hamsters) in order to better characterise the genotoxic potential in vivo in germ cells:

6. a test designed to demonstrate a dominant lethal event in a germ cell that does not cause dysfunction of the gamete, but which is lethal to the fertilised egg or developing embryo
7. a test designated to demonstrate the production of chromosome aberrations in spermatogonial cells
8. a test designated to demonstrate mutations in transgenic rats or mice that have transgenes containing reporter genes for the detection of various types of mutations through the germline.

Neurotoxicity studies

A neurotoxic effect is an adverse change in the structure or function of the nervous system (central or peripheral) that results from exposure to a substance. A neurotoxic effect may arise in offspring from exposure of the mother during pregnancy and lactation. Adverse changes may result from single or repeat exposure to a substance.

Tests should be designed to detect or characterise major neurobehavioural and neuropathological effects in test animals. While behavioural effects—even in the absence of morphological changes—can reflect an adverse impact on the organism, not all behavioural changes are specific to the nervous system. Therefore, any changes observed should be evaluated in conjunction with correlative histopathological, haematological or biochemical data as well as data on other types of systemic toxicity. A developmental and delayed neurotoxicity study should be considered based on all the available information. A developmental neurotoxicity study should be conducted when neurotoxicity is observed in acute or repeat dose studies. Delayed neurotoxicity studies (acute and repeat dose) should be conducted if the substance is an organophosphorous compound.

Relevant testing (acute, sub-chronic, developmental and delayed neurotoxicity) should be conducted in accordance with appropriate test guidelines.

Additional studies

Toxicity of metabolites and impurities

Although it is recognised that toxicity studies usually examine the toxicity of the active constituent, impurities or metabolites may contribute significantly to the toxicity of the compound. In general, studies employing the active constituent provide an overall estimate of toxicity of the parent compound and its metabolites. However, where metabolites produced in target animals are significantly different from those produced in laboratory animals, you should provide toxicity studies on those metabolites. Submitted data should allow the OCS to assess what metabolites should be included in the residue definition for risk assessment purposes.

All impurities with concentrations of one gram per kilogram or greater (or those impurities with concentrations of less than one gram per kilogram that are toxicologically significant) in the active constituent should be identified and, where necessary, subjected to appropriate toxicological studies or a scientific argument (see ‘Approval of an alternative source of an approved veterinary active constituent’ above). When undertaking toxicological studies, initially, you should provide acute oral and acute dermal toxicity studies and two in vitro genotoxicity studies (as outlined in ‘Genotoxicity studies’). These studies should be conducted on the new source of active constituent containing the listed impurities (or on the listed impurities). Depending on the results of these initial studies, the OCS may seek further toxicological studies.

Other adverse effects

Individual compounds that show specific toxicological effects (for example, immunotoxicity, neurotoxicity) during normal repeat dose testing should be further investigated using appropriate tests for the particular abnormalities induced to enable definitive hazard characterisation to be established. Similarly, new compounds that belong to chemical classes known to produce particular toxicological effects should also be tested appropriately, for example, delayed neurotoxicity with organophosphorous insecticides. In the absence of such information, the toxicity profile of a compound may be deemed incomplete. The OCS will determine the regulatory impact of an incomplete toxicity profile on a case-by-case basis.
Toxicity of mixtures

Where two or more active constituents are formulated together in a novel combination as determined by the OCS (that is, a hazard profile has not been previously established), toxicity studies should be performed with the formulated product to investigate the possibility of synergism or potentiation. In the absence of data, you should provide a scientific argument so that the OCS may determine the regulatory value of the argument. When undertaking toxicological studies, acute toxicity studies are usually sufficient for this purpose (that is, acute oral, dermal and inhalational toxicity studies, skin and eye irritation studies, and a skin sensitisation study).

Where synergism or potentiation is found, the OCS may seek further studies to clarify their toxicological significance.

Mechanistic studies and mode of action

Mechanistic studies may be undertaken to supplement data obtained from standard studies conducted in accordance with the adopted OECD guidelines for the testing of chemicals, or other recognised test guidelines, so as to explain the process involved in, or responsible for, an observed toxicological finding. Together, the data may identify the overall mode of action by which a substance produces its toxicological effect, from a subcellular level through to histopathological changes.

When proposing that the observed toxicological effect is of low relevance to humans, you should provide a scientific argument based on the available data, identifying the mode of action and using a weight-of-evidence approach for the relevance of the identified mode of action to human health based on the Bradford Hill criteria.

Immunotoxicity

An immunotoxic effect is an adverse effect on the components and/or function of the immune system from exposure to a substance resulting from either direct or indirect actions reflecting either permanent or reversible toxicity.

While OECD test guidelines for short-term, sub-chronic and chronic toxicity studies may provide data to give an indication of immunological effects, there is no specific OECD test guideline to determine functional immunotoxicity. If such studies provide an indication of an immunological effect, you should consider further testing to investigate immunotoxicity using appropriate tests. The US Environmental Protection Agency has a functional immunotoxicity test guideline designed to evaluate the immunosuppressive potential of a substance (OPPTS 870.7800).

Human toxicological data

You should provide all available information relating to human experience with the substance, as there are currently no specific OECD or other recognised test guidelines for respiratory irritation and respiratory sensitisation. Therefore, information relating to human experience may provide key data. The information may arise as a result of voluntary intake, occupational exposure during the manufacture of the substance, worker exposure during use, or reports of accidental poisoning.

You should include studies relating to occupational and/or worker exposure in Occupational health and safety (Part 6) section of your application.

No-observed-effect level

The no-observed-effect level is the highest dose of a substance at which there is an absence of observable effects on morphology, functional capacity, growth, development or life span from those observed in control (untreated) animals, and which are observed or measured at higher dose levels used in the study.

The no-observed-effect level is expressed in milligrams of substance per kilogram of body weight per day (mg/kg bw/day) or, in a feeding study, as parts per million (ppm) in food. For feeding studies, conversion to mg/kg bw/day should be made, calculated from substance intake by measured or estimated food intake over the study period.

Where the test substance is given in feed, and problems with the stability of the test compound occur, the feed should be analysed at frequent intervals.

Lowest-observed-effect level

The lowest-observed-effect level is the lowest dose of a substance at which there is an observable or measured effect on morphology, functional capacity, growth, development or life span at a greater incidence or severity from those observed in normal (untreated) animals.

The lowest-observed-effect level is expressed in milligrams of substance per kilogram of body weight per day (mg/kg bw/day) or, in a feeding study, as parts per million (ppm) in food. For feeding studies, conversion to mg/kg bw/day should be made, and where problems with the stability of the test compound occur in feed, the feed should be analysed at frequent intervals.

Acceptable daily intake for humans

The acceptable daily intake for humans is the level of intake of a substance that can be ingested daily over an entire lifetime without appreciable risk to health on the basis of the available information at the time of evaluation. It is expressed in milligrams of the substance per kilogram of body weight per day (mg/kg bw/day).

For this purpose, ‘without appreciable risk’ means that adverse effects are unlikely to result even after a lifetime of exposure. Furthermore, for a pesticide residue, the acceptable daily intake is intended to give a guide to the maximum amount that can be ingested daily in the food without appreciable risk to the consumer. Accordingly, the figure is derived as far as possible from feeding studies in animals.

You can view a list of current acceptable daily intakes on the Department of Health website.

Acute reference dose

The acute reference dose of a substance is an estimate of the amount of a substance in food and/or drinking water, expressed in milligrams of substance per kilogram of body weight (mg/kg bw), that can be ingested over a short period of time, usually in one meal or during one day, without appreciable health risk to the consumer, on the basis of all known facts at the time of the evaluation. For some substances, an acute reference dose
may not be necessary because the substance is not considered to cause appreciable acute risk after a single dose or exposure (that is, 24 hours or less).

You can view a list of current acute reference doses on the Department of Health website.

First aid instructions and safety directions

You may propose first aid instructions and safety directions applicable for each formulation. You should use standard phrases as published in the Department of Health’s First aid instructions and safety directions handbook.

You should note, however, that first aid instructions and safety directions are established by the OCS, taking into account the hazard profile of an active constituent or chemical product, as well as the occupational and/or residential risks associated with the proposed use patterns for the product.

Toxicological database and bibliography

Every application (including supplementary applications) should include a toxicological database comprising a full bibliography of all studies provided in the application. You should submit this database in electronic format.

Every application (including supplementary applications) that contains toxicological data should include a list of all studies on the active constituent and/or chemical product. You should clearly identify studies lodged as part of the application.

For each listed study, you should provide the following information:

- identity and the concentration or purity of the material tested (for example, active constituent, product)
- type of test (for example, acute oral study, two-year dietary study)
- species and strain of animal used
- study laboratory and names of authors
- study sponsor
- good laboratory practice status (including certification where applicable)
- title of the report, report number and date of report
- date the study was submitted in Australia
- location in the application (volume, page number).

Poison schedules

The schedules accompanying the states’ and territories’ Poisons Acts listing the various poisons under categories that are based on the recommendations published in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, produced by the Australian Government Department of Health). Active constituents intended for veterinary use and veterinary chemical products generally fall into one of the following categories:

Schedule 4: Prescription Animal Remedy

Substances that should, in the public interest, be restricted to medical, dental or veterinary prescription or supply.

Schedule 5: Caution

Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

Schedule 6: Poison

Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.

Schedule 7: Dangerous Poison

Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.

Schedule 8: Controlled Drug

Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

Appendix B

Those substances considered not to require control by scheduling because of low toxicity, or where other factors suggest that the potential public health risk would be minimal, are listed in Appendix B of the SUSMP. This appendix should be read in conjunction with Appendix A (general exemptions).

Template for submission of toxicology data

You should use the following template when submitting a toxicology data package. Please address all sections of the template:

- contents
- data summary
Information guidelines and standards

- toxicokinetics and metabolism
- acute toxicity studies
  - studies on the active constituent
  - studies on the product
- short-term toxicity studies (repeat dose)
- sub-chronic toxicity studies (repeat dose)
- long-term (chronic) toxicity studies (repeat dose)
  - chronic toxicity studies
  - carcinogenicity studies
  - combined chronic toxicity and carcinogenicity studies
- reproduction studies
- developmental studies
- genotoxicity studies
- neurotoxicity studies
- additional studies
  - toxicity of metabolites and impurities
  - other adverse effects
  - toxicity of mixtures
  - mechanistic studies and mode of action
  - immunotoxicity
  - respiratory irritation and/or sensitisation
- human toxicological data
- no-observed-effect level
- acceptable daily intake
- acute reference dose
- first aid instructions and safety directions
- summary of mammalian toxicity and overall evaluation
- toxicological database and bibliography.

References

We have provided below details for current editions at the time of publication. You should always ensure that you obtain the most recent edition of any publication.

Australian Government Department of Health, Standard for the Uniform Scheduling of Medicines and Poisons.

Organisation for Economic Co-operation and Development, OECD guidelines for the testing of chemicals

Office of Chemical Safety (Australian Government Department of Health), Acceptable daily intakes for agricultural and veterinary chemicals.

Office of Chemical Safety (Australian Government Department of Health), First aid instructions and safety directions handbook.

Office of Chemical Safety (Australian Government Department of Health), Acute reference doses for agricultural and veterinary chemicals.


VICH 2004, Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing, VICH Guideline no. 23, International Cooperation on Harmonisation of Technical Requirements of Veterinary Medicinal Products.


VICH 2004, Studies to evaluate the safety of residues of veterinary drugs in human food: repeat-dose (90-days) toxicity testing, VICH Guideline no. 31, International Cooperation on Harmonisation of Technical Requirements of Veterinary Medicinal Products.

VICH 2004, Studies to evaluate the safety of residues of veterinary drugs in human food: developmental toxicity testing, VICH Guideline no. 32, International Cooperation on Harmonisation of Technical Requirements of Veterinary Medicinal Products.

VICH 2009, Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to testing, VICH Guideline no. 33, International Cooperation on Harmonisation of Technical Requirements of Veterinary Medicinal Products.


The following content can be found at http://new.apvma.gov.au/node/901
If making a submission, please reference page number: 901

Veterinary—WAAVP guideline for lice and sheep keds on ruminants

The World Association for the Advancement of Veterinary Parasitology (WAAVP) is a not-for-profit organisation for scientists who study the parasites of non-human animals. The guidelines, developed by the international expert working groups of the WAAVP, assist in the international harmonisation of standards and procedures for the evaluation of veterinary parasiticides. The WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants aim to standardise the minimum set of data that should be submitted to demonstrate the efficacy of new ectoparasiticides for use on or in ruminants.
The APVMA has adopted the WAAVP guidelines for evaluating the efficacy of ectoparasitcides on ruminants to assist registration holders in the conduct of regulatory trials. The APVMA notes that in some instances the WAAVP guidelines advise consultation with the regulator. We also recognise that because of Australia’s unique environmental and geographic parameters, parasite burdens and their population dynamics, farm management practices and animal breeds, there are some differences between the WAAVP guidelines and the APVMA’s recommendations for efficacy trials for products to be registered in Australia. Therefore, applicants should conduct efficacy trials within Australia under typical farm management practices covering relevant geographical regions and the following additional guidance is provided to assist you in conducting these trials. If you follow this additional guidance, your data should generally be sufficient for the APVMA to assess its confidence in the product’s efficacy given Australia’s unique conditions.

This preamble refers to the following World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline: Holdsworth, PA, Vercruysse, J, Rebhein, S, Peter, R, Letonja, T & Green, P 2006, ‘World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of ectoparasitcides against biting lice, sucking lice and sheep keds on ruminants’, Veterinary Parasitology, vol. 136, pp. 45–54.

**Lice species**

In Australia, efficacy studies in sheep should use Bovicola ovis as the target parasite species.

**Claims and level of efficacy for lice**

The WAAVP guidelines refer generally to a ‘lice eradication/elimination’ claim (100 per cent) and a ‘lice management’ claim (95 per cent). For clarity and consistency in new and existing registered products, the APVMA uses the term ‘eradication’ for an ‘eradication/elimination’ claim, and the term ‘control’ for a ‘lice management’ claim.

**Eradication**

This claim is only applicable to products applied off-shears or in short wool. ‘Eradication’ is defined as: ‘Elimination of all live lice and viable eggs from treated animals, as determined by inspection of sheep 52 weeks after treatment.’

**Control**

For products used off-shears and in short wool, ‘control’ is defined as: ‘Elimination of all live lice and viable eggs from treated animals, as determined by inspection of sheep 20 weeks after treatment.’

For products used in long wool, ‘control’ is defined as: ‘Reduction of the lice population by more than 95 per cent after 90 days (or less as supported by data) in sheep examined in pen and field trials’.

For products used in long wool, if you present unequivocal evidence of a reduction in fleece damage caused by the lice at any time, then the 95 per cent figure may be modified. The term ‘aids in control’ would apply.

**Terminology:**

- off-shears: within 24 hours after shearing
- short wool: at least 24 hours and up to 6 weeks after shearing
- long wool: at least 6 and up to 43 weeks after shearing.

**Field trials for lice**

The World Association for the Advancement of Veterinary Parasitology guidelines provide general advice on field trials in section 3.4.3, and specific considerations for field trials for sheep in section 4.2. As additional guidance, for products used on sheep off-shears or in short wool, the APVMA recommends that five studies be conducted, with mob sizes of not less than 300 and ideally at least 500 sheep, for at least 20 weeks. Three of these trials should be conducted with fine-wool merinos. Fine-wool merinos are defined as having wool less than 20 mm. A mob is defined as all the sheep treated with the test product being maintained together at all times throughout the trial period. At least 25 tagged tracer sheep should be included in each mob.

For products used on sheep in long wool, the APVMA recommends six studies (two each at three, six and nine months), three of which (one per wool length) should be conducted in fine-wool merinos, with mob sizes not less than 300 and ideally at least 500 sheep, for 20 weeks or until next shearing (whichever occurs first). At least 25 tagged tracer sheep should be included in each mob.

**Lice counts**

For determining the level of infestation of biting lice in sheep, the World Association for the Advancement of Veterinary Parasitology guidelines specify examination of 40 sites (partings), about 10 cm wide, in total per animal or 80 sites (partings), about 5 cm wide, per animal. The sites should be spaced so that they are representative of the full area of the body covered by the fleece on each side of the sheep. In addition, the APVMA recommends that you divide the examination sites equally on each side of the animal, that is, 20 (10 cm) or 40 (5 cm) sites should be examined on each side of the body (total = 40 (10 cm) or 80 (5 cm) sites). Furthermore, the APVMA recommends that you distribute the number of partings on each side of the body equally between the neck, shoulder, withers, rump and flank, that is, 4 (10 cm) or 8 (5 cm) partings at each location on each side of the body.

**Level of lice infestation**

The World Association for the Advancement of Veterinary Parasitology guidelines specify that sheep in field studies should have at least a moderate infestation of lice (30 lice per animal) at the pre-treatment examination. The APVMA also recommends that sheep in field studies should have at least a moderate infestation of lice at the pre-treatment examination; however, the APVMA defines the level of infestation as follows:

- low infestation: less than 1 louse per 10 cm parting
moderate infestation: 1 to 5 lice per 10 cm parting
heavy infestation: more than 5 lice per 10 cm parting.

Therefore, sheep with a moderate infestation would have at least 40 lice per animal (based on 40 x 10 cm partings).

Persistency studies for lice

For persistent efficacy studies in sheep, the World Association for the Advancement of Veterinary Parasitology guidelines recommend infestation with 50 lice on the shoulder and/or flank. The APVMA finds this recommendation to be unclear, that is, the total could be 50 or 100 lice. To clarify, the APVMA recommends infestation with 50 live lice on the right shoulder and right flank (total = 100). The APVMA also recommends that the studies be conducted in merinos.

Wool or hide damage

Given the importance of the wool and cattle by-product industries to Australian commerce, it is recommended that applicants collect and submit data on wool staining or damage, hide or skin damage, or damage to animal products.

Veterinary—WAAVP guideline for mange and itch mites on ruminants

The World Association for the Advancement of Veterinary Parasitology (WAAVP) is a not-for-profit organisation for scientists who study the parasites of non-human animals. The guidelines, developed by the international expert working groups of the WAAVP, assist in the international harmonisation of standards and procedures for the evaluation of veterinary parasiticides. The WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants aim to standardise the minimum set of data that should be submitted to demonstrate the efficacy of new ectoparasiticides for use on or in ruminants.

The APVMA has adopted the WAAVP guidelines for evaluating the efficacy of ectoparasiticides on ruminants to assist registration holders in the conduct of regulatory trials. The APVMA notes that in some instances the WAAVP guidelines advise consultation with the regulator. We also recognise that because of Australia’s unique environmental and geographic parameters, parasite burdens and their population dynamics, farm management practices and animal breeds, there are some differences between the WAAVP guidelines and the APVMA’s recommendations for efficacy trials for products to be registered in Australia. Therefore, applicants should conduct efficacy trials within Australia under typical farm management practices covering relevant geographical regions and the following additional guidance is provided to assist you in conducting these trials. If you follow this additional guidance, your data should generally be sufficient for the APVMA to assess its confidence in the product’s efficacy given Australia’s unique conditions.

This preamble refers to the following World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline: Vercruysse, J, Rehbein, S, Holdsworth, PA, Letonja, T & Peter, R 2006, ‘World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of ectoparasiticides against (mange and itch) mites on ruminants’, Veterinary Parasitology, vol. 136, pp. 55-66.

Definition of claims

The WAAVP guidelines refer to ‘therapeutic efficacy’. In the interests of clarity and consistency for new and existing registered products, the APVMA will use the term ‘control’ and not ‘therapeutic efficacy’.

With respect to Pseorrgates ovis, ‘control’ is defined as: ‘Reduction of the mite population to non-detectable levels at all post-treatment examinations of treated sheep, in the presence of normal seasonal fluctuations in the population on untreated sheep kept under the same conditions’.

Wool or hide damage

Given the importance of the wool and cattle by-product industries to Australian commerce, it is recommended that applicants collect and submit data on wool staining or damage, hide or skin damage, or damage to animal products.

Veterinary—Guideline on the registration of selenium products for use in sheep

Purpose

This guideline clarifies the circumstances in which selenium products used in sheep do or do not require registration. It should be read in conjunction with the APVMA’s user guide: what is or isn’t a veterinary product.

Definition of a veterinary chemical product
The Agvet Code states that a veterinary chemical product includes a vitamin, a mineral substance or an additive, if (and only if) the vitamin, substance or additive is used for any of the following purposes:

- preventing, diagnosing, curing or alleviating a disease or condition in the animal or an infestation of the animal by a pest
- curing or alleviating an injury suffered by the animal
- modifying the physiology of the animal to alter its natural development, productivity, quality or reproductive capacity or to make it more manageable
- modifying the effect of another veterinary chemical product.

According to this definition, a selenium product with a label that makes none of these claims is not a veterinary chemical product and does not require registration.

However, selenium and selenium salts are also approved active constituents. At certain concentrations, selenium and selenium salts are used for the prevention or therapy of diseases such as white muscle disease in cattle and sheep and for dermatological conditions in companion animals.

### Which selenium products for sheep generally do and do not require registration?

<table>
<thead>
<tr>
<th>Therapeutic product claims?</th>
<th>Route of administration</th>
<th>Level of selenium</th>
<th>Dose of selenium</th>
<th>Registration required?</th>
<th>Label advisory statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td>Oral dosage forms administered in animal feed</td>
<td>Levels such that the product does not fall into S4 or S7 of the SUSMP</td>
<td>Any dose less than, or equal to, 0.1 mg/kg Se BW(^1)</td>
<td>NO</td>
<td>Refer to the Label advisory statement below</td>
</tr>
<tr>
<td>YES</td>
<td>Any route</td>
<td>Any level</td>
<td>The APVMA will assess the safety and effectiveness of the label recommended dose</td>
<td>YES</td>
<td>To be decided during registration</td>
</tr>
<tr>
<td>NO</td>
<td>Oral dosage forms provided in animal feed</td>
<td>Levels such that the product does not fall into S4 or S7 of the SUSMP</td>
<td>Any dose greater than 0.1 mg/kg Se BW(^1)</td>
<td>YES</td>
<td>Refer to the Label advisory statement below</td>
</tr>
<tr>
<td>NO</td>
<td>1. Injection</td>
<td>Any level</td>
<td>The APVMA will assess the safety and effectiveness of the label recommended dose</td>
<td>YES</td>
<td>To be decided during registration</td>
</tr>
<tr>
<td></td>
<td>2. Oral dosage forms for dosing the animal directly, not administered in animal feed (eg boluses or pellets)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>Any route</td>
<td>Levels such that the product falls into S4 or S7 of the SUSMP</td>
<td>The APVMA will assess the safety and effectiveness of the label recommended dose</td>
<td>YES</td>
<td>To be decided during registration</td>
</tr>
</tbody>
</table>

SUSMP = Standard for the Uniform Scheduling of Medicines and Poisons


### Label advisory statement

Even if the selenium product need not be registered, we strongly advise manufacturers to include a warning on the product label that care should be taken to avoid oversupplementing with selenium. The use of selenium pellets and treatment of the pasture at the same time can lead to excessive selenium levels in tissues of sheep. You should also consult a veterinarian or adviser to ascertain the animals’ selenium status. The product should not be used in areas of seleniferous plants or soils in Queensland before a veterinarian has ascertained the selenium status.

The following warning statement on the product is recommended:

**SELENIUM**

**Contraindication**

Excessive tissue levels of selenium are toxic. Care should be taken to avoid over-supplementation from this product and/or concurrent use of other products containing selenium (such as pasture top dressing, pellets, drenches or vaccine containing selenium). If blood selenium levels are high, this product should not be used. The user can determine an animal’s selenium status by consulting their veterinarian.
Information guidelines and standards

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (also known as VICH) was officially launched in Paris in April 1996, as a cooperative effort between members of the regulatory authorities and the veterinary chemical industry from the European Union, the United States and Japan. The program aims to harmonise technical guidelines for veterinary product registration, and has drawn on the experience of the human pharmaceutical harmonisation initiative, ICH.

The regulatory authorities of Australia and New Zealand have observer status on the VICH Steering Committee.

To evaluate the efficacy of equine, porcine, canine, feline and poultry anthelmintics, the APVMA has adopted guidelines developed by the VICH process, such as:

- VICH GL16 (Anthelmintics: Porcine): Efficacy of Anthelmintics: Specific Recommendations for Porcines
- VICH GL19 (Anthelmintics: Canine): Efficacy of Anthelmintics: Specific Recommendations for Canines
- VICH GL20 (Anthelmintics: Feline): Efficacy of Anthelmintics: Specific Recommendations for Felines

These guidelines are to be used in conjunction with the APVMA’s Part 8 Efficacy and Safety Guidelines, as well as the World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines for evaluating the efficacy of anthelmintics.

VICH GL7 (Anthelmintics General): Efficacy of Anthelmintics: General Requirements should be read in conjunction with the specific guidelines.

There are some differences between VICH/WAAVP recommendations and recommendations for products to be registered in Australia. The VICH and WAAVP guidelines generally consider a mean percentage reduction in parasite numbers of at least 90% to be effective to support a claim. Because suboptimal efficacy can increase selection pressure for resistance, we generally consider at least 95% to be the minimum effective threshold for a claim. In some situations we may consider an even higher threshold of efficacy for a claim (e.g. Dirofilaria immitis, Echinococcus granulosus). We encourage you to use these efficacy standards when generating data for equine, porcine, canine, feline and poultry anthelmintics in Australia.

Note on geometric versus arithmetic means

In relation to Section 4.2 Geometric versus arithmetic means of VICH GL7, the geometric mean is appropriate for statistical tests where data is non-normally distributed. However, the geometric mean may underestimate the biological significance of worms in the animals with the highest worm burdens. We consider that the current information on statistics does not support the adoption of geometric means as the sole means of interpreting trial data. If the arithmetic mean for the data provided in efficacy trials shows marked variance from the geometric mean, we may take the arithmetic mean into consideration (that is, we are likely to give more weight to the arithmetic mean when there is variability in the trial data).

The VICH guidelines can also be accessed from the VICH website.

The following content can be found at http://new.apvma.gov.au/node/805

If making a submission, please reference page number: 805

Agricultural chemical products—Environment (Part 7)

Introduction

This document sets out the considerations that applicants should make when submitting environmental data as part of applications for:

- registration of an agricultural chemical product
- variation or extension of a registration of an agricultural chemical product, or
- a permit to use an agricultural chemical product.

Generally, the Environment Protection Branch of the Department of the Environment evaluates environmental data on behalf of the states or territories, who then advise the APVMA.

You should submit the following information to allow an adequate assessment to be made about the potential environmental impact of the active constituent and related products:

- the expected volume of use
- the expected exposure, behaviour and fate of the active constituent(s) when the agricultural chemical product is used as proposed
- the potential harmful effects on birds, mammals, fish, terrestrial and aquatic invertebrates, algae plus aquatic and terrestrial plants.
- This information is important in establishing whether the risk to any of these organisms posed by the proposed use of the product may be considered unacceptable or whether there are other concerns due to the behaviour of the substance in the environment.

This document covers a very broad range of data elements. However, in many cases the data that are relevant will be a subset of these, and should be tailored to the nature of the proposed application and the anticipated environmental exposure pattern. Decisions regarding which data are relevant are based primarily on the expected environmental exposure. It is unrealistic to recommend uniform data dossiers for environmental assessments, as agricultural chemical products vary widely in their environmental properties and in the ways that they are introduced into the environment. Considerable variation in the nature of the receiving environment can also be expected for different applications. This will be discussed in more detail under Relevant data.

Reference materials

The details of documents referred to in this chapter (including codes and standards) are provided in the References section. Applicants should be aware that many of these documents are updated regularly, and thus should make sure they use the latest edition.

The Environmental risk assessment guidance manual for agricultural and veterinary chemicals (EPHC 2009—referred to in this document as the Risk assessment manual or RAM), developed through the Environment Protection and Heritage Council, is a useful document that provides more detailed explanations of how data are used in the assessment process. This may be located on, and downloaded from, the Standing Council...
The Guidelines for the registration of biological agricultural products (APVMA 2005) is a useful document that provides more detailed guidelines when registering biological agricultural products.

Overview of the assessment process

Under the legislation relating to agricultural and veterinary chemical registration, the APVMA, when granting or refusing an application, needs to consider whether the proposed use of an active constituent or product, in accordance with the instructions for its use, may have unintended effects that are harmful to ‘animals, plants or things or to the environment’ (see the Agricultural and Veterinary Chemicals Code Regulations 1995 under the APVMA legislative framework). It is the Environment Protection Branch in the Department of the Environment that generally provides advice to us on the environmental aspects of applications.

The practices used in undertaking environmental risk assessments for the APVMA are described in the RAM. Environmental risk assessment consists of:

- an exposure assessment to arrive at a predicted environmental concentration or estimated environmental concentration (PEC/EEC)—to do this, considerations include the method of use of the product, scale of use, situations in which the product is used, and fate of the active constituent in the environment. Various models may be used for which specific information is relevant; for example, to estimate concentration in surface waters from spray drift or runoff. For existing chemicals, monitoring data may also be considered.

- an effects assessment to identify and classify the hazards to the environment and to determine the most sensitive endpoints in the various compartments

- risk characterisation, relating the PEC/EEC to the most sensitive endpoints to determine whether or not the risk is acceptable and, if not, consider refinements of the process or models and if or how risks may be mitigated by appropriate label advice or other action (see Figure 1).

In Figure 1, the risk quotient (RQ) is the (most sensitive) endpoint divided by the PEC/EEC. For agricultural chemicals the acute RQ should be less than 0.1, as there is an inbuilt assessment factor of 10 (see page 75 of the RAM) for most species. The same relationship is also used for chronic risk assessments, except that no-observed-effect concentrations (NOECs) or no-observable-effect levels (NOELs) are used rather than LC , EC, IC, or LR50s (depending on the endpoint), and that the chronic PEC/EECs are used, together with the RQ that should be less than 1.

In addition to evaluating toxicity hazards to non-target organisms, consideration is given as to whether there are other concerns due to the behaviour of the substance in the environment, including persistence in soil, sediment, water or the atmosphere, bioaccumulation, potential to move into groundwater or, for volatile or gaseous substances, the potential to affect the ozone layer or act as a greenhouse gas in the atmosphere.

In assessing risks to the environment, the whole life cycle of the active constituent is taken into account. Consideration is given as to whether there is any environmental exposure in Australia as a consequence of the manufacture of the active constituent or formulation and the packing of the product. Assessment of the fate of the active constituent, once released to the environment, includes consideration of:

- the rate of degradation
- the means by which degradation occurs
- the identity and amount of degradation products produced and their further degradation
- the mobility of the active constituent and major metabolites.

If significant metabolites are produced during degradation, it is recommended an effects assessment is conducted to identify and classify the hazards to the environment they represent.

Figure 1: The iterative approach to determine risk acceptability
As well as assessing data provided by the applicant, consideration is given to information available from other sources, such as literature searches and foreign environmental agency reports (for example, from the United States Environmental Protection Agency (US EPA) or European Food Safety Authority (EFSA) reports).

Environmental risk

As stated above, the risk assessment is a synthesis of the results from the evaluation of the exposure and the toxic effects. Depending on the degree of environmental hazard, consideration may be given to actions to minimise the environmental risk. For example, the APVMA may impose:

- specific restrictions—such as, ‘do not apply on steep country above 20% or 11 degrees’
- other label instructions and warnings—such as, toxic to aquatic life.

This section provided an overview of Australia’s environmental risk assessment process. The following section considers the specific data elements to enable a full environmental risk assessment.

Types of applications

The nature of the application determines which data module in Part 7 (Environment) is relevant. Each module refers to the same broad set of environmental data elements, but the actual data element varies depending upon the nature and extent of environmental exposure from the proposed use pattern and the anticipated environmental behaviour of the product.

Relevant data

The relevant environmental data you should provide for an application depend largely on the product’s expected environmental exposure. You should provide sufficient data to allow us to make an adequate environmental assessment and draw a conclusion about whether or not your submission would satisfy the APVMA test (that the proposal would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment).

You should address all of the data elements discussed in this chapter. If you do not provide data to address a specific element, you should request a data waiver against the specific element and justify the waiver with a valid scientific argument; for example, by demonstrating that environmental exposure to this group of organisms will be minimal.

General

Quality of submitted studies

Data quality directly influences how confident our risk assessors can be in the results of a study and the conclusions they may draw from it. Therefore, your environmental fate and toxicity studies should be of sufficient quality for the study to be relied upon for regulatory decision-making. The process of determining the quality of data takes into consideration three aspects—adequacy, reliability and relevance of the available information to describe a given assessment endpoint.
Detailed information on how the quality of studies is determined and rated can be found in Chapter 4 of the RAM. To be suitable for regulatory purposes, your study should be of sufficient quality to achieve either a rating of:

- fully reliable, or
- reliable with restrictions

according to the Organization for Economic Co-operation and Development (OECD) approach, as used by the Department of the Environment (as described in Chapter 4 of the RAM).

Level of documentation

The documentation you provide should be complete, well organised and be presented in sufficient detail (for example, inclusion of raw data on concentrations measured or individual animal responses) to allow independent scientific assessment.

You should supply copies of original reports. Summaries, or reprints of published material, usually do not contain sufficient detail and may, therefore, only be suitable if they contain sufficient detail to allow independent scientific assessment and achieve an acceptable reliability rating.

Request for waiver of a data element

If you believe that a particular data element is not necessary, you should maintain the data heading, request a data waiver for the specific data element and provide a valid scientific argument as to why you have not submitted the data. In some circumstances, model data based on structure-activity relationships (SAR) may be suitable for submission in lieu of test reports, particularly where models have been validated.

Adverse reports

You should not omit reports, including published material, that could adversely influence the outcome of an environmental risk assessment. If you consider that such reports reach unsupportable conclusions, you should clearly justify this in the application.

Details of other regulatory applications

Your application should include details of any regulatory applications you have made for the same product to other regulatory bodies in Australia or overseas. Where available, you should provide the results of those applications and subsequent regulatory decisions (for example, copies of assessment reports, or links to where these and/or regulatory decisions may be found). If any data in those submissions have been rejected by an overseas regulatory body, you should identify this and provide justification to support why you have included the study in question.

Formulation data

Formulation toxicity is an important consideration. With the move to the OECD, format formulation data is covered in Parts III A 9 & 10.

The Department of the Environment usually focuses on data about the active constituent (for example, for aquatic toxicity), but formulation data may be more important for toxicity to honeybees, non-target arthropods and non-target vegetation, as these come into direct contact with spray or spray drift (as opposed to water or soil where there is more time for the formulation components to separate before exposure occurs). If results are available for the formulation data and the active constituent, the Department of the Environment will use the most sensitive value in its risk assessments.

For combination products involving two or more active constituents, the formulation results are used in the determination of the risks.

Chemistry and manufacture

For applications where environmental data are recommended, The OECD format is unlikely to be relevant for the limited data submissions for applications undergoing limited assessment. Therefore, for applications undergoing limited assessment, applicants should use the appropriate APVMA form as the template.

Individual data elements and the circumstances in which they are likely to be relevant are discussed in more detail below.

Elements that may be considered for any particular application

The relevant level of data for a submission is generally proportional to the potential for environmental exposure arising from the proposed use pattern. For example, for any proposal that includes broadacre, the full data set will generally be relevant, unless the Department of the Environment has previously assessed the chemical. If this is the case, the data set should only need to be updated and supplemented as appropriate.

The use pattern, together with its scale of use, type of formulation and mode of application are all relevant considerations when conducting environmental assessments.

Factors determining relevant data

Table 1 gives an idea of the potential for environmental exposure arising from four factors related to exposure. Each column is arranged in approximate decreasing order of potential environmental exposure, from high at the top, to low at the bottom. This may be used as an indicator of the extent of environmental data likely to be relevant.

<table>
<thead>
<tr>
<th>Use pattern</th>
<th>Scale of use</th>
<th>Formulation</th>
<th>Application method</th>
</tr>
</thead>
<tbody>
<tr>
<td>More</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grain and fibre crops</td>
<td>Broadacre</td>
<td>ULV</td>
<td>Aerial</td>
</tr>
<tr>
<td>Fruit crops</td>
<td>Multiple applications</td>
<td>EC</td>
<td>Mister</td>
</tr>
<tr>
<td>Vegetable crops</td>
<td></td>
<td></td>
<td>Boom</td>
</tr>
</tbody>
</table>

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Potential Environmental Exposure

<table>
<thead>
<tr>
<th>Use pattern</th>
<th>Scale of use</th>
<th>Formulation</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forestry</td>
<td>Pasture and seed crops</td>
<td>Single application</td>
<td>WP</td>
</tr>
<tr>
<td></td>
<td>Antifoulants, rodenticides</td>
<td>Granules</td>
<td>Seed dressing</td>
</tr>
<tr>
<td>Less</td>
<td>Glasshouse crops and turf</td>
<td>Small acre</td>
<td>Backpack</td>
</tr>
<tr>
<td></td>
<td>Premises</td>
<td>Home gardens</td>
<td>Individual baits</td>
</tr>
</tbody>
</table>

ULV = ultra-low volume; EC = emulsifiable concentrate; WP = wettable powder

The following scenarios, based on information in Table 1, are provided to demonstrate relevant data for various levels of environmental exposure. These scenarios are not exhaustive, and are indicative only. However, they may be used as an example and a guide for your decision-making process. Additionally, you may wish to make an application for a technical assessment.

Variations in relevant data—example scenarios

When addressing the data relevance, you may decide not to provide data, or provide minimal data, for a particular data element, because of the use pattern or indications from other data. For example, if the chemical’s volatility is low, then dissipation-in-air studies would not be recommended; or if acute toxicity studies indicate the chemical is practically non-toxic, then short-term and chronic studies may not be recommended, unless it was persistent, or there were good reasons to suggest the acute chronic ratio is very high, such as with insect growth regulators. If you wish to use this reason or scientific argument for the waiver of data, you should clearly state this.

The mode of application of a chemical, as illustrated in the examples above, can often decide the extent of environmental exposure. For instance, if the chemical is to be aerially sprayed, then the data relevance (both fate and toxicity) are likely to be high because this application type has the potential for widespread environmental exposure to non-target areas and non-target organisms. Misters or air-assisted sprayers in orchard situations are also likely to have potential for widespread environmental exposure to non-target areas and for these you should therefore submit a similar degree of fate and toxicity data.

Scenario 1: Insecticide

Use pattern | Scale of use | Formulation | Application |
-------------|--------------|-------------|-------------|
Grain and fibre crops | Broadacre | Ultra-low volume | Aerial |

For example, if you want to register a new insecticide that is aerially sprayed onto broadacre crops, you should address all data elements, given the wide dispersive exposure pattern. In addition, you should also place special emphasis on the potential for overspray and spray drift, as well as for run-off in surface water and the effect on non-target invertebrates.

For crops where integrated pest management (IPM) is routinely practiced, such as pome fruits, screening studies that are not following good laboratory practice may be useful in addition to the standard laboratory tests. Non-target organisms that should be considered include bees and earthworms, predators, parasites, and detritus feeders. Field efficacy studies addressing impacts on non-target organisms or screening tests for activity of metabolites will also be useful for environmental assessment.

Scenario 2: Herbicide

Use pattern | Scale of use | Formulation | Application |
-------------|--------------|-------------|-------------|
Grain and fibre crops | Irrigated | Emulsifiable concentrate | Boom |

For sugar cane, cotton or summer grain crops that are irrigated, even if the product is applied by boom spray, you should address most of the fate data requirements because of the potential for movement off-site in surface water (either as release of tail waters or storm water). The data should be reflective of soils typical for the area for the latter cases, most notably the heavy cracking clays. In contrast to Scenario 1 above, is the situation where an applicant registers a herbicide to control pre-emergent weeds that will be applied as a blanket spray by low-boom spray, with a coarse spray. Based on the proposed crops for which this will be applied, the soils are expected to range from a light sandy loam to heavier silt loam. In this scenario it is clear that the chemical has the potential, if moderately water soluble and applied at a high rate, to be transported in surface waters or leach to groundwater while the potential for spray drift is comparatively low.

Scenario 3: Insecticide or fungicide seed dressing

Use pattern | Scale of use | Formulation | Application |
-------------|--------------|-------------|-------------|
Grain and fibre crops | Broadacre crop | Emulsifiable concentrate | Seed dressing |

In contrast to Scenario 1, Scenario 3 deals with a situation in which, if the formulation were a granule or the application was as a seed dressing, there will not be a high degree of drift or spread of the chemical off target. However, there would be a greater relevance for avian toxicity studies because of the greater potential for poisoning birds from ingesting granules and treated seeds. A wider range of bee studies may also be relevant if the insecticide or fungicide is translocated to the pollen or nectar.

Scenario 4: Residential or commercial rodenticide

Use pattern | Scale of use | Formulation | Application |
-------------|--------------|-------------|-------------|
Rodenticides | Single application | Individual baits | Baiting |

If the product is a rodenticide and put out as field bait, then avian and non-target mammalian toxicity data would be relevant, but aquatic data would be less relevant because exposure to aquatic life is expected to be very low when the bait is used according to label directions. If the product is used on residential or commercial premises, then avian and non-target mammalian toxicity data requirements are potentially lower, due to the lower environmental exposure. However, some data are still relevant, particularly for anticoagulants, due to the length of time taken for the target animal to die, and the potential for dead or dying animals to move into the open. Further, it should be made clear if there are attractants in the formulation or baits that might result in non-target organisms being attracted to the baits.

Scenario 5: Poultry shed insecticide

Use pattern | Scale of use | Formulation | Application |
-------------|--------------|-------------|-------------|
Premises | Single application | Wettable powder | Backpack |

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Information guidelines and standards

For a poultry-shed insecticide, a basic set of environmental chemistry and fate is relevant, as well as some biodegradation (that is, metabolism or transformation) studies, especially those performed using relevant (that is, soil) test systems. A request for data waiver for mobility studies (particularly for spray drift, and possibly volatility and leaching potential) could be justified with a suitable argument as the insecticide will be applied to building surfaces, with an expected very limited exposure to soil.

If, however, the insecticide was expected to contaminate chicken litter (for example, because of different management practices or use pattern), then more biodegradation, mobility and field dissipation studies would be relevant because of the potential use of the litter as fertiliser. Similarly, only a limited set of environmental toxicology would be relevant because of the insecticide’s generally low environmental exposure, unless contaminated litter was subsequently used as a field dressing.

Other issues

For chemicals (and their major degradates—defined as more than 10 per cent of applied chemicals) that may persist in the environment (identified through laboratory studies on hydrolysis, photolysis, metabolism studies, and frequency of application), field accumulation studies will be relevant, particularly if exposure is high, and there is likely to be carryover of residues in soil, etc. between years or seasons. This can be tested through the use of some basic modelling using the half-life (see Chapter 5 of the RAM). In this case, the scale of field use (that is, broadacre versus glasshouse) is not likely to be sufficient justification to request a data waiver of these data elements, as a chemical used at high rates and mobile might be very persistent, and therefore of possible concern in its potential to accumulate and/or leach to groundwater, even if used in glasshouses.

All data generated from field dissipation studies, or other studies performed for ‘realism’ or ‘environmental relevance’ such as microcosms or mesocosms, should use the appropriate formulations for use in Australia to be of value in assessing the risk of the active constituent.

In summary, all data elements are likely to be relevant for active constituents in products that are used in broad scale applications, and it is mainly in the specialty areas that a data waiver for certain data elements may be applicable.

Other areas of toxicity testing

The areas of environmental risk assessments for which relevant data have changed over the past decade include:

- ecotoxicity tests for at least four algal species and Lemma species—these should be included for all herbicides and fungicides due to the potential for harm to these species from these types of pesticides (fewer data points may be adequate for other types of pesticides)
- information on non-target terrestrial plants—of which data for herbicides are particularly relevant, but is also important for fungicides
- sediment testing—this is an important area of toxicity in the aquatic environment, particularly for insoluble persistent pesticides. As noted in Chapter 6 of the RAM, the route of exposure is an important factor. Where exposure is primarily through chemical bound to soil or sediment (for example, run-off in the sorbed state), data based on OECD test guideline (TG) 218 are more appropriate as the test is performed with the substance pre-mixed with the test sediments. In contrast, for exposure directly to the water column (for example through spray drift), data based on OECD TG 219 using spiked water is more appropriate.

Combination toxicity testing

Combination toxicity data are relevant for formulations containing two or more active constituents, to allow assessment of any increased toxicity from the combination product. The extent of relevant combination toxicity will depend on both the exposure and toxicity; for example:

- for a seed dressing, combination aquatic toxicity may not be relevant
- for birds, combination toxicity may not be relevant if toxicity of both actives is low
- for aquatic toxicity, relevance might depend on whether one active constituent’s toxicity swamps the other
- for aquatic toxicity, if one group (say algae) is 100 times more sensitive for both actives, only that level should be tested
- if the taxonomic groups that are most sensitive for the individual active constituents are not the same as those of the combined constituents, formulation data is relevant for all three groups (see RAM, page 44).

Data will also be relevant for all deliberate (mandatory) tank mixes where the draft label’s directions for use or critical comments says ‘must always be applied with X’. This can apply to all applications or only in certain circumstances. These data will not be expected if directions are only present on another part of the label which says ‘Compatible with…’ or ‘May be tanked mixed with…’. Given the variable extent of mandatory tank mixing that may appear on labels, an estimation of toxicity based on the concentration addition equation is generally more acceptable than for combination formulations.

Data evaluation and guidelines

You are encouraged to conduct your own environmental risk assessment, based on the expected environmental exposure arising from the proposed use volume and pattern, and the data or argument submitted to address relevant data elements. This assessment is highly recommended, as it identifies which data elements require particular attention. The risk assessment forms part of the crucial determination of which elements are relevant for a particular application, as described above under the heading Elements that may be considered for any particular application due to their intrinsic nature.

This risk assessment corresponds to point 6.8 (environmental risk mitigation) in the tier III overall summary and assessment known as Document N under the OECD format. The risk assessment should be based on a concise summary of the data presented in the active substance and formulated product dossiers, supported with a statement of your overall assessment of the dossier and the conclusions you believe should be reached on the basis of the data and information you have provided. That statement should have regard to the weight of the evidence available (the extent, quality and consistency of the data) and the criteria and guidelines for environmental evaluation and decision making used by the APVMA. These criteria and guidelines are described below.

Four step process

As described in the RAM (pages 8–10), the environmental risk assessment is a four-step sequential process:

- step 1—problem formulation
- step 2—an environmental exposure assessment to determine the concentrations of the chemical that are likely to occur in the environment
- step 3—an environmental effects assessment, consisting of an evaluation of toxicity data for organisms that are likely to be exposed, based on the exposure assessment, to determine the concentrations that are likely to be harmful to these organisms
Information guidelines and standards

- step 4—environmental risk assessment that integrates the outcomes of the exposure and effects assessments to determine whether the use of the chemical according to label directions is likely to be harmful to non-target organisms in the environment.

The exposure and effects assessments are interdependent, in that the exposure assessment will determine which data elements are relevant for environmental effects, while the effects assessment will determine the level of detail and refinement relevant for the exposure assessment.

The procedures followed for environmental risk assessment are discussed in more detail below. The discussion is deliberately presented from a general perspective, as it is unrealistic to prescribe a specific procedure due to the variability of environmental exposures and risks across different products and use patterns. Further, some product types, such as antifoulants, have very specific data elements that do not pertain to crop protection chemicals. Such examples are presented in more in Specific recommendations for particular proposals.

Environmental exposure assessment

The amount of chemical likely to be released to the environment is a central tenet of environmental exposure assessment. The Department of the Environment considers the chemical in the context of ‘cradle-to-grave’. The environmental exposure assessment will determine which part(s) of the environment (air, soil, water and biota) will be exposed to the chemical, and the likely level of exposure through its use as stated on the proposed product label and predicted market volume. This includes consideration of environmental exposure arising from the manufacture or formulation, and from disposal of excess or spent chemical (for example, dipping solutions, after appropriate treatment), unused product, and empty containers.

Amount of chemical to be used

In your application, you should provide the estimated quantity (in tonnes or litres) of chemical or product to be imported, manufactured, formulated or repacked up to, and including, market maturity.

Manufacturing plant (active constituent) and formulating plant (product)

For active constituents where the manufacturing plant is located in Australia, and for all product formulation and packaging processes taking place in Australia, you should provide a brief summary of the following:

- details of the release of the chemical to the environment resulting from all manufacturing, formulation and packaging operations (for example, from disposal of bulk containers and rinsings from cleaning machinery). This will include total amounts released to water, air and land, concentrations in effluent streams, and the control technology used to minimise release.
- the proposed means of disposal of waste product arising from manufacturing, formulation and packaging operations (eg spilled material and off-specification batches).

Use and application

To allow an accurate assessment of the environmental hazard, you should provide information about label claims (uses) and application methods to determine which environmental compartments are likely to be exposed to the chemical. Therefore, information on the following is relevant:

- details of the method of application (for example, granules incorporated into the soil; type of spraying [ground directed, ground boom, ground misting, aerial]; baits or lures; fumigation; dipping)
- details of factors influencing mobility or transport or spray drift of the product (for example, droplet size, equipment used, nozzle type[s], size[s], pressure range and angle)
- fundamental characteristics of the environment that may influence transport and degradation of the chemical (for example, irrigated pasture or crop, type[s] of irrigation, soil types and range, rainfall, cropping system and area under cultivation to that crop).

Crop profiles are particularly useful when the active constituent is only proposed for restricted uses or limited applications, as the characteristics of the environment can play an important role in deciding the amount of fate and toxicity data required.

Product disposal

You should provide information on disposal of:

- empty containers
- unused product
- diluted-for-use chemical.

The applicant should consider developments in these areas.

- The National Farmers Federation (NFF), CropLife Australia, Animal Health Alliance (Australia) Ltd, VMDA and the Australian Local Government Association (ALGA) have together developed the following initiatives:
  - DrumMUSTER as the solution to the safe collection and recycling of cleaned chemical containers
  - ChemClear for the collection of unwanted rural and agricultural and veterinary chemicals.

General label statements for the proper disposal of product and used containers can be obtained from the Agricultural Labelling Code. Furthermore, part of the Department of the Environment’s assessment and advice to the APVMA may include appropriate label disposal instructions for the particular product under assessment.

Spent dipping solution disposal

The following criteria for disposal of spent dipping solutions to land have been adopted by the APVMA based on 10 active constituents used in dips and following their drafting and approval by its Registration Liaison Committee:

- the half-life in soil is less than 10 days at the likely concentrations following dip disposal, and/or
- the active constituent(s) should be able to be denatured safely, quickly and completely (more than 98 per cent in two hours) prior to disposal
- if repeat applications are to be made to the same site and denaturing is not possible, these should not occur until four half-lives have passed
- the spent dip should be evenly spread over flat land at a rate not exceeding 100 000 litres per hectare for spent sheep dips and 20 000 litres per hectare for spent fruit dips
- the disposal site must be dedicated and adequately banded (the soil should be at least 15 centimetres high).
While an examination of the data holdings and label statements of all current active constituents and their associated products used in dipping is being undertaken, any application for new active constituents or extension of existing actives and associated products to be used in dips should be accompanied by:

- data in the above areas to allow assessment of whether disposal to land is feasible, and/or
- the drafting of suitable label statements.

**Predicted environmental concentration**

Chapter 5, Environmental exposure assessment of the RAM provides a more detailed discussion of the predicted environmental concentration, and provides guidance and more details on the range of environmental chemistry and fate tests. In particular, it provides details for the determination of estimated or predicted environmental concentrations (PECs).

A key element of the exposure assessment is the spray quality, as this is one of the determinants of drift, and a key input in models used to estimate the amount of drift at different distances from the point of application. Spray quality parameters need to be clearly defined on product labels. Applicants should refer to the APVMA operating principles in relation to spray drift risk (APVMA 2008).

You should estimate PECs in water, air, soil, vegetation and/or animals depending on the use pattern. If no such exposure is expected in any compartment, applicants can request a data waiver and provide this as an argument for not providing particular data elements. For example, aquatic exposure would not be expected from the use of household rodenticides. Therefore, toxicity data for aquatic life would not be relevant for such an application; although you should provide such data if they are available.

**Tiered PECs**

The environmental exposure assessment is a stepwise or tiered process under which PECs are first determined under worst-case conditions using simple screening models. If the initial PECs are at harmful levels, based on the environmental effects assessment, they are progressively refined to reflect more realistic exposures. In this way, the analysis for a particular chemical will be kept to a minimum, allowing resources to be directed towards chemicals with the greatest potential for causing ecological harm.

**PECWater—spray drift**

The initial estimates of the predicted aquatic concentrations (PECWater) are based on the scenario of direct application to a water body that is three metres wide and 15 centimetres deep, at the maximum proposed rate. You should supplement the short-term (acute) PECs with long-term (chronic) PECs if the chemical is persistent or applied repeatedly within a season. Then, refine these estimates as necessary to reflect exposure through spray drift, again using progressive refinement from an initial worst case assumption that this represents 10 per cent of the maximum proposed rate. More realistic exposures are then modelled as needed. For ground-based application, AGDRIFT is used, while exposure from aerial application is modelled using AGDISP. These models are used to determine the buffer distances necessary to protect sensitive downwind habitats, such as aquatic environments or areas of native vegetation.

**PECWater—run-off and drainage**

Spray drift may not be the most significant route of aquatic contamination for many chemicals, particularly those that are persistent and mobile, and are widely used within a catchment. An OECD based model (Probst et al. 2005) has been developed that considers the edge-of-field concentration. The model considers that the application rate, topography—in particular the slope of the field to which the pesticide is applied—the magnitude of the rainfall and run-off events, and the persistence and mobility of the chemical are the most important factors. Additionally, placement of the pesticide, an allowance for the heterogeneity of fields and pesticide bound to suspended sediment are also considered.

Based on data available, the model considers a worst-case scenario of a 100 millimetre rainfall event with 20 per cent of that water running off. On a hectare basis this results in 200 cubic metres of run-off water. An initial screen that does not consider the properties of the chemical is performed. Depending on the likely topography of the cropping scenario, the run-off water is assumed to carry 5 or 10 per cent of the applied chemical, once heterogeneity of the field is allowed for. Consideration is given to the interception and retention of the applied chemical by foliage for foliar applications. Suspended sediment bound pesticides are generally only considered for sparingly soluble chemicals with solubility of less than one milligram per litre. This screen can be used to exclude low risk chemicals from further consideration.

**Refined run-off PECs**

If the predicted aquatic exposure from the screening model for run-off indicates that aquatic organisms may be exposed to harmful concentrations of the chemical, you should refine the assessment of the edge-of-field concentration.

Exposure scenarios for run-off and drainage are more complex than those for spray drift because the properties of the chemical and of the soils where it is used will influence the mobility and stability of the chemical, and consequently the levels of aquatic exposure.

The model assumes three days degradation of the chemical and the sorption/desorption coefficient (Koc) value, usually based on the organic carbon partitioning coefficient (Koc) of the chemical and the organic carbon content of soil as determined by ANRA (2001). The modelled, refined edge-of-field concentration may also be compared with any actual studies of run-off of the chemical of interest. Dilution of the edge-of-field water is considered in 1500 cubic metres of environmental water, which is equivalent to a one hectare water body of 15 centimetres deep, or the daily flow of a low-flow primary stream. Initially, it is assumed that the water body is entirely fed by a 10 hectare field that is 100 per cent treated at the maximum rate.

Refinement of the model considers partitioning of the chemical to sediment using the same model as that used for determining the PEC sediment as outlined in the RAM. The model is being further developed to consider the fate of the chemical in water and more hydrologically realistic catchments that consider the likely use pattern of the chemical in the catchment.

**PECsSediment**

As noted above, for hydrophobic chemicals rapid partitioning to the sediment may be expected. The PECsSediment may be estimated from the PECWater based on the partition coefficient. More information about estimating the PECsSediment can be found in the RAM.
PECSoil

PECs in soil are usually based on the maximum proposed application rate, as effects on soil organisms in treated areas need to be evaluated. A soil depth of 10 centimetres is generally assumed, but this may be decreased for chemicals that sorb strongly to soils, or increased for more mobile chemicals. PECs in soil can be refined where needed by considering the persistence of the chemical in soil. Similarly, the PECs in off-target soils can be refined based on modelling of spray drift. Measured data are generally preferred over model outputs and may replace the model predictions where necessary.

PECFood

Concentrations on vegetation are estimated using the modified Kenaga nomogram (Pfieger et al., 1996). The nomogram may also be used, with qualification, to estimate residues on insects. These estimates are used to evaluate dietary risks to non-target organisms such as birds and mammals. The highest residues generally occur on foliage, and can be used as the basis for an initial risk assessment based on the assumption that only treated foliage is consumed.

The risk assessment can be refined as needed, for example by considering a more realistic diet including insects as well as vegetation. The nomogram can be used to estimate residues on insects, based on those for fruits and seeds, but caution is needed as there are limitations in using fruits and seeds as surrogates for mobile organisms such as insects.

Environmental effects assessment

Chapter 6, Environmental effects assessment of the RAM provides a detailed discussion of this topic, including a very wide potential range of environmental effects tests.

Again, the amount of relevant data is likely to be dependent upon the extent of exposure to the various environmental compartments (air, water soil, sediment and biota, including plants), and the toxicity of the active constituent and products containing it, to organisms inhabiting these compartments. If the exposure is low to a particular environmental compartment, limited data will be relevant, particularly if the toxicity to representative organisms from the compartment is also low. Conversely, if the exposure to a particular compartment and the toxicity to representative organisms inhabiting this compartment are both high, a much more extensive suite of toxicity tests will be relevant.

Formulations, combinations and tank mixes

Toxicity information on the formulation to be used is also an important consideration, including for combination products, to clarify whether the toxic effects exerted by the different active constituents are additive or not. As noted above, you should address toxicity of the mixture in the case of deliberate tank mixes where the label instructs that for general, or for a particular use, the product and its active constituent(s) must always be mixed with another, different, active constituent contained in existing products.

Toxicity to non-target terrestrial plants

The discussion and guidance on the area of toxicity to non-target terrestrial plants should also be noted, in particular the need to extrapolate from a limited set of tested plants, usually other crop species, which emphasises the value of obtaining incident data during trialling and testing the active constituent and its proposed formulations.

QSARs versus field testing

The RAM also mentions the possible use of quantitative structure–activity relationships (QSARs). As noted, these are generally less useful in predicting toxicity of pesticides as opposed to industrial chemicals due to their relatively complex structures and because they have specific modes of action that are not easily incorporated into general structural relationships. Verified models should be used.

On the other hand, field testing studies such as microcosms or mesocosms are potentially very powerful tools in defining toxicity in actual or real-life situations; in particular, for testing any mitigating effects such as reduced toxicity in the presence of sediment as opposed to testing in clean laboratory tanks or vessels. Microcosm testing is the preferred approach.

Environmental risk assessment

Chapter 8, Risk characterisation of the RAM provides a detailed discussion of environmental risk assessment; the basic principles of which are outlined below. Applicants are encouraged to consult the RAM for further detail or clarification. Please note, however, that this chapter of the RAM is not in the order of the internationally agreed OECD format.

Risk quotient (RQ) method

The approach followed for environmental risk assessment is based on that used by the US EPA, as originally developed by Urban and Cook (1986). This is often referred to as the quotient or risk quotient (RQ) method. It compares the PEC as the numerator with the toxicity as the denominator. Acute toxicity is usually expressed as the median lethal concentration (LC50) or median effect concentration (EC50). For plants, a more sensitive measure (for example the EC25) may be used. Chronic toxicity is usually expressed as the NOEC. The objective is to ensure that the quotient does not exceed levels of concern.

Toxicity exposure ratio (TER) method

The approach followed by the European Union entails the determination of the toxicity exposure ratio (TER), which is the inverse of the risk quotient. Under this approach, the TER must be maintained above levels of concern. While the APVMA would prefer that applicants use the risk quotient method, it will accept risk assessments based on the TER approach, particularly for major data submissions in the agreed OECD format.

Level of concern (LOC)

The level of concern (LOC) that is generally adopted by the APVMA for risk assessment of acute toxicity to aquatic organisms (fish, invertebrates, algae and aquatic plants), terrestrial animals (birds, mammals and invertebrates) and plants is generally 0.1. As noted in the comparison tables in Section 8.9 of the RAM, this is often more conservative than the approach of the US EPA, though the US EPA’s level of concern (unity = 1.0) for
chronic toxicity is adopted by the APVMA. This contrasts with the stricter LOCs adopted by the EU.

The iterative approach

When assessing risk, it is generally the situation that every case cannot be accounted for, so the applicant should follow an iterative process (refer to Overview of the assessment process) by considering:

- a worst-case scenario such as a direct overspray to shallow water; and, if needed,
- a series of refinements that account for other factors and results in setting more realistic scenarios at each step, such as the 10 per cent spray drift followed by spray drift modelling (refer to Figure 1 above).

Mitigating risk

Where levels of concern are exceeded, the applicant should propose measures such as label instructions to mitigate the risk. For example, labels could require the observation of unsprayed buffer zones downwind of the treated area to protect sensitive aquatic or terrestrial environments.

Deterministic versus probabilistic risk

As the quotient method is deterministic, it can only indicate the possibility of harmful effects, and not their probability or extent. The size of the quotient bears no relation to the ecological significance of any harm that may be caused by exposure to the chemical.

You have the opportunity to present further data or argument where you consider that any harm arising from exposure to the chemical will be limited. For example, if exposures are transient and the affected organisms have a high reproductive capacity, you may present data or argument to support a more relaxed approach to mitigation than would result from rigid maintenance of quotients below levels of concern. The overriding consideration is protection of populations and ecosystems, rather than individual organisms.

Chapter 10. Probabilistic risk assessment of the RAM provides a discussion and comparison of OECD, US EPA and EU approaches to this emerging tool for conducting environmental risk assessments. Probabilistic risk assessment methods provide more information on the probability and extent of harm associated with the use of a chemical. Such methods provide a more realistic and often less conservative basis for determining the risk, and the nature and extent of any measures that may be necessary to mitigate the risk, but generally need to be supported by a much larger database. This method is used where sufficient data are available. Probabilistic approaches to risk assessment used by applicants will be evaluated on their merits.

Secondary exposure risk

Secondary exposure effects are emerging areas of risk assessment, particularly through the terrestrial food chain and its importance in bioaccumulative and persistent pesticides.

Specific recommendations for particular proposals

The APVMA recommends that you submit a comprehensive data package for products with specific-use patterns and/or situations, because of their intrinsic nature. Examples include:

- cooling system antifoulants and similar products
- timber preservative treatments (see OECD Scenario document)
- biotechnology products (see Reference materials for further details)
- products containing nanomaterial
- swimming pool products.

While it is not possible to address all of these specific-use patterns in this document, an example of a specific-use situation (marine antifoulant paints) has been addressed below to demonstrate the provision of additional data elements.

Marine antifoulant paints

For assessment of a marine antifoulant paint it is important to have a comprehensive set of fate data relevant to the fate of the active constituent(s) in estuarine or marine situations, and of ecotoxicity data relevant to estuarine or marine species. The dossier should also indicate clearly the method of use and types of vessels that are to be treated with the product.

The risk assessment will compare predicted and, if available, measured levels of the active constituent with ecotoxicological endpoints. Marina and harbour situations or other scenarios will be considered, as appropriate for the intended use of the paint.

MAMPEC model

Modelling is used to predict concentrations in water and sediment arising from release of the active constituent during the life of the coating. According to the procedures discussed in the Emission scenario document for antifouling products (OECD 2005), the MAMPEC model will be used. In the absence of reliable MAMPEC scenarios for representative Australian harbours and marinas, scenarios for major New Zealand harbours and marinas will be considered (Gadd et al. 2011), in addition to OECD default scenarios (van Hattum et al. 2002). You may also wish to submit your own modelling using MAMPEC or other models.

 Certain information on the physicochemical properties and environmental fate of the active constituent is important for modelling with MAMPEC, as described in the model and related guidance documents (van Hattum et al. 2002 and 2011, Baart et al. 2008, CEPE Anti-Fouling Working Group 2003).

Release routes

Information is also important on the release rate of the active constituent from the coating. Generally, the steady-state release rate is considered, as discussed in OECD (2005). Annex 2 to that document (CEPE Anti-Fouling Working Group 2003) explains how the release rate may be determined, including the use of ASTM/ISO laboratory methods to measure the release rate, field tests, and the European Paint Industry (CEPE) mass balance calculation method.
You should submit available results from such testing with the same or very similar paints, but we will compare these results with calculated results by the CEPE method to determine the most appropriate value for further modelling. You should provide various parameters if you are using the CEPE method, and these are often not evident from the product label or associated information.

**CEPE input data**

You should ensure that you provide all the necessary information to enable us to calculate the release rate, or to confirm a release rate which you have already calculated. As indicated in Appendix 1 of CEPE Anti-Fouling Working Group (2003), the input values for the equations that can be used include:

- the dry film thickness
- the specified lifetime for that dry film thickness
- the weight fraction of the active ingredient in the biocide
- the concentration of the biocide in the wet paint
- the solid volume ratio (volume of dry paint versus the volume of wet paint in per cent)
- the specific gravity of the wet paint.

**Monitoring data**

If monitoring data are available (including published scientific papers), you should submit these together with a discussion or risk assessment of the levels that have been found in the environment relative to ecotoxicity data.

**Emission scenario documents**

An Emission Scenario Document (ESD) is a document that describes the sources, production processes, pathways and use patterns of a chemical, with the aim of quantifying its emissions (or releases) into water, air, soil and/or solid waste. There are a range of ESDs prepared by the OECD for various situations, which may provide useful guidance to applicants in preparing risk assessments for some agricultural product situations. These documents may be located on, and downloaded from, the OECD web site.

Many of the ESDs listed on the OECD website relate more to industrial than agricultural or veterinary chemicals, but those currently available that may be useful for products considered to be agricultural products include:

- Series No. 2: Wood preservatives
- Series No. 4: Water treatment chemicals
- Series No. 13: Antifoulants main document and annex (OECD 2005)
- Series No. 14: Insecticides for stables and manure storage systems
- Series No. 18: Insecticides, acaricides and products to control other arthropods for household and professional uses.

The list of ESDs is continually growing, so you should check from time to time for updates. OECD scenarios are likely to be worst-case, and will be adapted as appropriate for local situation.

**Format for submission of Part 7 environment data**

**OECD format**

The APVMA recommends that all data submissions be made in accordance with the OECD common format for pesticide registrations. As the OECD states:

> 'Pesticide producers, who are responsible for testing any pesticide they want to register, usually have to present registration submissions in different formats for different OECD countries. The OECD common format should therefore reduce redundancies in the preparation of submissions by industry.'

You are advised to follow the comprehensive guidance documents and forms located on the OECD website, when preparing submissions.

**More information**

Applicants seeking further information about relevant environmental data for specific uses may wish to apply for pre-application assistance or make an application for a technical assessment.

**References**


Veterinary—Preamble for WAAVP guideline: Combination anthelmintic products for ruminants and horses

The World Association for the Advancement of Veterinary Parasitology (WAAVP) is a not-for-profit organisation for scientists who study the parasites of non-human animals. The guidelines developed by the international expert working groups of the WAAVP assist in the international harmonisation of standards and procedures for the evaluation of veterinary anthelmintics.

In 2012, the WAAVP published the following guideline for evaluating the efficacy of anthelmintic combination products targeting nematode infections of ruminants and horses:


We have adopted this WAAVP guideline and provide the following additional guidance to assist applicants conducting trials for the registration of such products in Australia.

This guideline is to be used in conjunction with the APVMA’s Efficacy and Safety Guidelines (Part 8), as well as the following WAAVP and VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guidelines for evaluating the efficacy of anthelmintics:

- **WAAVP** second edition guidelines for evaluating the efficacy of anthelmintics in ruminants (bovine, ovine, caprine)
- **WAAVP** second edition guidelines for evaluating the efficacy of equine anthelmintics
- **VICH GL7** (Anthelmintics: general)—Efficacy of anthelmintics: general requirements
- **VICH GL12** (Anthelmintics: bovines)—Efficacy of anthelmintics: specific recommendations for bovines
- **VICH GL13** (Anthelmintics: ovines)—Efficacy of anthelmintics: specific recommendations for ovines
- **VICH GL14** (Anthelmintics: caprines)—Efficacy of anthelmintics: specific recommendations for caprines
- **VICH GL15** (Anthelmintics: equine)—Efficacy of anthelmintics: specific recommendations for equines

Because of Australia’s unique environmental and geographical features, farm management practices, animal breeds and parasite burdens and their population dynamics, there are some differences between the WAAVP/VICH recommendations and our recommendations for products that are to be registered in Australia.

The following additional guidance is provided for applicants proposing to register combination anthelmintic products for ruminants and equines in Australia:

- Because of Australia’s history of parasite resistance selection, we recommend that most of the confirmatory field efficacy work be conducted within Australia under typical farm management practices covering relevant geographical regions.
- We will apply the same efficacy standards to combination anthelmintic products that we apply to single-constituent anthelmintic products (please refer to our additional guidance information for anthelmintics for ruminants and anthelmintics for non-ruminants). These efficacy

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standards are summarised in Table 1.

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Host species</th>
<th>Claim for treatment/control</th>
<th>Claim for persistent effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nematodes</td>
<td>Sheep and goats</td>
<td>&gt;95%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Nematodes</td>
<td>Cattle and equines</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Liver fluke</td>
<td>All</td>
<td>&gt;90%</td>
<td></td>
</tr>
</tbody>
</table>

We encourage you to use these efficacy standards when generating data for combination anthelmintic products for ruminants and equines in Australia. These criteria are usually sufficient to give us confidence in the product’s efficacy in Australia’s unique conditions.

Claims for efficacy against resistant parasite species will need to be demonstrated in the data provided for registration.

If you have efficacy data generated overseas, submit that data at the time of the product registration application.

**Geometric versus arithmetic means**

In relation to section 4.2 of VICH GL7 ("Geometric versus arithmetic means"), the geometric mean is appropriate for statistical tests where data are non-normally distributed. However, the geometric mean may underestimate the biological significance of worms in the animals with the highest worm burdens. We consider that the current information on statistics does not support the adoption of geometric means as the sole means of interpreting trial data. If the arithmetic mean for the data provided in efficacy trials shows marked variance from the geometric mean, we may take the arithmetic mean into consideration (that is, we are likely to give more weight to the arithmetic mean when there is variability in the trial data).

The VICH guidelines can also be accessed from the VICH website.

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**Veterinary chemical products—Environment (Part 7)**

**Introduction**

This document sets out the considerations that applicants should make when submitting environmental data as part of applications for:

- registration of a veterinary chemical product (VCP)
- variation or extension of a registration of a veterinary chemical product, or
- a permit to use a veterinary chemical product.

Generally, the Environment Protection Branch of the Department of the Environment evaluates environmental data on behalf of the states or territories, who then advise the APVMA.

You should submit the following information to allow us to make an adequate assessment about the potential environmental impact of the active constituent and related products:

- the expected exposure, behaviour and fate of the active constituent(s) when the veterinary chemical product is used as proposed
- the potential harmful effects on aquatic and terrestrial organisms.

This information is important in establishing whether the risk posed to any of these organisms by the proposed use of the product may be considered unacceptable or whether there are other concerns due to the behaviour of the substance in the environment.

In contrast to assessments of agricultural chemicals, there is internationally harmonised guidance available to determine the environmental impacts of veterinary medicines. This will be discussed in more detail under relevant data.

**Reference materials**

The details of documents referred to in this chapter (including codes and standards) are provided in the References section. Applicants should be aware that many of these documents are updated regularly, and thus should make sure they use the latest edition.

For veterinary chemicals, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is particularly important. Along with Canada, Australia is an observer in the VICH program, which is a trilateral (European Union [EU]–Japan–United States [US]) program aimed at harmonising technical guidance for veterinary product registration. As noted below, two phases of environmental assessment have been agreed, Phase I and Phase II.

The Environmental risk assessment guidance manual for agricultural and veterinary chemicals (EPHC 2009—referred to in this document as the risk assessment manual or RAM), developed through the Environment Protection and Heritage Council, is a useful document that provides more detailed explanations of how data are used in the assessment process. This document may be located on, and downloaded from, the Standing Council on Environment and Water (SCEW) website.

The VICH Phase I document indicates that it applies to veterinary medicinal products other than biological products. For biological veterinary products, you should refer to the environmental guidance section of the Guidelines for the registration of biological agricultural products (APVMA 2005).

**Overview of the assessment process**

Under the legislative framework relating to agricultural and veterinary chemical registration, the APVMA, when granting or refusing a product
The practices used in undertaking environmental risk assessments for the APVMA are described in the RAM. Environmental risk assessment consists of:

- an exposure assessment to arrive at a predicted environmental concentration or estimated environmental concentration (PEC/EEC) to do this, considerations include the method of use of the product, scale of use, situations in which the product is used, and fate of the active constituent in the environment. Various models may be used for which specific information is relevant; for example, to estimate concentration in surface waters from run-off. For existing chemicals, monitoring data may also be considered.
- an effects assessment to identify and classify the hazards to the environment and to determine the most sensitive endpoints in the various compartments
- risk characterisation, relating the PEC/EEC to the most sensitive endpoints to determine whether or not the risk is acceptable and, if not, consider if or how risks may be mitigated by appropriate label advice or other action (see Figure 1).

The assessment is based on the accepted principle that risk is a product of the exposure, fate and effects assessments of the VCP for the environmental compartments of concern. In this respect, it mirrors the approach described in the Data guidelines for agricultural chemicals. The assessment is based on a risk quotient (RQ) approach, which is the ratio of the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) on non-target organisms. The RQ (PEC/PNEC) is compared against a value of one. A value less than one indicates that no further testing is recommended.

The risk assessment is an iterative process and is further refined if the RQ is more than 1, as described under ‘Environmental risk assessment’ and in Figure 1.

Figure 1: The iterative approach to determine risk acceptability

As well as assessing data provided by the applicant, we consider information available from other sources, such as literature searches and foreign environmental agency reports (for example, from the United States Food and Drug Administration [US FDA] or European Medicines Agency [EMA] reports).

Environmental risk

As stated above, the risk assessment is a synthesis of the results from the evaluation of the exposure and the toxic effects. Depending on the degree of environmental hazard, we may consider actions to minimise the environmental risk. For example, the APVMA may impose:

- specific restrictions—such as, ‘do not apply within six months prior to shearing’
- other label instructions and warnings—such as, ‘toxic to aquatic life’.

This section provided an overview of Australia’s environmental risk assessment process for veterinary medicines. The following section considers the specific data elements to enable a full environmental risk assessment.

Types of applications

In an effort to harmonise the environmental assessment to the maximum extent possible, the APVMA has adopted the VICH harmonised guidance. The VICH guidance provides a common basis for environmental impact assessments for VCPs between the EU, Japan, US, Canada and Australia/New Zealand. Two phases of environmental assessment only involve actual data generation in phase II. The VICH website has guidance on both Phase I and Phase II assessments.

In Phase I, the potential for environmental exposure is assessed, based on the intended use of the VCP. It is assumed that VCPs with limited use and limited environmental exposure will have limited environmental effects and thus stop in Phase I.

In Phase II guidance is provided for the use of a single set of environmental fate and toxicity data to be generated by applicants to obtain marketing approval in all VICH regions for those veterinary medicinal products (VMPs) identified as recommending data during the Phase I process.

Applications that do not meet VICH Phase I criteria may be assessed under an Environment (Part 7) data module. The nature of the application determines which data module is relevant.

Relevant data

The environmental data relevant to an application depend largely on the product’s expected environmental exposure. You should address all of the data elements discussed in the VICH guidance. If you do not submit data to address a specific element, you should request a data waiver against that specific element and justify the waiver with a valid scientific argument; for example, by demonstrating that environmental exposure to this group of organisms will be minimal.

General

The APVMA has adopted the VICH internationally harmonised guidance. Please follow the VICH guidelines, while taking into consideration the following comments.

Quality of submitted studies

Data quality directly influences how confident our risk assessors can be in the results of a study and the conclusions they may draw from it. Therefore, your environmental fate and toxicity studies should be of sufficient quality for the study to be relied upon for regulatory decision-making. The process of determining the quality of data takes into consideration three aspects—adequacy, reliability and relevance of the available information to describe a given assessment endpoint.
Environmental effects can occur at various stages in the life cycle of the product and there may be some emission scenarios that are not applicable to a specific region. The route and quantity of a VCP entering the environment determines the risk assessment scenarios that are applicable, as well as the extent of the exposure. Residues are generally assumed as being uniformly distributed in the compartment, even though distribution may be patchy.

Following application of contaminated manures to soil or addition to water for aquaculture products, residues are generally assumed as being uniformly distributed in the compartment, even though distribution may be patchy.

Environmental fate and behaviour data

The environmental fate and behaviour data of a VCP describe the degradation of the active constituents, through abiotic and biotic mechanisms, and their mobility, likely transport and final destination in the environment. These data are used to help estimate the predicted environmental concentrations in different environmental compartments—soils, sediment, water and dung—as appropriate, based on the proposed use pattern and physicochemical properties of the chemical. Following application of contaminated manures to soil or addition to water for aquaculture products, residues are generally assumed as being uniformly distributed in the compartment, even though distribution may be patchy.

The route and quantity of a VCP entering the environment determines the risk assessment scenarios that are applicable, as well as the extent of the risk assessment that will be needed. The VICH Phase II guidance sets out a number of emission scenarios, using various assumptions. Emission can occur at various stages in the life cycle of the product and there may be some emission scenarios that are not applicable to a specific region.

Environmental effects

Basic data elements

The basic data elements with which you should comply for environmental risk assessment of a product include its:

- fate and behaviour in the environment (environmental exposure)
- hazard—effects on non-target species (environmental hazard).

These are explained in more detail below.

Environmental fate and behaviour data

The environmental fate and behaviour data of a VCP describe the degradation of the active constituents, through abiotic and biotic mechanisms, and their mobility, likely transport and final destination in the environment. These data are used to help estimate the predicted environmental concentrations in different environmental compartments—soils, sediment, water and dung—as appropriate, based on the proposed use pattern and physicochemical properties of the chemical.

Following application of contaminated manures to soil or addition to water for aquaculture products, residues are generally assumed as being uniformly distributed in the compartment, even though distribution may be patchy.

The route and quantity of a VCP entering the environment determines the risk assessment scenarios that are applicable, as well as the extent of the risk assessment that will be needed. The VICH Phase II guidance sets out a number of emission scenarios, using various assumptions. Emission can occur at various stages in the life cycle of the product and there may be some emission scenarios that are not applicable to a specific region.
Environmental effects data are obtained from tests on standard organisms, representing organisms that are likely to be exposed to the VCP or to residues arising from its introduction into the environment. These data are used in conjunction with the anticipated environmental exposure and environmental fate data to determine the potential risk to non-target organisms, and the need for precautionary label statements or other risk management measures to minimise the potential for harm.

Non-target species

The aim of the VICH Phase II guidance is to assess the potential for VCPs to affect non-target species in the environment, including both aquatic and terrestrial species. It is not possible to evaluate the effects of VCPs on every species in the environment that may be exposed to the VCP following its administration to the target species. Consequently, the taxonomic levels tested are intended to serve as surrogates or indicators for the range of species present in the environment.

The specific test guidelines or protocols recommended in VICH Phase II are those finalised by the OECD or International Organisation for Standardisation (ISO). By following these guidelines you will have the advantage that the environmental studies you do are current and broadly acceptable to regulatory authorities on a worldwide basis. Lack of a specific study recommendation, however, does not eliminate the importance for data on the specific organism class identified. In these situations, it is up to the applicant or sponsor to seek guidance from the appropriate regulatory authority.

Data that may be needed for any particular application

The VICH Phase II guidance contains sections for each of the major branches: (1) aquaculture, (2) intensively reared terrestrial animals and (3) pasture animals, each containing decision trees pertaining to the branch. The document also contains a section that lists the recommended studies for physical or chemical properties, environmental fate and environmental effects, as well as a description of how to determine when studies may be relevant. A two-tiered approach to the environmental risk assessment is used. The first tier, Tier A, makes use of simpler, less expensive studies to produce a conservative assessment of risk, based on exposure and effects in the environmental compartment of concern. If the assessment cannot be completed with such data—due to a prediction of unacceptable risk—then the applicant or sponsor progresses to Tier B.

The VICH Phase II guidance notes that in some cases it may be possible to implement a risk management option instead of moving to Tier B. In these cases, discussion with the regulatory authority is advised. The Phase II guidance notes that it should be recognised that risk management may not be identical for all regions and, where Tier B testing is omitted in one region, it may still be recommended in another.

For certain VCPs, the VICH Phase II guidance notes that it may be necessary to go beyond Tier B, because more complex studies, specific to issues that need to be addressed or are specific to a particular region, are necessary to complete the risk assessment. It states that such studies cannot comprehensively be dealt with in a harmonised guidance document. Therefore, these issues are outside of the scope of the Phase II guidance, and should be addressed on a case-by-case basis with the appropriate regulatory authority. Examples include cases that exceed relevant trigger values in Tier B, where further testing may be warranted and/or risk mitigation measures may need to be implemented. The VICH Phase II guidance notes that, as risk management measures are not within the scope of this guidance document, no guidance on these aspects is possible.

Factors determining relevant data

As noted above, it is assumed that VCPs with limited use and limited environmental exposure will have limited environmental effects and thus stop in Phase I. This is determined through the use of a decision tree that includes the trigger values of 1 µg/L and 100 µg/kg soil, which were established for aquatic and soil compartments, respectively. According to the guidance, if the predicted environmental concentration (PEC) value calculated is less than the trigger value, a Phase II assessment will not be required. In this way, Phase I identifies VCPs that should have a more extensive environmental assessment under Phase II. Some VCPs go directly to Phase II (for example, endo- and ecto-parasiticides and aquaculture products).

In keeping with other types of chemicals—and consistent with the VICH Phase I guidance document, which mentions several times the production of a Phase I environmental impact assessment report—all new veterinary chemicals should undergo environmental assessment in Australia, regardless of whether or not they proceed to Phase II. The VICH Phase I guidance also indicates that additional environmental information should be provided for some VCPs—that might otherwise stop in Phase I—to address particular concerns associated with their activity and use. These situations are expected to be the exception rather than the rule, and some evidence in support for the concern should be available.

The Department of the Environment thus considers on a case-by-case basis whether a new VCP can be stopped in Phase I, based on the exposure scenario and the nature of the active constituent. Experience with the use of the above trigger values has raised concerns that the uses of some new veterinary chemicals have been proposed, even though significant environmental exposure may result from the proposed uses of the chemicals. For example, chemicals used on a major proportion of the Australia-wide herd or flock, or in a number of intensive animal industry sectors, for which the potential environmental impact may not be properly considered in Phase I.

Metabolites

The VICH Phase II guidance notes that the fate of chemicals in the environment is dependent on their chemical or physical properties and degradability. These properties will vary between the parent compound and the individual excreted metabolites. For example, the latter may be more water soluble than the parent compound and may also be more mobile and/or more persistent in the environment.

In general, the data you will generate will be on the parent compound, yet the risk assessment should also consider relevant metabolites. This is particularly so for pro-drugs that are efficiently metabolised into a single metabolite for which testing may be more appropriate.

Consideration of the excretion data is not initially recommended at Tier A, where a total residue approach should be taken and a PEC_{initial} should be estimated. It should be assumed that the VCP is 100% excreted as the parent compound. If, for one or more of the tested taxonomic levels, the risk quotient (RQ) is 1 or more, the metabolism or excretion data from the residues, as well as the dossier requirements for absorption, distribution, metabolism, excretion (ADME) should be considered as part of the PEC refinement.

It follows that you should include such data (summaries only) in the environment part of your submission, particularly for the target animals.

Excreted metabolites that are 10 per cent or more of the administered dose and do not form part of biochemical pathways should be added to the active substance to allow the PEC to be recalculated. If the RQ is still 1 or more after this PEC refinement and testing at Tier B, then guidance should be sought from the regulatory authority, including guidance on whether testing of the major environmentally relevant metabolites should be considered.
As noted above, formulation data would be relevant in aquaculture if the product is applied directly to the aquatic environment, and particularly if used in the open environment. For products containing more than one active constituent, the combined effect of the active constituents on non-target aquatic organisms should be considered, and thus combination toxicity data for the aquatic compartment is relevant (for further details refer to Agricultural Chemical Products—Environment (Part 7)).

**Data evaluation and guidelines**

You are encouraged to conduct your own environmental risk assessment, based on the expected environmental exposure arising from the proposed use volume and pattern, and to submit data and/or argument to address relevant data elements. This assessment is highly recommended, as it will identify which data elements require particular attention, and provide an overview as to whether your data package contains sufficient information to satisfy the statutory criteria. This risk assessment forms part of the crucial determination of which VICH phase is relevant for a particular application, as described above under ‘General’.

As noted above, the VICH Phase II guidance contains sections for each of the major branches: (1) aquaculture, (2) intensively reared terrestrial animals and (3) pasture animals, each containing decision trees pertaining to the branch. Each section also contains guidance noting the recommended physical or chemical properties, the environmental fate and environmental effects at Tier A, as well as a description of how to calculate and compare the various PECs for surface waters, soil and sediment, etc.

During VICH Phase II negotiations, it was widely recognised that the environmental assessment would be country-specific, based on the practices and guidance for the jurisdiction. It was recognised that significant regional differences (for example, animal husbandry practices, climates, soil and water types) preclude fully harmonised guidance at the time. Full harmonisation on principles of fate, effects and risk assessment was possible. However, the parameterisation and decision making is the prerogative of the individual regulatory authority. For this reason, the scope and extent of information recommended for environmental assessments for all regions cannot be completely specified. To the extent possible, the above guidance document provides recommendations for standard datasets, and conditions for determining whether more information should be generated for a given VCP.

**Four-step process**

As described in the RAM (pages 8–10), the environmental risk assessment is a four-step sequential process:

- **step 1**—problem formulation
- **step 2**—an environmental exposure assessment to determine the concentrations of the chemical that are likely to occur in the environment
- **step 3**—an environmental effects assessment, consisting of an evaluation of the toxicity data for organisms that are likely to be exposed, based on the exposure assessment, in order to determine the concentrations that are likely to be harmful to these organisms
- **step 4**—environmental risk assessment that integrates the outcomes of the exposure and effects assessments to determine whether the use of the chemical according to label directions is likely to be harmful to non-target organisms in the environment.

The exposure and effects assessments are interdependent, in that the exposure assessment will determine which data elements are relevant for environmental effects, while the effects assessment will determine the level of detail and refinement relevant for the exposure assessment.

The procedures followed for environmental risk assessment are discussed in more detail below. The discussion is deliberately presented from a general perspective, as it is unrealistic to prescribe a specific procedure due to the variability of environmental exposures and risks across different products and use patterns. Further, some product types, such as sheep ectoparasiticides, have very specific data elements that do not pertain to general veterinary chemical products. Such examples are presented in more detail below under the heading Specific recommendations for particular proposals.

**Environmental exposure assessment**

The amount of chemical likely to be released to the environment is a central tenet of environmental exposure assessment. The Department of the Environment considers the chemical in the context of ‘cradle-to-grave’. The environmental exposure assessment will determine which compartment(s) of the environment (air, soil, water and biota) will be exposed to the chemical, and the likely level of exposure through its use as stated on the proposed product label and predicted market volume. This includes consideration of environmental exposure arising from the manufacture or formulation, and from disposal of excess or spent chemical (for example, dipping solutions, after appropriate treatment), unused product, and empty containers.

**Amount of chemical to be used**

You should provide the estimated quantity (in tonnes or litres) of chemical or product to be imported, manufactured, formulated or repacked up to, and including, market maturity.

**Manufacturing plant (active constituent) and formulating plant (product)**

For active constituents where the manufacturing plant is located in Australia, and for all product formulation and packaging processes taking place in Australia, you should provide a brief summary of the following:

- details of the release of the chemical to the environment resulting from all manufacturing, formulation and packaging operations (for example, from disposal of bulk containers and rinsings from cleaning machinery). This will include total amounts released to water, air and land, concentrations in effluent streams, and the control technology used to minimise release
- the proposed means of disposal of waste product arising from manufacturing, formulation and packaging operations (for example, spilled material and off-specification batches).

**Use and application**

To allow us to make an accurate assessment of the environmental hazard, you should provide information about label claims (uses) and application methods to determine which environmental compartments are likely to be exposed to the chemical. Therefore, providing us with information on the following is relevant:
Information guidelines and standards

- details of the method of product application (for example, intravenous or intramuscular injection, oral tablet or drench, inclusion into feed or drinking water, back striping, jetting, plunge or shower dip), as well as the length of treatment, including the interval between repeat dosing
- whether a single-animal treatment or a whole- or part-herd treatment is likely, plus the stage of the life cycle of the animal to be treated (for example, porker versus sow treatment, adult sheep or lambs)
- the manure clean-out cycle of the animal housing, any treatment of manures (for example, whether manure is left to mature before spreading), the maximum spreading rate to land, and the likelihood of incorporation of manures after spreading, such as through ploughing, irrigation or rainfall.

It follows that a good description of the specific animal husbandry practices for the target animals can be particularly useful to us; for example, are the pigs or chickens to be treated intensively farmed or will they be free range and what are the typical practices, flock sizes or housing requirements. The above information is all valuable when trying to calculate local PECs. From the above discussion it also follows that simply providing the PEC calculations done for Europe or North America is not satisfactory, as the calculations should be based on Australian practices.

A description of the disease to be treated, its prevalence and contagiousness is also very useful and can give us a better understanding of the likely environmental exposure and how to derive more accurate PECs.

Product disposal

You should provide information on the disposal of:

- empty containers
- unused product
- diluted-for-use chemical.

The applicant should consider developments in these areas. The National Farmers Federation (NFF), CropLife Australia, Animal Health Alliance (Australia) Ltd, VMDA and the Australian Local Government Association (ALGA) have together developed the following initiatives:

- drumMUSTER as the solution to the safe collection and recycling of cleaned chemical containers
- ChemClear for the collection of unwanted rural and agricultural and veterinary chemicals.

General label statements for the proper disposal of product and used containers can be obtained from the Veterinary Labelling Code. Furthermore, part of the Department of the Environment’s assessment and advice to the APVMA may include appropriate label disposal instructions for the particular product under assessment.

Spent dipping solution disposal

The following criteria for disposal of spent dipping solutions to land have been adopted by the APVMA based on 10 active constituents used in dips and following their drafting and approval by its Registration Liaison Committee:

- the half-life in soil is less than 10 days at the likely concentrations following dip disposal, and/or
- the active constituent(s) should be able to be denatured safely, quickly and completely (more than 98 per cent in two hours) prior to disposal
- if repeat applications are to be made to the same site and denaturing is not possible, these should not occur until four half-lives have passed
- the spent dip should be evenly spread over flat land at a rate not exceeding 100 000 litres per hectare for spent sheep dips and 20 000 litres per hectare for spent fruit dips
- the disposal site must be dedicated and adequately bunded (the soil should at least be 15 centimetres high).

While an examination of the data holdings and label statements of all current active constituents and their associated products used in dipping is being undertaken, any application for new active constituents or extension of existing actives and associated products to be used in dips should be accompanied by:

- data in the above areas, to allow assessment of whether disposal to land is feasible, and/or
- the drafting of suitable label statements.

Predicted Environmental Concentration (PEC)

Chapter 5, Environmental Exposure Assessment of the RAM provides a more detailed discussion of this area, providing guidance and more details on the range of environmental chemistry and fate tests. In particular, it provides details for the determination of estimated or predicted environmental concentrations (PECs).

You should estimate PECs in surface and ground water, soil, sediment or dung, as appropriate under Australian conditions, depending on the use pattern. If no such exposure is expected in any compartment, you can request a data waiver and provide this as an argument for not providing particular data elements.

Tiered predicted environmental concentrations

The environmental exposure assessment is a stepwise or tiered process, under which PECs are first determined under worst-case conditions using simple screening models. If the initial PECs are at harmful levels, based on the environmental effects assessment, they are progressively refined to reflect more realistic exposures. In this way, the analysis for a particular chemical will be kept to a minimum, allowing resources to be directed towards chemicals with the greatest potential for causing ecological harm.

PECSurfaceWater—Run-off and drainage

The most significant route of aquatic contamination for many veterinary chemicals—particularly those that are persistent and mobile and are widely used within a catchment—is from run-off following spreading or disposal to land of manure that is contaminated with them. An OECD-based model (Probst et al. 2005) has been developed that considers the edge-of-field concentration. This model considers that the application rate, topography (in particular the slope of the field to which the chemical is applied), the magnitude of the rainfall and run-off events, and the persistence and mobility of the chemical are the most important factors by which run-off can be modelled. It also considers the placement of the chemical, an allowance for the heterogeneity of fields, and chemical bound to suspended sediment.

The model is based on data available and considers a worst-case scenario of a 100 millimetre rainfall event, with 20 per cent of that water running
The VICH Phase II guidance recommends you use a seedling emergence toxicity test to estimate the risk to non-target terrestrial plants from the effects exerted by the different active constituents are additive or not. As noted above, formulation data may be relevant for certain topical products. Toxicity information on the formulation to be used is also an important consideration, including for combination products, to clarify whether the toxic effects exerted by the different active constituents are additive or not. As noted above, formulation data may be relevant for certain topical products (for example, applications of ectoparasiticides to sheep) or for products added directly to water.

Refined run-off PECs

If the predicted aquatic exposure from the screening model for run-off indicates that aquatic organisms may be exposed to harmful concentrations of the chemical, you should refine your assessment of the edge-of-field concentration. Exposure scenarios for run-off and drainage are more complex than those for spray drift because the properties of the chemical and the soils where it is used will influence the mobility and stability of the chemical and, consequently, influence the levels of aquatic exposure.

The OECD-based model (Probst et al., 2005) assumes three days for degradation of the chemical and the sorption/desorption coefficient (KOC) value, usually based on the organic carbon partitioning coefficient (KOC) of the chemical and the organic carbon content of soil as determined by (ANRA 2001). The modelled, refined edge-of-field concentration may also be compared with any actual studies of run-off of the chemical of interest. Dilution of the edge-of-field water is considered in 1500 cubic metres of environmental water, which is equivalent to a one-hectare water body of 15 centimetres deep, or the daily flow of a low-flow primary stream. Initially, it is assumed that the water body is entirely fed by a 10 hectare field that is treated for 100 per cent at the maximum rate.

Refinement of the model considers partitioning of the chemical to sediment using the same model as that used for determining the PECsediment as outlined in the RAM. The model is being further developed to consider the fate of the chemical in water and more hydrologically realistic catchments that consider the likely use pattern of the chemical in the catchment.

In the case of animals grazing on pastures, a PEC may also be calculated based on excreta that may be discharged from sheep or cattle into a stream that is 1 metre wide, 100 metre long and 0.3 metre deep and flows alongside a one hectare pasture. This PECwater is based on the guidance given by the European Medicines Agency (EMA) for sheep or cattle under a pasture scenario (CVCP 2007) that one per cent of the excreta ends up in the stream, but should be based on the lower Australian stocking rate compared with 10 animals according to the EMA.

PECsediment

As noted above for hydrophobic chemicals, rapid partitioning to the sediment may be expected. You can estimate the PECsediment from the PECwater based on the partition coefficient. More information about estimating the PECsediment can be found in the RAM.

PECsoil

PECs in soil are usually based on the maximum spreading rate of manures to land, and the likelihood that the manures are incorporated into the soil after spreading, such as through ploughing, irrigation or rainfall. The PECsoil is used to evaluate the effects on soil organisms in treated areas. We generally assume a soil depth of 10 centimetres, but may decrease this value for chemicals that sorb strongly to soils, or increase it for more mobile chemicals. PECs in soil can be refined where needed by considering the persistence of the chemical in soil.

A PECsoil calculation is also relevant for sheep that are dipped, in particular when draining pens are not available. In those cases there can be a significant amount of dip solution running off from the sheep when they are released from the dip. Most dripping from wet sheep is likely to occur on the soil around the base of the exit chute or ramp from the dip. Any PECsoil calculation would depend on:

- the concentration of the active constituent in the dip
- the volume of dipping solution applied per sheep
- an assumption of how much of the dip drips off (which could be dependent on the stripping or non-stripping nature of the active constituent)
- the extent of the area contaminated
- the throughput of sheep for the particular dipping operation.

A similar calculation may also be applicable for sheep held in a holding yard after dipping, in which case the sheep density in this yard would be relevant.

Step 3—Environmental effects assessment

Chapter 6, Environmental effects assessment of the RAM provides a detailed discussion of this topic, including a very wide potential range of environmental effects tests.

Again, the amount of relevant data is outlined in the VICH Phase II guidance and is likely to be dependent upon the extent of exposure to the various environmental compartments (surface and ground water, soil, sediment and dung), and the toxicity of the active constituent, and products containing it, to organisms inhabiting these compartments. If the exposure to a particular compartment is low, limited data will be relevant, particularly if the toxicity to representative organisms from the compartment is also low. Conversely, if the exposure to a particular compartment and the toxicity to representative organisms inhabiting this compartment are both high, a much more extensive suite of toxicity tests will be relevant.

Formulations and combination products

Toxicity information on the formulation to be used is also an important consideration, including for combination products, to clarify whether the toxic effects exerted by the different active constituents are additive or not. As noted above, formulation data may be relevant for certain topical products (for example, applications of ectoparasiticides to sheep) or for products added directly to water.

Toxicity to non-target terrestrial plants

The VICH Phase II guidance recommends you use a seedling emergence toxicity test to estimate the risk to non-target terrestrial plants from the spreading of contaminated manures on land.
Quantitative structure activity relationships

The RAM also mentions the possible use of quantitative structure–activity relationship (QSAR) models. As noted, these models are generally less useful in predicting the toxicity of agricultural and veterinary chemicals (as opposed to industrial chemicals) due to their relatively complex structures and because they have specific modes of action that are not easily incorporated into general structural relationships. You should use verified models in these situations.

Step 4—Environmental risk assessment

Chapter 8, Risk characterisation of the RAM provides a detailed discussion of environmental risk assessment. The basic principles, as applicable to veterinary medicines are outlined below.

Risk quotient (RQ) method

As noted in the VICH Phase II document, the environmental risk assessment is based on the accepted principle that risk is a product of the exposure, fate and effects assessments of the VCP for the environmental compartments of concern. In this respect, the assessment mirrors the approach described in the Data guidelines for agricultural chemicals. The assessment is based on a risk quotient (RQ) approach, which is the ratio of the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC) on non-target organisms. The RQ (PEC/PNEC) is compared against a value of one. A value less than one indicates that further testing is recommended. However, in some circumstances, professional judgement is needed for a final determination.

The PEC is defined as the concentration of the parent compound and metabolites predicted to be present in the soil, water and sediment or dung compartment. Worldwide harmonisation of PEC calculations is not practical or possible at this time. Therefore, the VICH Phase II guidance document does not contain any examples of PEC calculations, but gives some general qualitative guidance needed to determine PECs. However, when calculating PECs, you should take into account the regional differences in animal husbandry practices, the different environmental conditions in the VICH regions, and the differences in treatment rates and frequency. You are responsible to determine the most appropriate method of estimating exposures for the region of interest for a particular VCP, based on regulatory guidance.

The PNEC is determined by dividing the experimentally determined effects end-point by an appropriate assessment factor (AF). The AF is intended to cover uncertainties such as intra- and inter-laboratory and species variation, the need to extrapolate from laboratory study results to the field, and from short-term to long-term toxicity (acute to chronic ratios). The PNEC value varies depending on the type of study conducted. As always, you should clearly justify any variation in the applied AF in your submission.

AFs of between 1000 and 10 are generally used in the assessment. A factor of 1000 is designed to be conservative and protective and is applied when only limited data are available. This value may be progressively reduced to 10 as more evidence becomes available. Such evidence could include:

- availability of data from a wide variety of species, including those that are considered to represent the most sensitive species
- information from structurally similar compounds, to suggest that the acute to chronic ratio is likely to be lower than that for many other compounds
- information to suggest that the chemical is rapidly degraded and not repeatedly administered, to suggest its application may not lead to chronic exposure.

The iterative approach

When assessing risk it is generally the situation that every case cannot always be accounted for. This means that you should follow an iterative process (refer to Overview of the assessment process) by:

- using a worst-case scenario, such as a total residue approach; and, if needed,
- a series of refinements to the assessment process that account for other factors and results, by setting more realistic scenarios at each step —initially through consideration of the metabolism or excretion information and the data on biodegradation in manure, soil or aquatic systems (refer to Figure 1 above).

Risk assessment at Tier A

The risk assessment approach that is recommended in the VICH Phase II guidance is to compare the PEC_{initial} based on the total residue with the PNEC derived for each of the tested taxonomic levels, as described above. If the RQ for all taxonomic levels is less than one, this should be sufficient to conclude that the VCP does not pose a risk to the environment, unless, when based on the persistence of the active substance, there is a potential for it to accumulate in the environment. Where the RQ is one or more, a risk to the environment cannot be excluded and further assessment is recommended.

PEC refinement

The first step when refining the PEC, should be to refine the PEC_{initial} based on the total residue at Tier A through consideration of the metabolism or excretion information and the data on biodegradation in manure, soil or aquatic systems. Excreted metabolites that represent 10 per cent or more of the administered dose and do not form part of biochemical pathways should be added to the active substance to allow the PEC to be recalculated. You should then compare the PEC_{Refined} with the PNEC for the affected taxonomic level and determine a new RQ for each. If the RQ is now less than one for all taxonomic levels, the assessment stops.

If the RQ is still one or more for any of the taxonomic levels tested, then the assessment moves to Tier B and we recommend that you do additional tests for the affected taxonomic level.

For pasture treatments, if the RQ is one or more for dung insects for the PEC_{Dung-initial}, then you should examine the excretion data and use the PEC_{Dung-refined} to recalculate the RQ. The PEC_{Dung-initial} assumes that the entire dose is excreted in a single day's dung. The PEC_{Dung-refined} is more realistic, as it takes account of how many days the active substance is excreted in dung and at what concentrations. If, after using this refinement, the RQ is still one or more, you should seek further regulatory guidance.

Mitigating risk
Where levels of concern are exceeded, you should propose measures such as label instructions to mitigate the risk. For example, labels could require the observation of wool withholding periods to protect aquatic environments following scouring of wool.

**Specific recommendations for particular proposals**

Due to the intrinsic nature of the data, we recommended that you submit a comprehensive data package for products with specific use patterns and/or situations; for example, sheep ectoparasiticides.

An example of a specific use situation (using sheep ectoparasiticides) has been included below to demonstrate the additional data elements that are required in such a situation.

**Sheep ectoparasiticides**

Special considerations apply for the assessment of sheep ectoparasiticides. These include taking into account sheep wool residue depletion data, and the fate of these residues during the wool scouring process. These assessments are outlined in the APVMA’s Guidelines for producing wool residue data for sheep ectoparasiticide products and also as exemplified in the Sheep ectoparasiticides report.

**Emission Scenario Documents**

An Emission Scenario Document (ESD) is a document that describes the sources, production processes, pathways and use patterns of a product, with the aim of quantifying the emissions (or releases) of a chemical into water, air, soil and/or solid waste. There are a range of Emission Scenario Documents prepared by the OECD for various situations. These may provide useful guidance to applicants in preparing risk assessments for some veterinary chemical product situations. These documents may be located on, and downloaded from, the OECD web site.

Many of the ESDs listed on the OECD website pertain more to industrial than agricultural or veterinary chemicals, but, the following document may be useful for products considered to be veterinary medicine products: Series No. 14: Insecticides for stables and manure storage systems.

The list of ESDs is continually growing, so you should regularly check the website for updates. OECD scenarios are likely to be worst-case scenarios, and should be adapted as appropriate for local situations.

**Format for submission of environment data (Part 7)**

When preparing submissions, you are advised to follow the VICH guidance documents located on the VICH website.

**More Information**

Applicants seeking further information on relevant environmental data for specific uses may wish to apply for pre-application assistance or make an application for a technical assessment.

**References**


APVMA 2005, Guidelines for the registration of biological agricultural products, Australian Pesticides and Veterinary Medicines Authority M/mark>.


The following content can be found at http://new.apvma.gov.au/node/899 If making a submission, please reference page number: 899

**General—Products of gene technology**

Some active constituents and agvet chemical products that the APVMA regulates are produced using gene technology. These constituents and products are derived or produced from a genetically modified organism (GMO). Such products are referred to as GM products.

The *Gene Technology Act 2000* applies to GMOs and GM products and operates in conjunction with other Commonwealth and state regulatory schemes relevant to these materials. If a GM product is used for a purpose that fits the definition of an agricultural chemical product or a veterinary chemical product, it is within our jurisdiction, in addition to being under the *Gene Technology Act*.

The *Agricultural and Veterinary Chemicals (Administration) Act 1992* requires us to consult with the Gene Technology Regulator when we decide whether to approve an active constituent, register an agvet chemical product, approve a label, vary or reconsider any approvals or registrations, or issue a permit for a GM product. We must ensure that any advice given by the Gene Technology Regulator is taken into account when we make a decision on the approval, registration or reconsideration of such products.

Therefore, if your application contains any active constituent or product derived from or produced by a GMO, you must inform the APVMA. This includes any organism that has been modified by gene technology and any organism that has inherited particular traits from an organism in which the traits in the parent organism were the result of genetic modification.
In lodging an application involving a GM product, you should include:

- information addressing the statutory criteria
- information clearly identifying any constituent that is a GMO or that has been produced by or from a GMO
- data detailing any hazards that are additional to the primary hazard or that alter that hazard
- any proposed risk-management strategies for these hazards, to allow us to apply risk-management strategies on a case-by-case basis.

If you are planning to seek approval for an active constituent for a GM product, register a GM product or seek a permit for a GM product, you should contact us for guidance on specific data for that application.

Compliance and Enforcement guidelines

Guidance on suspensions and cancellations, enforceable directions, formal warnings, consent to import, notices to attend and infringement, substantiation and recall notices.

These pages contain information about the APVMA’s administration of Australia’s agvet legislation and what you need to do to comply with that legislation.

The legislation includes:

- the Agricultural and Veterinary Chemicals Act 1994 (the Agvet Act)
- Agricultural and Veterinary Chemicals Code scheduled to the Agricultural and Veterinary Chemicals Code Act 1994 (the Agvet Code)
- the Agricultural and Veterinary Chemicals (Administration) Act 1992 (the Admin Act)
- the Agricultural and Veterinary Chemical Products (Collection of Levy) Act 1994 (the Collection Act).

The legislation allows us, and in some cases compels us, to:

- issue substantiation notices
- issue formal warnings
- enter into enforceable undertakings
- issue enforceable directions
- issue infringement notices
- issue stop supply and recall notices
- cancel or suspend licences or approvals because of noncompliance or prior convictions
- cancel or suspend permits to prevent imminent risk
- issue a notice to attend, give information or produce documents or things.

Substantiation notices

The APVMA has powers under the Agricultural and Veterinary Chemicals (Administration) Act 1992 (Admin Act) and the Agricultural and Veterinary Chemicals Code scheduled to the Agricultural and Veterinary Chemicals Code Act 1994 (the Agvet Code) to require a person to produce information or documents to substantiate claims or representations made about agricultural and veterinary (Agvet) chemical products and active constituents. The substantiation powers relate to information about the import, export, supply, manufacture, efficacy and safety of the product. The authority to issue substantiation notices is intended as a preliminary investigative tool to be used if we suspect that a representation might not be able to be substantiated and is subsequently in breach of the Admin Act, Agvet Code or the Agricultural and Veterinary Chemical Products (Collection of Levy) Act 1994.

We can issue a notice when the basis for claims or representations made in the promotion of the supply of the product or active constituent is not clear.

We issue substantiation notices via registered post or through the engagement of a process server.

This page explains the types of information that you might be required to supply, when it is required, what it must include, how to comply with a substantiation notice, and how we might respond to noncompliance.

What is in a substantiation notice?

The notice specifies the claims that we are seeking information about and indicates the types of information or documents that must be provided. It can apply to one or more claims.

Overview of the legislative provisions

A substantiation notice under section 69EN of the Admin Act requires you to provide information in relation to imports, possible imports or exports of the product or constituent. A substantiation notice under section 145G of the Agvet Code requires you to provide information in relation to the supply, manufacture, safety or efficacy of the product or constituent.

The substantiation notice must name the person to whom it is given, specify the claim or representation to which it relates and explain the effects of sections 69ENA; 145GA (Compliance with substantiation notices) and 69ENB; 145GB (Failure to comply with substantiation notice) of the Admin.
Act or Agvet Code respectively.

Section 69ENA of the Admin Act and section 145GA of the Agvet Code require you to comply with a substantiation notice within the period specified in the notice. We can allow an extension of time, determined by us, if you apply to us within 21 days of receiving the notice.

Failure to comply with the substantiation notice within the required period will result in a contravention of s 69ENB of the Admin Act or s 145GB of the Code respectively. However, you will not contravene ss 69ENB or 145GB if you refuse to produce particular information or documents that might tend to incriminate you or expose you to a penalty.

Failure to comply with a substantiation notice is an offence, and a civil penalty provision for which we may seek an order for a pecuniary penalty.

What can the substantiation notice require?

The substantiation notice can require the provision of information or documents. To comply with the substantiation notice, you must mail or deliver the information to the address specified in the substantiation notice within the specified timeframe. Alternatively, we may advise you of a place and contact for you to deliver the information or documents in person.

What timeframes apply?

You must deliver the documents or information required by the substantiation notice within the period specified in the notice.

We can grant an extension of time for your response if you request one in writing. It is up to us whether we grant or refuse an extension. If one is granted, you must comply with the new timeframe.

Can the notice be withdrawn?

We can withdraw a substantiation notice at our discretion. We may decide to do so if we receive additional information that resolves our concerns or if you show us that there was a reasonable excuse leading to the claim and withdraw the claim.

What happens if the notice is complied with?

If you comply with the substantiation notice and submit the required information, we will acknowledge receipt of the information and advise you whether the issue is resolved, or whether further compliance and enforcement action is needed.

What happens if the notice is not complied with?

If you fail to respond to a substantiation notice within the specified time, we may issue an infringement notice, issue a formal warning or commence court proceedings to seek a civil penalty order if we consider it to be in the public interest to do so.

If you, as an individual, reasonably believe that the information or documents we ask for would incriminate you or expose you to a penalty, you may refuse or fail to provide the material on those grounds. In those circumstances, you must still respond to the notice, advising that you do not intend to provide the material on that basis.

What if a person responds to a substantiation notice and provides false or misleading information?

It is an offence to provide false or misleading information in response to a substantiation notice.

Enforceable undertakings

When the APVMA believes that a person or company has contravened certain provisions of the Agvet legislation, it can use enforceable undertakings rather than taking the matter to court. It is up to APVMA whether we accept the undertaking.

What is an enforceable undertaking?

An enforceable undertaking is a binding written agreement between a person and the APVMA. By offering and entering into the undertaking, you are saying that you will do or not do specified things to comply with the Agvet legislation.

This is an alternative to prosecution and provides a transparent and efficient resolution of alleged or actual noncompliance. We may seek the enforcement of the terms of an undertaking in a court.

Overview of the legislative provisions

Under section 69EL of the Agricultural and Veterinary Chemicals (Administration) Act 1992 (Admin Act) and section 145E of the Agvet Code, we can accept any of the following:

- your undertaking that you will take specified action in order to comply
- your undertaking that you will refrain from taking specified action
- your undertaking that you will take specified action to ensure that you do not commit an offence against the Agvet Code, Admin Act or
If we consider that you have breached the undertaking, we may apply to a court under section 69ELA(2) of the Admin Act or section 145EA(2) of the Agvet Code for:

- an order directing you to comply with the undertaking
- an order directing you to pay to the Commonwealth an amount up to the amount of any financial benefit that you have obtained directly or indirectly and that is reasonably attributable to the breach
- any order that the court considers appropriate directing you to compensate any other person who has suffered loss or damage as a result of the breach
- any other order that the court considers appropriate.

Objective

Enforceable undertakings are intended to provide efficient and effective resolution of noncompliance with the Admin Act, Agvet Code or Collection Act as an alternative to costly court proceedings. The development of an enforceable undertaking replaces the punitive outcome of court proceedings with positive actions that are intended to deliver sustained compliance.

Duration

In forming a view about the duration of an undertaking, we take into account the relevant circumstances of the particular case and the nature of the action involved. Where the action involves planning, commissioning and reporting of activities, the timeframe should be long enough for the effectiveness of the action to be assessed. Where the action is in lieu of a penalty, it is reasonable to ask for the action to be commenced or undertaken within the time in which the penalty would be payable (although there might be circumstances warranting a longer period).

Who can offer an enforceable undertaking?

Undertakings are given by the entity which the APVMA considers has committed or, without taking the offered action, would commit the noncompliance. That entity might be an individual, a corporation, or another type of legal person. It must be a legal entity against which enforcement (court proceedings) can be taken.

In some situations, a person who is secondarily involved in a contravention (as opposed to being the primary contravener) is nonetheless to be treated as having committed the contravention. In such cases, we can accept an enforceable undertaking from that person in addition to an undertaking from the primary contravener, if that acceptance is otherwise appropriate. An enforceable undertaking cannot bind a third party.

What happens when an enforceable undertaking is accepted?

If we accept an enforceable undertaking, we will cease any relevant investigation upon which the development of the undertaking was based.

Changing an enforceable undertaking

Enforceable undertakings may be varied, withdrawn or cancelled.

Varying

You may vary the undertaking at any time, but only with our written consent. You may seek our consent to a variation by making a request to us in writing.

We will only consider variations in circumstances where we consider that:

- the variation does not alter the spirit of the original enforceable undertaking
- there has been a material change in circumstances
- compliance with the original undertaking has been found to be impractical.

Withdrawing

You may withdraw the undertaking at any time under section 69EL(3) of the Admin Act or section 145E(3) of the Agvet Code, but only with our written consent. A request to withdraw must be made in writing to us.

The APVMA is only likely to agree to withdrawal in exceptional circumstances. For example if the holder of a registration or approval for a chemical product or active constituent or manufacturing licence requests the APVMA to cancel the registration or approval or licence, and it is consequently no longer able to comply with the undertaking. In such circumstances the APVMA may agree that it would not be reasonable to maintain the undertaking. If we agree to the withdrawal, you will no longer be bound by the agreement.

Cancelling

We may, by written notice to you, cancel the undertaking under section 69EL(5) of the Admin Act or section 145E(5) of the Agvet Code.

What happens when the undertaking is complete?

When we are satisfied that all the elements of the enforceable undertaking are complete, we will send you a letter advising that the undertaking has been discharged.

Monitoring and compliance
We monitor the implementation of enforceable undertakings.

If the terms of the undertaking are not complied with, we will seek a court order to enforce compliance.

Publication or disclosure

In accordance with the principle of transparency outlined in the APVMA’s Compliance and Enforcement Policy, every enforcement matter that is dealt with through litigation or formal resolution is made public.

In accordance with this principle, the APVMA maintains a register on its website where we publish enforcement outcomes. We are required to publish enforceable undertakings under section 69EL(6) of the Admin Act and section 145E(6) of the Agvet Code. However, we will not publish any part of the undertaking that we are satisfied:

- is confidential commercial information
- is personal information (within the meaning of the Privacy Act 1988)
- should not be disclosed because it would not be in the public interest to do so.

Subject to the same considerations, we may also publish any variation, withdrawal from, cancellation of or completion of an enforceable undertaking.

The APVMA considers that publishing information about the enforceable undertakings provides for a broader educative and deterrent effect.

Additional considerations

We have established an enforcement committee to provide oversight and additional governance of our use of our enforcement powers and tools. This is not a requirement of legislation, and the committee plays only an advisory role. The committee has oversight of the development of enforceable undertakings.

Information to be provided with a request for a section 70 certificate

The APVMA may require certain information in order to issue a certificate under section 70 of the Agricultural and Veterinary Chemicals (Administration) Act 1992, where the purpose of the request is to satisfy export requirements.

You should supply, as a minimum:

- the product name or active constituent name
- the registration number of the product (if applicable to the request)
- the registration holder’s name and address details (if applicable to the request)
- the name and manufacturing site address of the company that manufactures the product
- the APVMA manufacturer’s licence number (if applicable to the request)
- the active constituents that appear on the label for the product
- the full formulation of the product (if applicable to the request)
- the label approval date range (if applicable to the request)
- the number of certificates required

Please note:

- We can only provide information on a certificate that we are able to validate.
- Where the certificate you request includes commercial confidential information, we will ask for additional information to establish both your right to receive that information and our ability to lawfully provide it to third parties (if requested).
- We are unable to liaise with the Department of Foreign Affairs and Trade about certificates issued under section 70 (see also section 69D Export Certificates).

GMP—Providing evidence of good manufacturing practice (GMP) for veterinary chemical products
This is a guideline about the types of good manufacturing practice (GMP) evidence that you should submit when making an application to register, or vary the particulars of registration of, a veterinary chemical product.

The GMP evidence that is submitted to the APVMA for assessment is used to confirm that the manufacturing facilities responsible for the manufacture of veterinary chemical products are compliant with the Manufacturing Principles and the Australian Code of Good Manufacturing Practice for Veterinary Chemical Products (GMP Code). Some manufacturers and product types are considered exempt from GMP licensing provisions under Part 7 of the Agvet Code Regulations.

As part of this regulatory framework, the APVMA operates two programs that monitor industry compliance with these requirements:

- the Manufacturers’ Licensing Scheme for veterinary products manufactured in Australia (Part 8 of the Agvet Code). The Agvet Code requires anyone carrying out a step in the manufacture (including finished product testing, release for supply, etc.) of a veterinary chemical product at premises in Australia to be appropriately licensed by the APVMA (unless a relevant exception applies)
- the Overseas GMP Scheme for veterinary products manufactured overseas.

The APVMA does not currently require registration holders to submit GMP evidence for active pharmaceutical ingredients used to manufacture veterinary medicines. However, where a product is comprised of 100 per cent active constituents (commercially available as a raw material) and the product undergoes any other steps of manufacture (for example, filling, final packaging, labelling, testing of finished product and release for supply), then evidence of licensing or approval of the manufacturer is required. Evidence of GMP compliance is also required where the active constituent is an intermediate product (for example, pre-blend or vaccine antigen). Evidence of GMP is not required for listed, reserved or exempt products such as agricultural chemical products.

How to prepare information about manufacturers

At the time of making an application to register a new veterinary chemical product or to vary the particulars or conditions of registration of a veterinary chemical product, you should provide evidence that all proposed manufacturing sites are licensed, or supply evidence of GMP compliance for overseas sites. The evidence should demonstrate to the APVMA that the manufacturer carrying out any manufacturing steps has been assessed (audited) by an appropriate recognised regulatory body and has an appropriate and effective quality management system in place.

We strongly encourage you to make sure that you hold acceptable evidence of GMP prior to applying for registration, as the process to obtain GMP evidence may be lengthy. We cannot grant the application and register the product until acceptable GMP evidence is submitted within the specified timeframe.

You may apply for pre-application assistance to discuss the GMP requirements associated with your application.

Types of GMP evidence accepted for registration of veterinary chemical products

Evidence of GMP for veterinary products manufactured in Australia

For veterinary products manufactured in Australia that require evidence of GMP, an APVMA licence is the only evidence that we will accept. For details on how to obtain relevant details or a copy of the licence, refer to the Manufacturers’ Licensing Scheme information.

At the time of making an application, you should confirm that all Australian manufacturing sites nominated are appropriately licensed to carry out the steps of manufacture at the particular premises for the proposed product type for which you are seeking registration. For example, a site that is licensed for non-sterile solid dosage forms only cannot carry out manufacture of sterile liquids.

You do not need to provide a copy of the APVMA licence with your application; however, you should provide the following information:

- the company name and street address of all manufacturing sites (this information should match the details on the licence exactly)
- the steps of manufacture of the product carried out by each manufacturer, including those performing testing and release for supply
- the APVMA licence number.

We will check the details provided against the issued licence to make sure that the nominated manufacturing facility (or facilities) is appropriately licensed for the manufacturing steps of the proposed product type and dosage form.

Evidence of GMP for veterinary products manufactured overseas

We carry out an assessment of overseas GMP evidence as part of the application process. The evidence we require is usually an official and current certification from the relevant agency in the country of export, provided that the agency’s certificates are recognised by the APVMA.

If you are seeking to register, or vary the particulars of registration of, a veterinary chemical product manufactured overseas, you must supply satisfactory evidence of the product being manufactured to a standard comparable to the Manufacturing Principles and the GMP Code.

Where the expiry period on the evidence of GMP is less than the timeframe for evaluation, you must provide an updated certificate before your application can be finalised.

Once we complete an audit of an overseas manufacturing site, we will send a confirmation letter to whoever commissioned the audit advising of the outcome of the audit. This confirmation letter is specific to whoever commissioned the audit and product types assessed, and cannot be solely used as evidence by another applicant. If a request is made to access records of approved evidence of GMP for another applicant, we will require written authorisation from that applicant.

The following content can be found at http://new.apvma.gov.au/node/864

**Exemptions from offence provisions of the Agvet Code**

The APVMA has the power to exempt substances, active constituents and chemical products, or certain activities, from the operation of certain offence and civil penalty provisions of the Agricultural and Veterinary Chemicals Code (the Agvet Code), scheduled to the Agricultural and
Veterinary Chemicals Code Act 1994. The following information explains how we exercise this power.

Which legislative provisions apply?

Offence provisions that apply in relation to a substance, active constituent or chemical product, or certain activities, unless, among other things, we have given an exemption include:

- section 74(2A)—possession or custody of unapproved active constituents with the intention of supply
- section 75(2A)—possession or custody of chemical products, other than registered or reserved products, with the intention of supply
- section 76 (2A)—supply of unapproved active constituents
- section 78 (2A)—supply of chemical products that are not registered products or reserved products
- section 84 (2A)—making a claim inconsistent with an approved label.

**Principles**

In considering whether it is appropriate to exempt substances, active constituents, chemical products or particular activities from the operation of an offence provision, we consider:

- the particular circumstances of the noncompliance (if any) with the Agvet Code
- the APVMA Compliance and Enforcement Policy
- whether an application has been lodged with us for an approval, registration, permit, licence or other authorisation relevant to the substance, person or activity
- precedent treatment of comparable substances, activities or persons
- the length of time that an exemption would be needed
- risk
- whether giving an exemption is preferable to other available options, such as approval of an active constituent under section 14A, or the development of an additional Regulation or instrument, such as for a listed or reserved chemical product.

If we give an exemption, we publish a notice with the details of the exemption in the APVMA Gazette.

**How long will an exemption last?**

The period for which we give an exemption is at our discretion. We consider that exemptions should be temporary but long enough to permit a return to compliance or the development of alternative regulatory treatment. We can vary or revoke an exemption that we have granted at any time.

**Can I apply for an exemption?**

The Agvet Code does not provide for you to apply for an exemption. If an exemption is given, it will be at our volition and discretion.

Approval of active constituents for which information is not readily available

The Agricultural and Veterinary Chemicals Code (Agvet Code), scheduled to the Agricultural and Veterinary Chemicals Code Act 1994, normally requires the APVMA to be satisfied about a number of things before granting an approval for an active constituent, including that:

- an application has been made and the application meets the application requirements
- the active constituent meets the statutory safety criteria.

In limited circumstances, the APVMA may approve an active constituent for a proposed or existing chemical product without having regard to all of the information we are required to have regard to, provided we are satisfied on the information that is readily available that the constituent would meet the safety criteria. We can approve an active constituent in this way whether or not an application has been made. If an application has not been made, the APVMA will be entered in the Record as the holder of the approval.

**Which legislative provisions apply?**

Section 14A of the Agvet Code provides that the APVMA may approve an active constituent for a proposed or existing chemical product, whether or not an application for approval has been made, if:

- either of the following applies:
  - we consider that the information required in respect of the constituent is not readily available, or
  - the constituent is, or is part of, a product which has a standard specified in the European pharmacopoeia, the British pharmacopoeia (veterinary), the United States pharmacopoeia or any other publication considered by the APVMA to be appropriate, and
- having regard to information that is readily available, we are satisfied that the active constituent would meet the safety criteria.

**Principles**

In considering whether it is appropriate to approve an active constituent under section 14A we take into account:

- whether an application has been lodged with the APVMA for approval of the active constituent under section 14A
- all information provided in support of the application
- whether or not there is readily available information to satisfy us that the active constituent would meet the safety criteria, in particular:
Information guidelines and standards

- whether the constituent is, or is part of, a product in respect of which a standard is specified in the European pharmacopoeia, the British pharmacopoeia (veterinary), the United States pharmacopeia or any other publication that we consider appropriate
- whether the characteristics of the active constituent are well known and understood due to common use in industrial, non-agricultural or non-veterinary uses; for example, a substance may be commonly used in food for human consumption.
- whether it would be preferable to exempt the active constituent from the operation of the Agvet Code (or parts of it).