




Australian Government
**Australian Pesticides and
Veterinary Medicines Authority**

ADVERSE EXPERIENCE REPORTING PROGRAM FOR VETERINARY MEDICINES

GUIDELINES FOR REGISTRANTS

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ADVERSE EXPERIENCE REPORTING PROGRAM FOR VETERINARY MEDICINES

GUIDELINES FOR REGISTRANTS

*The APVMA's Adverse Experience Reporting Program for veterinary medicines (AERP Vet) is a quality assurance program established by the APVMA to facilitate responsible management of veterinary medicines throughout their lifecycle. The aim of the AERP Vet is to ensure that products on the market remain safe, effective, are of acceptable quality and are used in the best possible way, and that instructions and warnings on labels are appropriate. For definitions of terms used in the AERP Vet please refer to the **AERP Vet Glossary** (KP81P3).*

Introduction

The APVMA is the independent Australian government authority responsible for the assessment and registration (marketing authorisation) of pesticides and veterinary medicines prior to sale, and their regulation up to and including the point of retail sale. 'Veterinary medicines' include all veterinary chemical products such as vaccines, antibiotics, worming treatments, flea and tick washes and other parasiticides for both domestic and production animals.

As a Commonwealth Statutory Authority, the APVMA operates in accordance with its governing legislation. The principal responsibilities of the APVMA are described in the *Agricultural Chemicals (Administration) Act 1992* and the *Agricultural and Veterinary Chemicals Code Act 1994*.

In accordance with these 'Agvet Codes' the APVMA is required to ensure that pesticides and veterinary medicines sold in Australia:

- are of a high quality,
- do not pose a threat to people, domestic or native animals, crops, plants, things or the environment,
- will not pose any unacceptable risk to trade with other nations, and
- continue to work effectively.

It is essential that risk management systems (such as the regulatory system operated by the APVMA) have strong feedback loops to ensure that decisions being made are appropriate and effective¹.

Section 161 of the *Agvet Codes* requires registrants² to provide the APVMA with any 'new information' that they become aware of. This 'new information' includes adverse experience information relating to human health issues, harm to animals, damage to plants, property or the environment and lack of efficacy when the products are used according to label directions.

The 'registrant' component of the AERP Vet is one method that product registrants can meet certain legislative obligations of section 161 of the *Agvet Codes* (**Attachment 1**). The APVMA acknowledges that many product registrants already have in place programs for receiving, recording, investigating, evaluating and classifying adverse experience reports that they receive. The APVMA

¹ The Australian Agricultural and Veterinary Chemicals Management System, A Report to Government by the APVMA on recent reviews of the system, June 2003.

² Refers to product registrants, active approval holders and APVMA permit holders.

does not wish to cause duplication of such programs and agrees that processes and procedures consistent with the guidelines of the AERP *Vet* would be acceptable evidence to the APVMA that registrants are meeting their obligations under section 161 with respect to adverse experience reports. Any inquiries regarding the level of equivalence of individual programs can be directed to the APVMA.

It is important to note that if product registrants do not wish to participate in the AERP *Vet* then the onus is on them to demonstrate compliance with the mandatory requirements of section 161.

Objectives of the AERP *Vet*

Specifically objectives of the AERP *Vet* are to:

- facilitate product registrant compliance with the requirements of section 161 of the *Agvet Codes*,
- ensure that registration decisions being made by the APVMA are appropriate and effective, and
- promote and maintain public confidence in the APVMA and the National Registration Scheme.

Information received regarding suspected adverse reactions, or '*adverse experiences*' (see below) may identify a need for corrective actions with respect to the product label (eg additional instructions, warning statements or precautions), manufacturing process, formulation, batch recall or review of registration, or education of the agricultural industry and the general public (via mechanisms such as articles in appropriate journals and publications) in better use or safety practices.

Scope of the AERP *Vet*

The Scope of the AERP *Vet* covers adverse experience reports involving:

- animal health issues, including both domestic and native birds and animals,
- human health issues, where people are exposed to veterinary medicines either by using them or as bystanders,
- lack of efficacy,
- residue issues, and
- environmental damage.

The scope does not include:

- registered pesticides (these are dealt with as part of the AERP *Ag*),
- trade issues as these do not fall within the definition of an '*adverse experience*' (see below),
- packaging design faults, which also do not fall within the definition of an '*adverse experience*',
- illegal off-label uses (ie contrary to label directions without veterinary advice, which includes instances where products are used on resistant or suspect resistant pest populations if the label specifically warns against such use), or
- products not registered by the APVMA.

It is also noted that submission of other forms of information such as trial data would fall within the scope of section 161, but would not be part of AERP *Vet*. The APVMA is considering clarifying other information reporting requirements under section 161.

Definition of an '*adverse experience*'

The following definition of an ‘*adverse experience*’ captures the elements of section 161 of the *Agvet Codes* and is to be used by product registrants when determining what information should be submitted to the APVMA. The definition is “descriptive” rather than “prescriptive” because it is almost impossible to provide a complete list of what constitutes an adverse experience. This will leave the definitions open to some interpretation, however the APVMA considers that what should be included in these definitions is fairly straightforward.

“An adverse experience is an unintended or unexpected effect on animals, human beings or the environment, including injury, sensitivity reactions or lack of efficacy associated with the clinical use of a veterinary chemical product.”

The following definition outline what constitutes ‘*serious*’ adverse experiences that are expected to be reported quickly to the APVMA by the product registrant.

Definition of a ‘serious’ adverse experience

“A serious adverse experience is any adverse experience that results in death, is life-threatening, results in persistent or significant disability/incapacity, prolonged duration of serious signs or is a congenital abnormality or birth defect. A serious adverse experience in humans is one that requires medical treatment or involves death.

Within animals managed and treated as a group only an increased mortality or increased occurrence of serious signs, exceeding the rates normally to be expected in that particular case, are to be considered as a serious adverse experience.

The following table is offered as a guide only in determining if an adverse experience is to be regarded as serious.

<i>Small animals Death Hospitalisation Welfare implications</i>	<i>Horses Death Hospitalisation or more than one veterinary visit Welfare implications</i>	<i>Humans Death Medical treatment required</i>
<i>Cattle, sheep and pigs Deaths More than one veterinary visit >10% morbidity Welfare implications</i>	<i>Poultry >5% increase in base mortality >10% morbidity Welfare implications</i>	

Where there is any doubt about the seriousness of a suspected adverse experience or where the complainant or the reporting person disagrees with the Registrant’s assessment of seriousness, the incident must be reported by the Registrant to the APVMA within seven (7) working days.”

Reporting Requirements

The APVMA has developed the following timeframes that product registrants should use when providing this information to the APVMA:

Serious Adverse Experiences

- All reports of adverse experiences of a ‘*serious*’ nature that are reported directly to the registrant should be reported to the APVMA in writing within seven (7) working days of receipt of all such reports.
- Where there is any doubt about the seriousness of a suspected adverse experience or where the complainant or the reporting person disagrees with the registrant’s assessment of seriousness, the incident should be reported to the APVMA within seven (7) working days.

Currently Registered Products

- For currently registered products (including all veterinary medicines that were registered at some time during the reporting period), registrants are requested to provide the APVMA with an annual summary of all suspected experiences (including both lack of efficacy and animal safety), unless the APVMA requests an interim report or more frequent reporting. The annual summary should be submitted at the end of each financial year and no later than close of business 30 September. A reminder notice will be published in the APVMA Gazette each year.

Voluntary Reports

- Voluntary adverse experience reports submitted directly to the APVMA will be copied and forwarded to the relevant registrant(s) for investigation and assessment. All voluntary reports should be investigated, and an initial investigation report containing as much of the required information as possible (see below) submitted to the APVMA within twenty-eight (28) working days of receipt. With the concluding investigation report to be provided within three (3) months of receipt of the original adverse experience report.

Information Required

All adverse experiences reported to registrants of veterinary medicines should be recorded, investigated and assessed by the registrant and reported to the APVMA in accordance with the *Adverse Experience Reporting Program for veterinary medicines – Registrant’s Reporting Form (Periodic Summary Update) (KP81F4)* (this information does not need to be provided in this format, but all the information listed in this form should be provided). The APVMA only requests a line listing of adverse experience reports classified as ‘probable’ or ‘possible’, with an indication of whether there was off-label use involved or not (see Classification below).

The registrant should ensure:

- any adverse experience reports sent directly to any and all manufacturers of their products are recorded, investigated and assessed by an appropriately qualified representative;
- all the information required by these guidelines is submitted to the APVMA within the required timeframes; and
- the appropriate Form is:
 - signed by the Registrant or their legally responsible person/representative;
 - submitted with a covering letter containing a brief overview of all the adverse experience reports included in the summary (eg the number of products involved, the

- number of reports for each product, the types of reports – lack of efficacy, crop safety, human safety, animal safety and environmental damage) and comments on any reports that should be highlighted; and
- accompanied by a copy of the actual label text of the respective veterinary medicines involved.

All adverse experience reports for each product should be grouped together and specific comments made at the end of the listing for the product as per the *Adverse Experience Reporting Program for veterinary medicines – Registrant’s Reporting Form (Periodic Summary Update) (KP81F4)*.

Investigation

The APVMA will request registrants to investigate all adverse experience reports that they receive for the purposes of determining whether the adverse experience is related to the use of or exposure to the product or not. Only reports that fit within the scope of the AERP *Vet* should be investigated for possible submission to the APVMA.

Evaluation

The APVMA will request that registrants evaluate the investigation findings for all adverse experience reports that they receive for their products for the purposes of classification. The use of The Causality Assessment Algorithm³ (Attachment 2) was established as a scientifically valid and rigorous method for assessing causality of adverse experience reports after consideration of methods used by international agencies dealing with adverse experience reports. The algorithm will be provided in the registrant guidelines for the AERP *Vet*, and registrants will be requested to use the algorithm for assessing causality.

Classification

Registrants will be requested to provide the APVMA with their classifications of all adverse experience reports that they receive. The APVMA will then conduct validation of the registrant classifications by conducting our own causality assessment of all ‘voluntary’ adverse experience reports that have been referred to the registrant for investigation, all ‘serious’ adverse experience reports and a random sample of all ‘non-serious’ reports.

Trend analysis

Registrants will be requested to conduct trend analysis of the cumulative reports for all products they are responsible for. Included in this analysis registrants will be requested to provide the APVMA with the following information:

- a calculation of the relationship between the number of adverse experience reports classified as probably product-related or possibly product-related against the total amount of product sold for the reporting period, and
- a brief statement assessing the safety and/or efficacy of the veterinary medicine with reference to published scientific articles/papers, where applicable.

Corrective action

³ Kramer MS, Leventhal JM, Hutchison TA, Feinstein AR (1979) An algorithm for the operational assessment of adverse drug reactions. *Journal of the American Medical Association* **242** (7): 623-632.

Registrants will be requested to provide the APVMA with a short narrative on what corrective action is necessary in light of the evaluation/classification and trend analysis of the adverse experience information, or provide justification for why no action is required.

The APVMA will then consider the adverse experience information for all products with similar formulations, the respective registrant comments and determine recommendations for corrective action required.

The APVMA will write to each affected registrant and include a summary of the details of all other adverse experiences for the products involved and provide a recommendation on corrective action proposed. All registrants will have the opportunity to provide the APVMA with comments on the proposed recommendations and provide a submission as to why they do not consider that the recommended corrective action is required.

After taking into account all submissions and comments the APVMA will provide all affected registrants with its final conclusions and recommendations. Registrants will also be given a timeframe in which the corrective action is to be completed.

The AERP Vet Advisory Committee

The AERP *Vet* Advisory Committee, will consist of the following members:

- the AERP Coordinator,
- an AERP *Vet* Reviewer, and
- the Principal Scientist, Veterinary Medicines Program (supported by appropriate members of the relevant Veterinary Medicine Program Teams and Review Team as required).

Meetings of the AERP *Vet* Advisory Committee will be held on an as-needs basis depending on the numbers and types of adverse experience reports received.

Feedback

The conclusions drawn by the APVMA during investigation and evaluation of each adverse experience report will be reported back to the reporting person. This will include an explanation of whether the APVMA considers that the observed adverse effects (including health symptoms) were related to the use of or exposure to the product (see also Classification above). The APVMA will explain what these conclusions are and what corrective action recommendations, if any, will be taken in response to the information.

It should be noted that in some instances if a causal link is not established between the use of or exposure to the product, or if there is not enough information to make a definite conclusion, then regulatory action may not be taken.

Reporting

The APVMA has previously published annual *Reports of Adverse Experiences* and will continue to publish such periodic reports, as appropriate. The information in these reports is arranged according to the active constituent of the products, therefore individual products are not identified. A summary of regulatory actions taken by the APVMA is also included in these reports.

The APVMA will also publish interim reports if appropriate.

Confidentiality, Consumer Rights and Responsibilities

All information provided on suspected adverse product experiences will be treated as confidential. The name of the person reporting the incident will not be released except to another Government Regulatory Authority, a State/Territory member of the APVMA's Registration Liaison Committee, or the registrant in the normal course of investigating the incident.

The APVMA or any other body or persons involved in investigating the suspected adverse product experiences shall not make any verbal, written or other communication that:

- is unsubstantiated and likely to cause commercial damage to the veterinarian, the APVMA, the registrant or the product;
- misrepresents the facts or makes subjective analyses not based on fact; or
- fails to take into account other legitimate differential diagnoses where appropriate.

The AERP *Vet* is not intended to replace a consumer's right or responsibility to complain to the registrant or manufacturer about an adverse experience with a veterinary medicine. In fact, the APVMA will make it clear to people reporting adverse experiences that they should also report the matter to the registrant, the manufacturer or to the person from whom they bought the product, as they would do with a problem experienced with a purchased item.

Further Information

For further information about the AERP *Vet* contact:

AERP Senior Reviewer
Australian Pesticides and Veterinary Medicines Authority
PO Box 6182
KINGSTON ACT 2604
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The three complementary components of the AERP *Vet*:

1. The '*voluntary*' component that encourages veterinarians and the general public (including animal owners, farmers and other chemical users) to report any adverse experiences to both the APVMA and the product registrant.
2. The '*state*' component through which state agencies are encouraged to report to the APVMA any adverse experience reports that they receive that are within APVMA jurisdiction. It also provides a mechanism for the APVMA to inform the relevant state authority of any information that it becomes aware of that falls within state jurisdiction (such as state control of use issues etc).
3. The '*registrant*' component that provides a mechanism for registrants of veterinary medicines to report to the APVMA any adverse experiences that they become aware of for their products.

The Causality Assessment Algorithm

Each registrant should conduct a causality assessment for each adverse experience report. The following algorithm has been adapted from published information and **may be used as a guide** by registrants to conduct causality assessments of adverse experience reports. If registrants wish to conduct causality assessment using another method, then the results of the assessment must be consistent with the APVMA’s requirements.

The APVMA will validate the registrant’s assessments using statistical random sampling techniques.

1. Previous experience with product

Assessment	Score
Clinical signs generally recognised to occur in this species at the dose used	+1
Clinical signs are not generally recognised to occur in this species at the dose used, but has been previously reported in veterinary and/or human medicine	0
Product has limited accumulated clinical experience	0
Clinical signs previously unreported and product has substantial accumulated clinical experience	-1

2. Alternative aetiological candidates

Assessment	Score
There is no good alternative that can explain the clinical signs exclusive of product administration	+2
An alternative exists, but does not explain the clinical signs well	0
The clinical signs commonly occur spontaneously in this type of patient and situation, usually in the absence of any recognisable alternative	0
There is a good alternative explanation for the clinical signs exclusive of product administration	-1

3. Evidence of overdose

Assessment	Score
The clinical signs are clearly dose-related and there is unequivocal evidence that the amount of product used was an overdose for this animal	+1
The clinical signs are not dose-related or there is no evidence of an overdose	0

4. Timing of events

Assessment	Score
Timing was consistent and as expected for these types of clinical signs to this product	+1
Do not know what timing to expect	0
Timing was inconsistent for these types of clinical signs to this product	-2

5. Dechallenge

Assessment	Score
Clinical signs diminished or disappear after discontinuation of suspect product or administration of a specific antidote	+1
Clinical signs are known to be dose-related and they diminish after dosage reduction	+1
Dechallenge difficult, impossible or inappropriate to assess	0
A non-specific agent or manoeuvre (non-antidotal was administered that was directed against the clinical sign and that usually produces the degree and rate of improvement observed in this case)	0
Clinical signs characteristically transient and episodic and there is no established pattern episode (regardless of what occurs after discontinuing the product)	0
Clinical signs known to be dose-related and did not diminish or disappear after dosage was reduced	0
Clinical signs did not diminish or disappear after discontinuing suspect product or administration of a specific antidote	-1
Clinical signs improved without dechallenge and the improvement cannot be attributed to the development of tolerance	-1

6. Rechallenge

Assessment	Score
Clinical signs unequivocally recurred or exacerbated after rechallenge	+1
There was no rechallenge	0
A non-specific agent or manoeuvre (non-antidotal) was administered that obscured the response of the clinical signs	0
Clinical signs failed to recur or exacerbate on rechallenge, but the dosage or duration of product administration on rechallenge was substantially less than that suspected of causing the original clinical signs	0
Recurrence or exacerbation of clinical signs was impossible to assess because it was progressing or was at a level of severity that any further increase would be difficult to appreciate	0
Clinical signs failed to recur or exacerbate on rechallenge	-1

Causality assessment

The relationship between the use of the veterinary chemical product and the reported clinical signs, assessed after investigation of the incident has been carried out. The relationship is expressed in terms of:

Probable (algorithm score 3 to 7)

For inclusion in the category 'probable' all of the following minimum criteria should be met:

- there should be a reasonable association between the administration of the product and onset and duration of the reported adverse experience,
- the description of the clinical signs should be consistent with or at least plausible given the known pharmacology and toxicology of the product, and
- there should be no other equally plausible explanation (or contributing factors) for the clinical signs.

When any of the above criteria cannot be satisfied (due to lack of sufficient information or conflicting data) then the association cannot be assessed as 'probable'.

Probable/Off-label (algorithm score 3 to 7)

As per the classification of 'probable' and where there is obvious evidence of off-label use (including use in species not listed on the product label, over-dosing or under-dosing). It is acknowledged that depending on State and Territory legislation, veterinary prescribing privileges, APVMA Permits and other legal exemptions may allow off-label use in some situations.

Possible (algorithm score 0 to 2)

For inclusion in the category 'possible' association of the adverse experience with administration of the primary suspect product is one of other possible and equally plausible explanations (or contributing factors) for the described adverse experience.

Possible/Off-label (algorithm score 0 to 2)

As per the classification 'possible' and where there is obvious evidence of off-label use (including use in species not listed on the product label, over-dosing or under-dosing). It is acknowledged that depending on State and Territory legislation, veterinary prescribing privileges, APVMA Permits and other legal exemptions may allow off-label use in some situations.

Unlikely (algorithm score -1 to -6)

Where sufficient information exists to establish that the described adverse experience was not likely to have been associated with administration of the product(s), or other more plausible explanations exist, the assessment should be categorised as 'unlikely'.

Unknown

All adverse experiences where reliable data is either unavailable or is insufficient to make an assessment should be categorised as 'unknown'.