Australian Government

Australian Pesticides and Veterinary Medicines Authority



Risk assessment manual

Efficacy and target animal safety of veterinary medicines

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Comments and enquiries regarding copyright:

Assistant Director, Communications
Australian Pesticides and Veterinary Medicines Authority
GPO Box 574
Canberra ACT 2601 Australia

Telephone: +61 2 6770 2300
Email: communications@apvma.gov.au.

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Risk assessment of efficacy and target animal safety

A veterinary chemical product must be shown to be safe and efficacious for its intended use and claims in order to be registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA). Lack of efficacy or safety in a veterinary chemical product has the potential to adversely affect animal health and livestock productivity. The APVMA conducts risk assessments to ensure that the proposed use of a veterinary chemical product meets the statutory efficacy criteria and safety criteria related to target animal safety.

Efficacy assessment

Veterinary chemical products are required to meet the criteria determined by the APVMA by legislative instrument (Agricultural and Veterinary Chemicals Code (Efficacy Criteria) Determination 2014) or contained in an established standard. The APVMA must be satisfied that a veterinary chemical product will be effective when used according to label instructions under practical Australian field conditions.

APVMA considers the following for the purposes of being satisfied as to whether a chemical product meets the efficacy criteria:

1. The results of trials or laboratory experiments carried out to determine the efficacy of the product.
2. Any conditions to which its registration is, or would be, subject.
3. Any relevant particulars that are, or would be, entered in the register for the product.
4. Whether the product conforms, or would conform, to any standard made for the product.
5. Any matters prescribed by the Agvet Code Regulations.

Target animal safety assessment

The APVMA must be satisfied that the use of a product in accordance with the APVMA-approved instructions will be safe for the treated animal.

In accordance with any instructions approved (or to be approved) by the APVMA, or contained in an established standard, a chemical product meets the safety criteria if use of the product is not, or would not be:

1. an undue hazard to the safety of people exposed to the product during its handling or people using anything containing its residues
2. likely to have an effect that is harmful to human beings
3. likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

The target animal safety assessment determines whether use of the chemical product is likely to result in unintended harmful effects in target animals.

The risk-based assessment approach practised by Australia is similar in structure to that of other countries including Canada, the USA and EU member states.

Regulatory framework

The *Agricultural and Veterinary Chemicals Code* (Agvet Code), scheduled in the *Agricultural and Veterinary Chemicals Code Act 1994* (the Act), provides the basis for using risk analysis to regulate activities with agricultural and veterinary chemicals (agvet chemicals) in Australia.

The objective of the Agvet Code is for the evaluation, approval, and control of the supply, of active constituents for proposed or existing agricultural chemical products or veterinary chemical products; and the evaluation, registration, and control of the manufacture and supply of agricultural chemical products and veterinary chemical products.

The decision whether to approve an active constituent or an agvet product is made by the Australian Pesticides and Veterinary Medicines Authority (the APVMA), an independent statutory office holder established by the Act.

The Act mandates that the APVMA implement the Agvet Code in a manner that reflects '…established best-practice principles for the assessment and management of risk, based on science.' To do this, APVMA's regulatory scientists must balance regulatory effort and regulatory burden with the risk that agvet chemical use will present to the health and safety of human beings, animals and the environment.

With respect to **efficacy**, the APVMA must be satisfied under s14 of the *Agricultural and Veterinary Chemicals Code Act 1994* that:

- the proposed use of the product meets the efficacy criteria with respect to s5B(1);
- the requirements of s5B(2)(a), (b), (c), (ca) and (d); and s5B(3) (a) and (b) are met;
- the proposed label meets the labelling criteria under s5D(1) and 5D(2), with respect to efficacy considerations.

With respect to **target animal safety**, the APVMA must be satisfied under s14 of the *Agricultural and Veterinary Chemicals Code Act 1994* that:

- the proposed use of the product meets the safety criteria with respect to s5A(1)(c);
- the requirements of s5A(2)(a) (i), (v), (vi) and (vii); s5A(2) (b); s5A(3)(a) (i), (ii), (iii), (iv), (v), (vi), (via) and (vii); and 5A(3) (b) (iv), (v) and (vi) are met;
- the proposed label meets the labelling criteria under s5D(1) and 5D(2), with respect to target animal safety considerations.

Efficacy

Efficacy risk assessment

Risks to animal health and welfare can arise if the use of a product, or its failure to achieve claims, results in unnecessary or unreasonable pain or distress in the target animal. Data on the efficacy of a chemical product must demonstrate that a veterinary medicine will prevent or treat diseases characterised by unnecessary pain or distress.

Risks to livestock productivity can also arise if a veterinary chemical product fails to achieve its claims. Efficacy data must verify the product will perform according to the proposed label claims.

A risk assessment process is conducted to integrate the data, assumptions and uncertainties relating to a product, to help the risk assessor understand the product's expected efficacy.

Technical report templates providing specific guidance on the type of information, comments, and critical assessment expected in the assessment report for efficacy and target animal safety are available for reviewers. The templates are intended to provide guidance to assessors preparing assessment reports for veterinary medicinal products and ensure that there is consistency and coherence in the assessment of technical dossiers.

It is vital that an assessor is fully cognisant of the relevant general APVMA and specific guidelines relating to the product type under assessment. The specific guidelines include adopted international guidance such as VICH guidelines.

Information that assists risk assessment

The data required to be submitted in support of a registration of a veterinary chemical product will depend on the nature of the product and its active constituents.

General guidance on the types of information and the circumstances in which they are likely to be required to address the efficacy and safety criteria for veterinary chemical products is provided in the Efficacy and target animal safety general guideline (Part 8). Product specific guidance is also available for some veterinary chemical product types.

Data for risk analysis

Data assessment

Data or scientific argument on efficacy provided by the applicant should support proposed label claims, directions for use and advisory statements. Assessment of these data focuses on determining whether the APVMA is satisfied that the product meets the requirements of legislation; that is, it will be effective, if used according to label instructions.

In reviewing efficacy data, consideration may be given to:

- Pharmacological data – a combination of pharmacokinetics and pharmacodynamics studies that build a foundation for laboratory, field and clinical efficacy and safety studies (and therefore use), demonstrating the underlying nature of drug/body interactions.
- Laboratory efficacy studies – these studies build the evidence for the efficacy of the product in target animal species, testing probable effective doses, rates and frequency derived from the results of the analysis of initial pharmacokinetic and pharmacodynamic assessments.
- Target animal efficacy data – demonstration and confirmation of the efficacy of a veterinary chemical product generally uses a three-step approach involving dose determination studies, dose confirmation studies and confirmatory clinical/field studies:
  - Dose determination studies – using a formulation identical to, or closely similar to, the formulation that is to be registered.
  - Dose confirmatory studies – usually laboratory-style studies where many variables are controlled; ideally using the final product formulation.
  - Confirmatory clinical/field assessments – confirm that under clinical or field conditions, and when used according to label instructions, the product's final formulation is effective. The studies should be applicable to Australian conditions. Clinical case studies are not a replacement for confirmatory clinical/field studies.
  - Palatability – work that establishes the palatability of certain oral dose formulations.
- International data – When assessing international data, the following may be considered:
  - Significant differences between the use of the product in Australia and in the foreign country.
  - Different environmental factors (for example, animal breeds, husbandry practices and geographical regions) affecting the use of the product in Australia and in the foreign country.
  - Significant differences in disease-causing pathogens or parasites.
  - Significant additional information relating to the efficacy of the product that has become available since the conduct of the submitted experiments or trials.
  - Significant differences in the way decisions or evaluations are made in Australia, or by the national regulatory authority in the foreign country, related to efficacy.
- Other studies or data – bioequivalence studies, clinical case studies and scientific arguments may be used to support applications for the registration of generic products, and for some formulation changes.
  - Bioequivalence studies – provide supporting evidence that the efficacy, and possibly safety, of one formulation are equivalent to those of another registered by the APVMA. Should be conducted for each species and route of administration claimed on the label particulars of the product to be registered.
  - Clinical case studies – may support the efficacy, but more commonly safety, of a product. Should only be considered in support of products that will be used by, or under the direct supervision of, a registered veterinary surgeon.
  - Scientific references or extrapolated scientific argument – for some product types on a case-by-case basis, the APVMA may consider extrapolation from available data as part of its risk analysis, such as:

- Evidence of efficacy for the proposed formulation in a non-target species and/or a related formulation in the target or a non-target species.
- Evidence of registration by certain regulatory authorities (e.g. Canada, European Union, New Zealand or United States) of the proposed or related formulation in the target or non-target species. Evidence of registration by other regulatory authorities should include an officially stamped copy of the registration notice and registered label.
- Trial data for the proposed formulation and target species that is supportive of effective use.
- Relevant scientific information from peer-reviewed journals, recognised textbooks or other reputable sources for the active constituent(s) in the target species.

In addition, valid scientific arguments relevant to pharmaceutical considerations may be considered in the risk assessment such as:

- The effects that excipients in a formulation may have on the bioavailability of the active constituent.
- The effects that excipients may have on the solubility or biological permeability of the active constituent.
- The effects that excipients may have on gastric motility and gastric emptying.
- The physicochemical properties of the excipients (for example, excipients that adjust pH may affect the biological activity of active constituents that are pH-dependent, and excipients that adjust viscosity may affect the distribution of a pour-on product).
- The change in the drug – excipient ratio when excipients are substituted, deleted or added to a formulation.
- Polymorphism and in particular polymorphic transitions of active constituent/s that may impact the efficacy of a formulation.

Assessing the risk of product use according to label instructions

A risk assessment draws together risk information from single studies or pieces of data or information for consideration on a weight-of-evidence basis. Specific product type guidelines and efficacy thresholds should be referred to, when available.

The APVMA must be satisfied that the use of the product in accordance with label instructions would be effective as claimed on the label. Proposed efficacy label instructions include:

- Constituent statements.
- Statement of claims for use.
- Dosage and administration.
- Duration of treatment.
- Frequency of use.
- General directions of use.

If the product has been shown to be able to achieve the effect claimed on the label when used according to label instructions, then the APVMA must be satisfied that the product meets the statutory criteria for efficacy.

Assessment of label claims

The type of claims that can be made on an approved label, and the amount and type of data needed to support these claims, depend on the type of product, the active constituent, and the type of application.

Therapeutic claims may be made for the stand-alone use of a product, or those requiring other supporting or complimentary treatments. For some products, there are specified parameters for claims that the product can be said to treat, prevent or aid in the control of a disease, infection or condition. Where specific guidelines exist, particularly for products such as vaccines and parasiticides, these should be referred to for detailed information.

Table 1: Efficacy demonstration requirement and associated label claims for veterinary chemical products recognised by the APVMA

Claim term	Regulatory intent	Level of effect demonstrated	Typical interpretation
Treatment	Direct therapeutic action on existing disease/ infection/infestation	High – clinically meaningful resolution, cure or killing effect	Acts on animals already affected to eliminate or resolve disease/agent or kill parasites
Control	Reduce incidence/severity/spread/ infestation	High – reduces burden but may not eliminate. Or High -stop reinfestation from occurring due to persistent killing effect	Manages disease within an individual or population
Prevention	Blocks infection/disease/parasite establishment	High – stop disease/infestation from occurring	Protects healthy animals at risk – use in healthy animals to avoid disease onset, infection or infestation
Alleviation	Relief of clinical signs	Symptomatic – does not necessarily affect underlying disease	Improves welfare by reducing signs (e.g. pain, inflammation, pruritus)
Reduction	Decrease in a defined parameter (burden, severity, incidence)	Variable – quantitative decrease	Demonstrated statistical decrease, not necessarily clinical resolution
Repels	Deters contact/feeding without necessarily killing/eliminating	High – prevent contact/exposure to pest	Protects healthy animals at risk
Promotion/Improves/ Increase	Enhance performance (non-therapeutic)	Non-therapeutic – improves growth/productivity/feed efficiency	Applies to healthy animals

Claim term	Regulatory intent	Level of effect demonstrated	Typical interpretation
May aid in the control/ prevention/ reduction/alleviation	Indicating a supportive or contributory effect, rather than a direct, primary therapeutic action	Conditional or variable	The product can assist in achieving an outcome. But the effect is not guaranteed, not standalone, and likely dependent on context

Target animal safety

Target animal safety risk assessment

The APVMA must be satisfied of the statutory criteria related to target animal safety before it can approve an active constituent or register a chemical product. With respect to target animal safety, the risk is that the product when used according to label instructions, will have unintended negative effects.

The following criteria are considered for the purposes of being satisfied as to whether a chemical product meets the safety criteria related to target animal safety:

1. The toxicity of the product in relation to relevant organisms (target animal).
2. Any conditions to which its registration is, or would be, subject.
3. Any relevant particulars that are, or would be, entered in the register for the product.
4. Whether the product conforms, or would conform, to any standard made for the product.

The safety assessment examines the risk that a product may have unintended effects, even when used according to the label instructions. This safety assessment process combines all the information from the data, assumptions and uncertainties in a way that helps the risk assessor understand the relationships between the expected safety and the product.

Information that assists risk assessment

Local, or international data on the safe use of the proposed product are acceptable.

Individual data elements and the circumstances in which they are likely to be required are discussed in more detail in the APVMA data guidelines. These provide applicants with guidance on what data and information to prepare to support their application.

Data for risk analysis

Data assessment

Safety data, or scientific argument provided by an applicant should indicate the margin of safety to target animals, and should take into consideration factors such as age, sex, breed, condition, dose regimen, animal husbandry practices, pregnancy, nutritional status and any other matters that could reasonably be expected to affect safety in use.

In reviewing safety data, consideration is given to:

- **Pharmacological data** – a combination of pharmacokinetics and pharmacodynamics studies that build a foundation for safety studies, determining the underlying nature of drug/body interactions.

- **Margin of safety studies** – as described in VICH43, these are pivotal studies that aim to demonstrate unintended toxicological effects in target animal species at expected and excessive doses, compared to a negative control. Ideally, safety studies should use the formulation intended for marketing, administered by the means recommended on the product label, and under the proposed conditions of use.
- **For immunobiologicals**, animal laboratory studies should conform to VICH GL44 on target animal safety for veterinary live and inactivated vaccines. Field safety studies should conform the GCP.
- **Other laboratory safety studies** – additional safety studies may be appropriate for a particular product, depending on the conditions of use and the characteristics of the product.
  - **Injection site assessments** – as described in VICH43, tissue irritation studies where appropriate for drugs administered by injection or implants. Standard toxicity tests may be used for dermal, ophthalmic, intranasal, vaginal, intra-uterine and inhalation drugs.
  - **Administration site assessments** for dermally applied products – as described in VICH43, accelerated or delayed healing if the product is intended for application to wounds, and systemic toxicity if the product is likely to be appreciably absorbed after topical application or is likely to be ingested as a result of licking.
  - **Reproductive tract safety assessments** – as described in VICH43, in the absence of reproductive studies risk manage by considering the inclusion of a precautionary statement on the label e.g. advising the user that such studies have not been done and that the effect of the chemical on the reproductive function of treated breeding, pregnant or lactating animals or their offspring is therefore unknown.
  - **Mammary gland safety assessments** – as described in VICH43 for products used in the mammary gland (e.g. intra-mammary infusions).
- **Target animal safety field studies** – as described in VICH43 clinical case reports may be submitted to support the safety of a product.
- **Related studies**:
  - **Compatibility assessments** – particular treatments, conditions or procedures are likely to be used in combination with the proposed new product so information on compatibility should be provided. These studies may be necessary if compatibility with particular treatments or conditions is claimed, this should be demonstrated.
  - **Effects on hides and fleece** – Data or valid scientific argument may be used to demonstrate or contend, respectively, that chemicals applied externally to cattle, sheep and other hide- or fibre-producing animals will not cause damage to the hides, skins, fleeces or fibres produced by those animals.
  - **Accidental administration or exposure to non-target animals** – consider available data or valid scientific argument in assessing the risk of unintended effects in non-target animals and any risk mitigation strategies (e.g. label warnings) that may be necessary to avoid unintended effects on non-target animals.
  - **Effects on taste of animal produce (organoleptic effects)** – This may include taste-panel tests or other organoleptic tests, to verify that no unacceptable tainting occurs.

Scientific references or extrapolated scientific argument for animal safety

For some types of products, the APVMA may consider as part of its risk analysis, on a case-by-case basis, extrapolations from available data, such as:

- Evidence of registration by a regulatory authority from one of the following countries: Canada, European Union, New Zealand or United States of the proposed or related formulation in the target or non-target species (evidence of registration by other regulatory authorities should include an officially stamped copy of the registration notice and registered label).
- Trial data for the proposed formulation and target species that is supportive of safe use.
- Evidence of safety for the proposed formulation in an appropriate non-target species and/or a related formulation in the target or a non-target species.
- Placing contraindications, precautions and/or side effects statements on the main panel of the label.

In addition, valid scientific arguments relevant to pharmaceutical considerations may be considered in the risk assessment such as the:

- effects that the excipients in a formulation may have on the bioavailability of the active constituent that might affect the safety of the product
- effects that the excipients may have on the solubility or permeability of the active constituent in terms of safety
- effects that the excipients may have on gastric motility and gastric emptying
- physicochemical properties of the excipients (for example, excipients that adjust pH may affect the biological activity of active constituents that are pH-dependent, and excipients that adjust viscosity may affect the distribution of a pour-on product)
- comparison of specifications of the active constituent from different sources
- toxicity profile of an excipient when addressing the safety aspects of the product
- change in the drug: excipient ratio when excipients are substituted, deleted or added to a formulation
- polymorphic form and in particular polymorphic transitions of the active constituent/s that may impact the safety of a formulation.

Assessing risk of product use according to label instructions

Risk assessment brings together risk information from each of the single studies or pieces of data/information to consider, on a weight-of-evidence basis, the overall risk of unintended effects.

The risk assessment and identification of management requirements relating to target animal safety is based on the product being used according to label instructions. Proposed label instructions relating to target animal safety include:

- Constituent statements.
- Contraindications.
- Precautions.
- Side effects.
- Dosage and administration.
- Duration of treatment.
- Frequency of use.
- General directions.

As part of risk management, additional appropriate instructions and restrictions may be required on labels to warn of possible unintended effects and to reduce the likelihood of unintended effects in target animals.

Weight of evidence analysis and expert judgement

The use of tools for identifying reliable data and expert judgement for determining relevancy and adequacy helps to ensure that high-quality data are used. They do not, however, remove the need for a weight-of-evidence analysis during the assessment of these data. Some veterinary chemical products may not have reliable experimental data, or it may be difficult to model safety in a target animal species. In these cases, the available evidence needs to be weighed and considered as a whole. Reference is made to VICH GL43 and VICHGL44 for veterinary vaccines.

Expert judgement is used in the evaluation of risk, including when only less than adequate, reliable or relevant information are available for a product. The APVMA will consider, on a case-by-case basis, which of the above matters are necessary to demonstrate efficacy and safety in a particular case.

Acronyms and abbreviations

Shortened term	Full term
APVMA	Australian Pesticides and Veterinary Medicines Authority
GCP	Good clinical practices
GMP	Good manufacturing practices
VICH	International Cooperation on Harmonization of Technical Requirements of Veterinary Medicinal Products