Australian Government
Australian Pesticides and Veterinary Medicines Authority

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Pesticides efficacy and crop safety general guideline (Part 8)

1. Introduction

Applicants wishing to register a product, vary the particulars or conditions of registration, or hold a permit to use a chemical product, need to satisfy the Australian Pesticides and Veterinary Medicines Authority (APVMA) that the chemical product meets the statutory criteria set out in the Agvet Code for efficacy and safety.

This guideline is relevant to:

- applications to register agricultural chemical products (that is, any pesticide registered by the APVMA) containing new or existing active constituents
- applications to vary the particulars or conditions of registration of a registered agricultural chemical product, such as changes in the use pattern or a major formulation change
- applications for a permit to allow ‘minor use’ (and possibly supply) of an agricultural chemical product.

Efficacy data, argument or use of a reference product to satisfy efficacy criteria may not be needed in an application submission for some products. For more information see the legislative instrument.

1.1. How to satisfy the efficacy criterion

This guideline should be read in conjunction with any relevant product-specific guidelines available under efficacy and safety (Part 8) of the data guidelines.

One method of satisfying the APVMA of the efficacy and crop safety of a product is to submit the results of properly designed and conducted laboratory and/or field-scale trials that demonstrate the product’s efficacy and crop safety.

You may submit reports provided by the APVMA (provided they meet the validity criteria), along with argument or additional data to address any additional matters that we may need to be satisfied about for you to meet the criterion for efficacy.

You can also choose to address the efficacy criterion by making a valid scientific argument in lieu of supplying data.

The APVMA will always consider alternative information provided by applicants where that information can be demonstrated to be relevant for the particular situation.

Finally, you can nominate a relevant reference product as evidence of the efficacy of the proposed product based on the level of chemical and use pattern similarity between the 2 products.

An efficacy and safety dossier must demonstrate that, when the product is used according to label directions, it will be effective as per the label claims and that its application to the target crop (or other situation) will not cause any unintended adverse effect.

This guideline sets out broad principles for generating and submitting an acceptable dossier that addresses the efficacy and, where relevant, crop or situation safety criteria. The guideline should be read in conjunction with any relevant product-specific guidelines.

The principles in this guideline are generally consistent with those established by the United States Environmental Protection Agency; the Canadian Pest Management Regulatory Agency; the United Kingdom Pesticides Safety Directorate, Department for Environment, Food and Rural Affairs; the United Kingdom Biocides and Pesticide Unit, Health and Safety Executive and the European and Mediterranean Plant Protection Organization.

1.2. Statutory criteria for efficacy

The Agvet Code sets out the criteria for efficacy for agricultural and veterinary chemicals that must be satisfied to achieve registration or variation of an agvet chemical product, or to be issued with a permit for the use of a product. The chemical product, when used in accordance with the proposed label instructions and in the situations described on the label, must perform in accordance with all efficacy-based claims made on the label.

This guideline provides general advice about satisfying the statutory criteria for efficacy, along with links to guidelines that can assist you to plan and conduct efficacy trials and compile an efficacy dossier to lodge with your application. Along with this general guideline, there are also some product-specific guidelines that provide more specific guidance about satisfying the efficacy criteria for those products.

1.3. Pre-application assistance and technical advice

After considering the information provided in this and related guidelines, you may wish to seek further assistance about your planned research and application. The APVMA offers technical advice to applicants, known as pre-application assistance, which gives applicants the opportunity to reduce the uncertainty associated with a specific prospective application. It is offered on a fee-for-service basis and can take the form of a written response, a face-to-face meeting or a teleconference.

2. Satisfying the efficacy criterion

Read this guideline in conjunction with any other guidelines available for particular product types. If there is no specific guideline for the proposed product type, follow the principles in this guideline.

You may address the statutory criteria for efficacy by one or more of the following means:

- Nominating a relevant reference product (and demonstrating that you have obtained consent for us to access any protected data associated with the reference product).
- Providing data to the APVMA.
- Providing valid scientific argument.
- Using overseas data assessments or decisions.
- Using previously provided reports from the APVMA (provided they meet the validity criteria).

Further information about these options is provided in a separate guideline 'Satisfying the statutory criteria'.

You should provide all data relevant to product efficacy and safety for the particular product and uses, including data for less successful trials. Under section 160 and section 161 of the Agvet Code, you are obliged to provide any information in your possession that may be adverse to the proposed registration, variation or permit or to an existing product registration or

permit.

2.1. General guidance on satisfying the efficacy criteria

2.1.1. Demonstrate efficacy and safety for all label uses

It is your responsibility to present adequate information to support all product uses on the label and any related efficacy and safety claims, including the rates, frequencies of use and application equipment stated on the label. Any information that is necessary to interpret or understand the data or published information referred to in your application should be included in the dossier.

You should interpret the information that you provide, demonstrating how it supports the label claims and proposed instructions. It is not sufficient to simply provide trial reports and other papers without explaining their relevance to the proposed use of the product. Provide copies of any reference publications or documents cited and demonstrate their relevance to the application. Each application should be accompanied by an efficacy overview that explains the relevance of the results obtained from each data point to the claims being made for the product.

2.1.2. Providing data from trials

Trial data to support claims and instructions for use should be generated through properly designed, conducted and analysed trials using the product formulation proposed for registration. A separate guideline provides detailed information about the design and analysis of trials.

2.1.3. Alternatives to trial data

Information from sources other than trials may be acceptable, and you may use more than one alternative method of satisfying the criteria. For example, you could provide data using a variation on a published method, along with valid scientific argument and supporting published references to demonstrate efficacy against a particular pest.

Extrapolation of available information on other situations and/or pests to support applications involving related pests or situations may be possible, and will be considered on a case-by-case basis. Examples include extensions from major to minor pests or crops and demonstrating bioequivalence between similar products using bioequivalence on key pests or crops. For further details, see the Demonstrating bioequivalence and Use of extrapolation sections in this guideline.

Testimonials and anecdotal reports on their own are not acceptable as evidence of efficacy.

2.1.4. Conduct of trial

Efficacy trials should be conducted in a scientifically sound manner and be adequately documented and presented in an appropriately formatted report. We have published a guideline on experimental design and analysis of trials to assist with these aspects. We recommend that you seek professional advice on design and analysis where appropriate.

2.1.5. Non-Australian data

Data generated overseas may be used to support an application if it can be demonstrated that the product, its use, the pests and target crops and the climatic and soil conditions are relevant to the product formulation and use proposed in Australia. In most cases, Australian confirmatory field studies should be conducted to show that the efficacy and safety of the product under Australian conditions is at least equal to that demonstrated overseas.

Overseas field studies should be done under conditions that are typical of Australian climatic conditions and, if applicable, production conditions. If the trials are not conducted in that way, you should demonstrate why they are relevant.

Data and study information should not be submitted in languages other than English, unless an acceptable English translation is also provided.

2.1.6. Formulation or test material

The formulation to be registered should be used in studies submitted as pivotal studies demonstrating efficacy. If the studies use a formulation that differs in any respect from the formulation to be registered, that must be clearly identified at the beginning of each study report and in the overall summary, where the implications of the differences must be discussed.

For studies using a formulation still in the developmental stage, company codes are often used to describe the formulation under test. Where company codes are used, they should be clearly identified and referenced to the product name and formulation to avoid confusion. The relationship between the company code, formulation and product name could be presented as a table in the overall summary. As far as possible, product names should be used rather than company codes.

Where a formulation used in important studies to support efficacy and safety differs considerably from the formulation to be registered, you should provide data and/or arguments demonstrating bioequivalence. See the Demonstrating bioequivalence and Using extrapolation sections of this guideline for more information.

2.1.7. Pilot, pivotal and commercial-scale studies

Studies can be classified as pilot (developmental), pivotal or commercial-scale, depending on their place in the product design and development process.

Pilot studies are developmental trials that may use different versions of the formulation and/or multiple rates and application methods. They are usually used to confirm rates and instructions before pivotal studies are conducted and often provide direction for further development. Pilot studies in an application provide a useful history of the development of a product. They also indicate why the product and label instructions are presented in their final form. By themselves, however, they are usually insufficient for registration purposes.

Pivotal studies usually involve the final formulated product being tested as per the proposed label instructions. They are often small-scale replicated field trials, the results of which can be appropriately analysed by statistical methods. These studies provide the most valuable evidence for efficacy and are therefore crucial in satisfying the APVMA.

You can also provide data from commercial-scale (demonstration) trials, which use commercially available equipment and are usually unreplicated due to the scale of the trial. However, you should understand and discuss the relevance of the trials in demonstrating efficacy. Grower or commercial-scale trials are typically conducted to ensure that the product is able to be used with typical commercial equipment without any physical compatibility problems. When discussing such trials, you should focus on these issues and how they relate to the label instructions. Record enough detail to explain how the product was prepared and applied. Because commercial-scale trials are rarely replicated, any assessment of efficacy is indicative only and should not be relied on for that purpose in the absence of other trials.

2.1.8. Optimal rate

Label rates should include the lowest rate that provides acceptable efficacy (the optimal or lowest effective rate). This minimises potential risks to the product user, the public and the environment from the product. Pilot studies using multiple rates and/or pivotal studies using treatments at the proposed rate, at double the proposed rate (2x) and at a half rate (0.5x) are a good way of demonstrating the optimal rate and dose-related effects. Ideally, the lower rate(s) tested should demonstrate inferior efficacy, including inferior duration of control for residual products, or inconsistent performance under different conditions. Failure to demonstrate these effects at the lower rates may indicate that the proposed rate is unnecessarily high. Where resistance of a pest or weed has been demonstrated, selecting a suitable rate may require additional research.

For products that claim residual control or protection from a particular pest, you should still demonstrate that the rate you are proposing is the lowest one that can achieve the length of protection claimed. Similarly, when attempting to control a low pest ‘abundance’ situation, a rate lower than that required for high pest abundance may be sufficient.

2.1.9. Number of trials

The number of trials required in a data set is largely dependent on the nature of the product and how it is to be used, including the overall importance of the crop and pest and the severity of the damage caused. The number of different trial locations and crop varieties that must be tested to demonstrate efficacy will also be a factor, as will the number of years or growing seasons to demonstrate efficacy under a variety of seasonal conditions. New agricultural chemical products with

new active constituents or the first use of an active constituent in a major crop may require up to 10 fully supportive separate trials per crop–major pest combination to demonstrate efficacy, depending on how widely the crop is grown and on the crop's economic importance.

Some trials may be used for multiple pests if there is adequate pest pressure for all species. New formulations of existing active constituents, or extensions of registered products to new minor crops or minor pests in a major crop, would need fewer trials to demonstrate efficacy (generally 3 as a minimum) under the use direction on the label. A similar reduction would apply if a similar pest species is already present on the label (see the Use of extrapolation section in this guideline).

The quality of the trials and the consistency of results may also determine how many trials are needed to satisfactorily demonstrate efficacy. A highly consistent and clearly efficacious product, as determined by high-quality trials conducted under high pest pressure, will need fewer trials than a product that delivers variable results. We generally apply a 'weight of evidence' approach unless there are serious risks in ignoring low efficacy (for example, for public health products).

Where we have guidelines for specific product types and situations, we may suggest the number of trials. Alternatively, you can ask us for pre-application assistance of a trial protocol.

2.1.10. Trial series and length of trials

For products to be used in commercial agricultural settings, trials are usually conducted over a minimum of 2 growing seasons or years to capture any variation between seasons that could affect the efficacy of the product. If you propose to conduct only a single season or year of trials, you should consider whether we can be satisfied by those trials that the product is efficacious. In those circumstances, you should explain why a single season of data should be enough to satisfy us about the efficacy criteria.

For other product types, the number of seasons might not be critical, depending on the nature of the product and the types of claims made on the label.

2.1.11. Trial locations

Products should be tested in each major geographic or climatic area that the product is expected to be used in. The trial sites should represent or simulate the actual use situations as closely as possible. The aim is to satisfy us that the efficacy is acceptable across a range of settings where the product is used.

For commercial agricultural products, we encourage you to conduct trials in areas that are sufficiently separate geographically (that is, regions) to represent all major growing areas for the particular crop or situation proposed on the label. If 2 or more areas share similar agricultural, environmental and climatic conditions, trials need not be conducted in all those areas. You should explain your selections for the location and number of sites in the efficacy dossier. When you are planning trials, we can provide advice through our pre-application assistance scheme.

Products for use in protected cropping environments (such as shadehouses or greenhouses) should be trialled in a representative set of those environments. Crops grown in both protected and open environments should be trialled in both. Extrapolations from open to protected and vice versa are unlikely to be acceptable because pesticide deposition and degradation, pest abundance and plant responses can vary considerably.

For other products, the geographic areas will depend on the nature of the product.

2.1.12. Cultivars/situations

For crop protection products, the most widely used commercial cultivars of a crop should be used during trials to reflect the usage of the product following registration. Because commercial cultivars have varying degrees of disease resistance, both susceptible and resistant cultivars should be included. Multivarietal screening at one or more sites can provide a valuable guide to potential varietal differences. Similarly for non-crop situations, the situation to be tested should be equivalent to the most common situation in use or a situation likely to provide the most rigorous test for the product. Explain your selection of cultivars or situations for trials in the efficacy dossier.

2.1.13. Application method

Study conditions and application technology should match current industry practice and reflect good agricultural practices (GAP). This should also be reflected on the product label.

In some instances, it is allowable to use smaller scale methodology – rather than the equipment identified on the product label – for field trial work because of the practicalities of obtaining meaningful replicated results from pivotal field studies. For example, hand-held boom sprays are usually used in small plot field trials instead of commercial boom sprays. In these situations, it may be important to include 3 or 4 large-scale trials with normal commercial application equipment to demonstrate that application using that equipment will not affect product efficacy. Conversely, extrapolation from high water volume to low-volume application technology should be tested separately to ensure that efficacy is consistent for both application technologies, if these are both recommended on the product label. All test equipment should be calibrated and documented before each trial to ensure the accuracy of application rates.

Some application methods are very unlikely to be included on a label unless efficacy has been demonstrated for the particular method. For example, if a product is to be applied by air, we expect you to provide supporting data from aerial studies. Similarly, if the product is applied diluted in both oil and water, data using both oil and water should be provided. All claims on the label should be supported by data and/or valid scientific argument. It is important that you record as much detail on the application methods (such as equipment, volume, placement, spray quality, timing, crop and pest development stage, and frequency) as is relevant to the use.

2.1.14. Pest identification

Target pests (including pathogens and weeds) should be identified to species level wherever possible. If there are difficulties in identifying certain organisms, your submission should outline the characteristics of the pest, disease or weed and/or the classification system used in attempting to identify it or distinguish it from other related organisms that are present.

2.1.15. Pest abundance

For field trials, you should choose sites with a history of high pest abundance (activity, population, density, incidence, as appropriate) to have the best possibility of ensuring a proper test of the product. Ideally, the product will be tested against a range of pest abundances, as that will help to determine whether different rates are appropriate under different pest pressures.

For laboratory trials or any trials in which the pest abundance is artificially created, you should ensure that the abundance is adequate to provide a sufficient challenge to the product. Any artificial inoculation methods used should be fully described. It is often valuable in laboratory trials to provide an unrealistically high pest density to provide additional confidence in the results.

If the product is not tested against adequate pest abundances, we are likely to have less confidence that it will be efficacious in all scenarios in which the product would be expected to be used after registration. In such cases, we may consider limiting the claim on the product label to accurately reflect our level of satisfaction against the efficacy criteria that we have derived from the information provided with the application.

2.1.16. Good agricultural/industry practice

The APVMA expects that researchers will conduct trials in accordance with good agricultural practice (GAP) for agricultural pesticides and good pest management practice in other industries, such as urban or turf pest control. For example, trials should not be undertaken using outdated technology or application methods that are not comparable to those currently available and in use. If you do not use GAP, you must justify that choice and explain whether any differences, and what type of differences, would be expected when the product is used in accordance with GAP.

Results from trials not conducted according to GAP or a similar code of practice are less likely to satisfy us about the efficacy criteria.

2.1.17. General guidance on satisfying crop or situation safety

For products to be used on crops (including pastures), on areas where crops will be grown or next to cropped areas, you should provide justification in the form of data and/or valid scientific argument to demonstrate the presence, extent and type of any crop damage that may occur through the use of the product, including which factors influence the extent and degree of damage.

If the product is not used in agricultural situations (for example, wood preservative products, urban pest control agents and antifouling paints), but has the potential to adversely affect the situation it is used in, you should provide information about any such impacts.

Unless the product has a new active constituent or is a herbicide, plant growth regulator or soil fumigant, most crop and other situation safety data are captured as part of the efficacy trials. Where this is the case, this information should be collected, tabulated where possible, and discussed in the light of the proposed label instructions. However, if crop damage from the proposed use is suspected or observed in efficacy trials, separate phytotoxicity-specific trials should be undertaken to estimate the full extent and type of damage that may be encountered. In determining effects on yield, it is often beneficial to run this type of trial in areas where the pest is absent, as pest damage can obscure the plants' response to the product. Comparing crop safety in efficacy trials with low and high pest abundance can also be useful for this purpose.

More detailed crop safety trials should be conducted for certain product types, such as selective herbicides, in order to test specific parameters. Refer to the product-specific guidelines if they exist or seek advice from us when planning product trials. You can also apply for assessment of a trial protocol.

Safety studies should use the formulation intended for marketing, applied by the means recommended on the proposed product label and under the proposed conditions of use. Any variances from this should be justified with relevant scientific argument. Further details may be available in separate guidelines. You may also wish to consult the European Plant Protection Organization (EPPO) Phytotoxicity assessment standard (PP 1/135(4).

Any unanticipated reactions occurring during any other studies, or known or suspected by reports from users in Australia or overseas, must be reported and submitted with the application.

2.1.18. Safety to (target) host crops

The type of data that could be provided to demonstrate target crop safety varies depending on the toxicity to plants of the active constituent and excipients. Environmental toxicity information can be helpful in describing the likely phytotoxic effects of the active constituent, and safety data sheets (SDSs) may provide evidence about the toxicity of excipients. Labels of other products with similar formulations and use patterns may also provide some indication of likely phytotoxic effects.

Your data should indicate the margin of safety to target crops and take into consideration any factors that could reasonably be expected to affect safety in use. The safety of a product for a crop is likely to be influenced by factors such as:

- the application rate, method of application, use of adjuvants, etc.
- soil moisture and soil type (for example, for soil-applied herbicides)
- temperature, light, frost, dew, rain, hail and humidity at the time of application and after application
- varietal susceptibility
- crop size, age, physiological condition, etc.
- crop management practices.

Although those factors will be likely to determine the type of damage to be expected, some of the symptoms to consider reporting include the following, from the EPPO standard PP 1/135(4):

- Modifications in the development cycle, such as timing differences in certain growth stages.
- Thinning (for example, loss of whole plants within a plot).
- Modifications in colour (chlorosis, intensity, etc.).
- Necrosis (tissue death).
- Deformations, such as any abnormal or undesirable morphological change (for example, epinasty [curling, rolling]).
- Yield quantity or quality.

Phytotoxicity can be assessed by the frequency, type and/or magnitude of damage, depending on the situation. It can be estimated visually or measured. Measurable characteristics should always be considered when attempting to compare a product statistically against another product.

Different varieties of the same crop can have different sensitivities to pesticides. If earlier phytotoxicity studies have demonstrated a small margin of safety between the use rate on the label and unacceptable phytotoxicity, trials should be conducted on other varieties, especially those already known to be sensitive. Trials should include a number of different varieties and locations, ensuring that the growing conditions are as similar as possible, in order to discount effects other than those caused by the pesticide. Active constituents that may have an effect on seed quality (systemic, residual in plants, applied late in crop development, etc.) should also be tested to determine any effect. Effects to consider are seed viability, germination capacity and development. Standard seed testing methods are available; for examples, see the International Seed Testing Association (ISTA) website.

2.1.19. Safety to following crops

The effect of repeat treatments and carryover of soil residues on subsequent crops should be considered for persistent herbicides and any other products with such potential. Arguments about safety to following crops should be based on environmental fate data. If environmental fate data are not conclusive and other available information indicates a hazard to certain crops (such as persistent herbicides used to control broadleaf weeds in a cereal crop that carry over to subsequent broadleaf crops or pastures), provide data that allow the extent of that hazard to be determined. Labels may need to carry restraints or warnings about such hazards. Although safety to following crops might not necessarily be stated on the label, you should provide an explanation that demonstrates how study results justify the absence of any label warning to that effect.

If experiments, such as rotational crop or carryover experiments, have been conducted to demonstrate safety to following crops, you should report full details of the experimental particulars, methods used and results.

2.1.20. Safety to non-target crops

The following product characteristics could signal the need to consider the safety to non-target crops:

- Chemicals applied from aircraft or by other methods that might be subject to spray drift.
- Persistent chemicals.
- Volatile chemicals such as long chain 2,4-D esters.
- Chemicals subject to bioaccumulation.
- Chemicals applied in or near waterways.

If the use of a product could be hazardous to non-target crops and plants commonly encountered near or adjacent to the target crop, present data from tests indicating the product's toxicity to such species. Environmental toxicity tests will provide evidence for non-herbicidal products. If experiments have been conducted, give full details of the experimental particulars, methods used and results. State the conclusions drawn from the data and include any appropriate warning statements on product labels.

2.1.21. Effect on taste or appearance of produce (organoleptic tests)

If there is any reason to believe that the use of an agricultural chemical product (or a metabolite of a chemical in that product) could adversely affect the appearance, taste or flavour of produce or cause tainting, there should be an adequate investigation of those effects (organoleptic tests) to determine the likelihood and risk of potential impacts. Report this in the dossier and propose appropriate instructions for product labels.

2.2. Other related studies and information

2.2.1. Implications for resistance management

Where relevant, address the likelihood of resistance development in pest populations where relevant. This may be particularly relevant for crops that have been genetically modified to express insecticidal proteins. For these types of products, this aspect should be addressed in detail in the Environmental Chemistry and Fate part of the Environment dossier

(Part 7A). Consider any environmental assessment reports on the active constituent already received from previous applications and provide them. If signs of resistance development are observed during efficacy or crop safety trials, there should be reported and discussed.

Several comprehensive resistance management strategies have been developed and published on the website of CropLife Australia, which is a peak organisation representing the plant science industry in Australia. If a comprehensive resistance management strategy exists for pests and/or crops relevant to your application, you should discuss the implications for your product and how the product can be used in a manner consistent with the strategy. Label recommendations should be consistent with any relevant resistance management strategy.

Resistance management recommendations are common on labels for herbicides, insecticides and fungicides used in commercial agriculture. These types of products are also assigned codes that reflect their mode of action, which are included on product labels to help users plan chemical rotation.

2.2.2. Effects of residues on subsequent processing

Where relevant, consider the implications of the effects of residues on subsequent processing and address them in detail in Residues – Part 5A and Trade – Part 5B. Any residue or trade reports on the active constituent already received from previous applications should be considered and provided where necessary. In addition, if deleterious effects are observed during efficacy trials, record and discuss them. The format of the discussion should be as for the efficacy and crop safety section.

Where residues occur on natural commodities as a result of pre-harvest or post-harvest applications of agricultural chemicals, the effects of those residues on subsequent processing operations should be determined and reported. Examples include an agricultural chemical applied to barley grain that is intended for malting or to grapes intended for wine production. In such cases, provide evidence of the effect of the residue on the malting or vinification process (this is separate from, and additional to, information required to establish maximum residue limits as described in the residues guidelines).

2.2.3. Herbicides used over the top of herbicide tolerant crops

Herbicide tolerant crops are developed to be treated over the top with a relevant herbicide during an application window that is wider than would be the case in a non-herbicide tolerant crop.

The application of a herbicide over the top of a herbicide tolerant crop may present increased risk in regards to:

- the efficacy and crop safety or phytotoxicity of the herbicide
- the resulting residues and
- potential development of weed resistance.

An applicant for such herbicide product registration should address these areas of risk via the provision of appropriate data and/or scientific argument. As a guide, data to address the risks identified above would include:

- efficacy and crop safety data from trials over 2 growing seasons of the herbicide tolerant crop using the specific formulation contained in the proposed new or varied product application. The trials should be conducted over the top of the specific herbicide tolerant crop for which over the top use is being sought. Data from trials conducted on crops with superseded commercial herbicide tolerant traits or varieties are not acceptable
- crop safety data for the specific formulation should be generated from an appropriately representative number of growing regions as herbicide tolerant crop varieties are grown under a wide range of climatic and edaphic conditions. For example, herbicide tolerant cotton crops grown in hot (tropical) conditions are more susceptible to phytotoxicity when treated with certain herbicides. Applicants should provide appropriate data to satisfy the APVMA that the particular formulation for which over the top registration is being sought does not affect crop safety of the specific herbicide tolerant crop in all such representative environments

The repeated application of a herbicide increases the potential for weeds to develop resistance to the active constituent/s contained in the herbicide product/s The APVMA will impose specific conditions of registration that are designed to enforce the practice of preventative weed resistance management by users of the chemical product. Through conditions of registration, registration holders will be required to implement an appropriate resistance management strategy that:

- provides users with adequate instructions regarding the need for preventative resistance management on the product label
- includes regular consultation with a suitable group of experts that is acceptable to the APVMA for the purposes of reviewing the ongoing adequacy of the strategy for managing resistance. Typically for herbicide tolerant cotton, the approval of the resistance management strategy is required from the Transgenic and Insect Management Strategies Committee of the Australian Cotton Growers Research Association.

The APVMA will also apply conditions of registration that oblige registration holders to conduct weed audits, report weed escapes identified from such audits, and taking follow up action to deal with weed escapes. These conditions are necessary as the over-the-top use pattern of a herbicide can result in an increased potential for the development of weed resistance to the relevant active constituent.

2.2.4. Effects on other industries and unintended effects

Address the effects of the use of the product on other industries or any other possible unintended effects or implications of its use. See the data guidelines (Part 7) for more comprehensive guidance on effects on the environment. Consider and provide any environmental assessment reports on the active constituent already received from previous applications where necessary. If deleterious effects are observed during the efficacy trials, record and discuss them in the same format as for the efficacy and crop safety section.

Consider the movement of mobile chemicals by water in the soil to non-target crops, and the potential carryover of herbicide residues in dead plant material, such as straw from treated crops that may be used to mulch sensitive crops, such as grapevines. Secondary poisoning effects may need to be considered; for example, killed rodents may need to be disposed of to avoid poisoning predatory or scavenging birds, and carnivores and insectivorous birds may be poisoned by eating insects treated with insecticide.

2.2.5. Animal welfare

In Australia, it is a legal requirement that all research trials on animals (terrestrial vertebrates only) must first be approved by an animal ethics committee established and operating in accordance with the *Australian code of practice for the care and use of animals for scientific purposes* (8th edition, 2013). This includes animal trials designed to generate and collect data for applications to the APVMA for product registration.

The role of the animal ethics committee is to ensure that:

- the use of the animals is justified
- the welfare of the animals is provided for during the experiment
- the principles of replacement, reduction and refinement (the ‘3 Rs’) have been considered in the experimental design.

In considering the use of experimental animals to generate regulatory information, the APVMA takes the 3 Rs into account in accordance with its duty of care for the welfare of experimental animals.

Some agricultural chemical products are designed to kill vertebrate pests. Where a product is used on a vertebrate pest or safety experiments are required for non-target animals such as pets and livestock, you should be mindful of all applicable laws covering animal experimentation. If you wish to register or obtain permits for vertebrate pest poisons, you should also provide data to demonstrate that the product is safe to non-target animals when used according to label instructions. Normally, these data are provided as part of agricultural chemical products – Environment (Part 7) dossier.

2.3. Minor use efficacy and safety information

Minor uses are those uses of agricultural chemical products in which either the crop is considered to be of low economic importance at the national level (a ‘minor crop’), or the pest is of limited importance on a major crop (a ‘minor pest’).

Applications for minor use permits should include evidence or other justification that the proposed use under permit will be efficacious and not have an unintended effect on the target crop or use situation.

For many minor uses, efficacy could be justified by a scientifically sound argument alone (for example, using a registered product on a different crop for the control of a pest already registered on a similar crop). If the proposed minor use has the same rate, frequency of application and application method as on the approved label and the new crop is very similar in morphology, growth habit and sensitivity to pest damage, a scientific argument that the proposed minor use could be argued to be equally efficacious may be sufficient to satisfy the efficacy criteria.

For further details, see the guideline on efficacy and crop safety for minor use guideline.

You may also wish to refer to the EPPO efficacy and crop safety extrapolations for minor uses standard (PP1/257), which describes the principles for extrapolation involving the efficacy and crop safety of agricultural chemical products intended for minor uses.

2.4. Demonstrating bioequivalence

Bioequivalence studies can be used as supporting evidence that the efficacy, and possibly the safety, of one formulation or product is equivalent to that of another without conducting trials for all label uses (that is, by using only acceptable 'bridging' data). These studies may be used to support applications for the registration of generic products (products considered 'similar' to a reference product) and for some formulation changes, including those that could arise during the course of product development. Bioequivalence may be determined by one of several direct or indirect methods. The selection of the method depends upon the purpose of the study, the analytical method available, and the type of product. Bioequivalence testing should be conducted using the most appropriate method available for the specific use of the product.

If you choose to use bioequivalence to demonstrate efficacy that is comparable to a reference product, the reference product must be an APVMA-registered product. If an overseas-registered product is used in the bioequivalence study, you will need to demonstrate that the overseas product is the same as an APVMA-registered product.

When designing trials to demonstrate bioequivalence, you should consider the following:

- The reference product(s) should largely have the same uses and instructions as presented for the new product.
- The trial should test the products in equivalent situations (for example, side by side, or suitably close, so that environmental conditions are the same).
- The results should be amenable to appropriate statistical analysis; (for more detail, see the Efficacy experimental design and analysis guideline). Experimental designs with large coefficients of variation will show non-significant differences between treatments and will not be accepted as demonstrating bioequivalence between treatments.
- Where the product label includes a number of different crops or situations and pests, the trials should include a representative sample that, if the product is efficacious, can be extrapolated to all crops, situations and pests claimed. When considering which to choose, consider using (in the following order):
  - the most difficult crop–situation–pest combination in which to achieve efficacy (the hardest test is likely to show any weaknesses)
  - the most economically important crops, situations and pests
  - the most commonly treated crops, situations and pests
  - the crops most sensitive to pesticides
  - crops from each significantly different agronomic group and with considerably different biology, such as morphology, sensitivity to pests (for example, different Codex Alimentarius crop groups such as cereals, leafy vegetables and the major fruit groups) where each is present on the label
  - the longest duration, where residual claims are made, noting that some products can demonstrate this indirectly where the residual action of the active constituent is independent of the formulation type (the submission of soil dispersion studies for termiticides containing certain active constituents is an example in which such claims are acceptable).

One season or year of trials is usually sufficient, as long as the testing conditions are not abnormal (that is, there are no unusual climatic conditions or there is low pest abundance).

Demonstrated bioequivalence might not be sufficient to satisfy the efficacy criteria if both the proposed and reference or comparator products exhibit poor control.

Be aware of the presence of any protected data when attempting to demonstrate equivalence with a registered reference product. If the reference product has protected efficacy data, bioequivalence data are not sufficient to satisfy the efficacy criteria because, in effect, the application relies on the protected data to demonstrate equivalence. If you are claiming that your product is similar to a product with protected data, you must match that data with your own stand-alone data or obtain consent from the authorising party for the APVMA to use the protected data (see limits on use of information for more details).

Small changes in a formulation or small differences between 2 formulations can have significant effects on efficacy and may affect crop safety. The most common differences involve the adjuvants used to improve efficacy (such as surfactants, wetters, spreaders and penetrants) and ingredients used as attractants or stability modifiers.

When demonstrating bioequivalence, the formulation of the reference product might not be completely known. Chemical analysis can be performed to identify types and concentrations of ingredients. However, the provision of these data is rarely acceptable by itself in demonstrating chemical similarity or bioequivalence due to the variable reliability of testing methodologies and possible changes in excipients or changed proportions of formulation components.

Changes to, or differences between, formulations that we may consider acceptable without requiring bioequivalence data include:

- small changes (up to 10%) of the same non-active constituents
- changes in the source or purity of active constituents, if the source is approved (where active constituent approval is required) and the purity remains within the APVMA standard (where a standard exists)
- additions of or changes to minor constituents, such as dyes and preservatives, if their addition is known not to affect the stability of a formulation.

We consider other changes on a case-by-case basis. Some changes may require only a simple discussion of the properties of each ingredient involved, their purpose in the formulation and why the change should not affect efficacy, the stability of the formulation or crop or situation safety. The bioequivalence of some formulations with certain other changes, such as introducing half-strength or double-strength formulations, may also be justified by sound scientific argument in lieu of data. For example, if the product label includes instructions to use dilution to ensure that the same amount of active constituent is applied, and similar proportions of the same adjuvants and other critical constituents are present in the diluted form, a scientific argument for bioequivalence may be acceptable.

2.5. Use of extrapolation

Extrapolations may be used to satisfy the efficacy criteria if you are proposing to extend an existing label approval to include additional crops or situations, or related pests in the absence of specific data on those crops or pests. In such situations, a limited number of efficacy and safety studies using a sample of the crops or situations and pests may be sufficient to satisfy the efficacy criteria when coupled with a valid scientific argument to extrapolate to the other similar crops and pests.

See the guideline on crop groupings for further information about crops that are considered to be sufficiently related for extrapolations.

A typical example involves many of the different fruit groups, such as citrus and stone fruit, where the same pest problem affects all or many members of the crop group. It is acceptable to conduct studies in only a subset of the group in order to have the entire crop group on the label (for example, apples and pears for pome fruit, oranges and mandarins for citrus, or peaches and plums or cherries for stone fruit). The extent of the data that would be recommended in a particular situation varies and is contingent on:

- the current knowledge of both the pest and crop biology
- the similarity of responses to pests and pesticides for each crop within the crop group
- the mode of action of the active constituent.

You should also consider crop safety issues when extrapolating to untested crops. When considering which crops to test, it is prudent to consider which crop or variety has previously shown the most sensitivity to pesticides.

Before commencing any trials to establish bioequivalence or trials that will be used for extrapolation, we encourage you to contact us to discuss the proposed studies. A trial protocol assessment may be useful in determining whether the proposed set of trials and trial protocols is acceptable and sufficient to address the efficacy criteria.

Under certain circumstances, such as those of minor use permit approvals, extrapolation may also allow us to accept less supporting data than would normally be expected to support an additional use. See the efficacy and crop safety for minor use guideline for more details about extrapolation for minor uses.

3. Label claims and instructions

The types of claims that can be made on an approved label and the instructions for how the product is to be used are dependent on the data and argument used to satisfy the APVMA of the efficacy criteria. Some products have specific levels of efficacy that must be demonstrated before a particular type of claim can be made (for example, a barrier claim should not allow any breach for the length of the claim, and eradication of a pest cannot be claimed when the trial has not been designed to demonstrate that claim).

Products that can demonstrate only a lower level of efficacy will have a label statement of claims that matches the level of efficacy demonstrated to us. Lower levels of efficacy may be acceptable for certain types of products (for example, products of biological origin) if you can provide a valid argument about why the level of efficacy is acceptable in that particular use situation or cropping system. Before allowing such other levels of efficacy on product labels, we may seek the validation of your argument from the relevant jurisdictional authorities. If a lower level of control is likely to be achieved from the use of the proposed product, you should clearly state this.

Some product types may need specific levels of efficacy for certain claims. The specifics of efficacy levels needed for particular product types are included in the legislative instrument for efficacy.

Label instructions relating to product use must be supported by data. For example, it is not acceptable to have instructions indicating that only one application of the product is sufficient to achieve the desired effect when the trial data showed that at least 3 applications were required. Similarly, if trials used to support efficacy have consistently included the use of adjuvants (for example, penetrants, wetters, spreaders or feeding stimulants), the label must also include the necessary instructions for the use of adjuvants in the directions for use.

3.1. Recommendations for product mixtures

Labels can provide instructions and recommendations for mixing certain products or types of products. This can be in the form of rates of use for both products in the directions for use section or simply a list of products that are physically compatible with the product in question.

If instructions are provided in the directions for use to combine 2 products before applying them, we expect you to provide data (or valid scientific argument) that the product will be efficacious as claimed, safe to the crop (where relevant) and chemically stable when mixed in accordance with the label instructions. The situation, pest, rate and frequency of use, and method of application must appear on the labels of both partner products. The instructions for the specific product mix are not always needed (for example, on adjuvant labels), but the label of the mixing partner must indicate that the 2 products can be mixed.

Conversely, where trials used to support product efficacy have involved the use of other products, those mixes must be included on the label in manner consistent with the supporting information.

If adjuvants, oils, wetters or other additives are recommended, you should present data to indicate that efficacy is improved and that crop tolerance, where applicable, is not reduced. Ideally, the use rate of any additive should be proven to be necessary by providing data using treatments with and without the adjuvant.

We recognise that on occasions there could be a time lag before the relevant information appears on all partner product labels. In these situations, an appropriate letter of intent using letterhead of the company responsible for the relevant product should be provided indicating timing by when the information will appear on the label.

4. Specific product guidelines

This general efficacy guideline should be read in conjunction with any relevant product-specific guidelines that have been published by the APVMA.

There is also a range of other product-specific protocols (also known as standards) published by several international regulators or agencies that may contain information that could assist you in planning and conducting efficacy trials and preparing an efficacy dossier for lodgement with the APVMA. Not all international standards are relevant to Australian crops, pests and conditions, and we recommend that you consider the relevance of overseas standards before relying on them in your application. Some standards, although available publicly, need to be purchased.

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6. Links

- Pest Management Regulatory Agency (Health Canada)
- United Kingdom Pesticides Safety Directorate
- United States Environmental Protection Agency
- The European and Mediterranean Plant Protection Organization
- Standards Australia

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Version	Date	Description
3	3 November 2015	Clarified crop safety data terminology to reference 'specific formulation' instead of 'relevant herbicide' (2.2.3 Herbicides used over the top of herbicide tolerant crops)

2	8 July 2014	Added reference to the fact that efficacy data, argument or use of a reference product might not be needed for some products including a link to the legislative instrument for efficacy criteria.
1	1 July 2014	First version

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is the Australian Government regulator of agricultural and veterinary (agvet) chemical products.

We acknowledge the traditional owners and custodians of country throughout Australia and acknowledge their continuing connection to land, sea and community. We pay our respects to the people, the cultures and the elders past, present and emerging.