Adverse Event Reporting Programme for Veterinary Medicines

ACVM guideline for registrants

1. Introduction

The adverse event reporting programme is part of the quality assurance programme developed by the Ministry for Primary Industries (MPI) to ensure that all veterinary medicines in the marketplace are safe, efficacious, of acceptable quality, used appropriately, and that product labels provide sufficient consumer information for correct use.

2. Statutory basis for adverse event reporting

Every registration of an agricultural compound trade name product has conditions imposed under section 23 of the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997. It is an offence not to comply with the conditions of registration.

One of the conditions of registration imposes an obligation to advise MPI of adverse events related to the product. The conditions are:

- **The registrant must investigate the significance of every adverse event associated with the use of the product; and report to MPI within 20 working days the outcome of this investigation.**
- **The registrant must notify MPI immediately upon becoming aware of an adverse event that seems to have seriously jeopardised the health and welfare of the treated/exposed animal(s); and may require the use of the product to be stopped or restricted to prevent similar adverse events.**

Compliance with these conditions of registration is your responsibility as registrant of the product. In some cases,

STATUTORY BASIS FOR REPORTING NEW INFORMATION RELATED TO ADVERSE EVENTS

A separate condition of registration imposes an obligation to advise MPI of any new information about the product. The condition is:

- **The registrant must, as soon as practicable after becoming aware of new information, advise MPI of any new information that relates to the relevance, reliability or correctness of information provided at the time of registration and upon which the decision to register the product was made.**

Compliance with this condition of registration is your responsibility as registrant of the product.

MPI considers analyses of adverse events and identification of trends may constitute new information that must be reported to MPI, if these trends show that assumptions made and conclusions drawn at the time of registration may not be (or no longer be) relevant, reliable or correct.

It is your responsibility to analyse adverse events to identify trends that may constitute new information that must be reported to MPI. We will monitor adverse event reports (AERs) and, if a significant trend is suspected but no analysis report has been received, we will ask to review any analyses that you have carried out.

3. Definitions

ADVERSE EVENT

An adverse event is any observable or measurable negative effect in treated or exposed animal(s) that is (or is suspected to be) associated with administration/application of a veterinary medicine or oral nutritional compound. In other words, any negative physiological or pharmacological side effect, target animal safety issue, residue issue, lack of efficacy or alleged interactions with other products or compounds should be considered an adverse event. This includes all unfavourable and unintended events (that may or may not have been identified as possible when the product was registered) that are associated with the use of the product in an on-label or off-label manner.

SERIOUS ADVERSE EVENT

A serious adverse event is any adverse event that results in death, is life-threatening, results in persistent or significant disability/incapacity, a congenital anomaly or birth defect, interference with diagnosis or control, or some specific adverse events in humans (such as the transfer of human pathogens [salmonella in animal feed] or development of antibiotic resistance).

For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event.

The following table is offered **as a guide only** to help you determine if an adverse event should be regarded as serious.

Companion animals	Horses	Cattle, sheep, pigs	Poultry
Death and/or Hospitalisation and/or Welfare implications (moderate to severe pain or distress)	Death and/or Hospitalisation or More than one veterinary visit and/or Welfare implications (moderate to severe pain or distress)	Deaths and/or More than one veterinary visit and/or >10% morbidity and/or Welfare implications (moderate to severe pain or distress)	>5% increase in base mortality and/or >10% morbidity and/or Welfare implications (moderate to severe pain or distress)

While serious adverse events are always serious to the animal or human affected, they do not always have implications for the continued use of the product. Examples of serious adverse events that are not considered to have implications for the continued use of the product are:

- **a report of levamisole toxicity due to overdosing, where a warning about the potential for serious illness due to overdosing is present on the product label. Such a case, while serious, would not need to be classified as a Product Alert (see below);**
- **a report of the death of a horse due to a product designed to be administered intravenously being mistakenly administered interarterially. While such a case may cause the death of the treated animal, such a case would be expected to be a singular occurrence and thus has no implications for the continued use of the product.**

PRODUCT ALERT

A Product Alert is a serious adverse event that requires immediate notification to MPI. The use of the product may have:

- **caused death or moderate to severe pain or distress in the treated/exposed animal(s); and**
- **there may be more serious adverse events if the use of the product is not stopped or restricted.**

The notification may result in MPI requiring you to recall the implicated batch of product or the suspension of the product registration.

MODERATE PAIN OR DISTRESS

The pain or distress caused does not prevent normal behaviour but the animal remains aware of the pain or distress and is not easily distracted.

SEVERE PAIN OR DISTRESS

The pain or distress caused debilitates the animal and prevents normal behaviour.

4. Statutory obligations

IMMEDIATE NOTIFICATION

All Product Alerts must be notified to MPI immediately (within one working day).

A small number of serious adverse events require immediate notification to MPI (Product Alert). These are situations where the registered product use may need to be stopped or restricted as a consequence of a decision by MPI.

Immediately means you must notify MPI on the same working day or the first working day after you become aware of the event.

In addition to the initial notification, once an investigation has been concluded the outcome must be reported to MPI. The subsequent reporting of the investigation of a Product Alert event is the same as for any other adverse event (see below).

REPORTING ADVERSE EVENTS

The outcome of the investigation into the link between an adverse event involving a registered veterinary medicine trade name product, the use of the product and the significance of the adverse event must be reported to MPI within 20 working days. If the investigation cannot be concluded within this timeframe, the event, scope of investigation and any interim conclusions must be reported to MPI within the 20 working days, with a timeframe given for completion of the investigation. Once the investigation is completed, the conclusions and causality assessment must be reported to MPI.

Failure to immediately notify MPI of a Product Alert adverse event or to report the outcome of an adverse event investigation may be a breach of the conditions of registration and an offence that, on summary conviction, may attract a term of imprisonment of up to 2 years or a fine of up to $30,000 for an individual or $150,000 for a corporation.

INFORMATION ADVICE OBLIGATION

It is expected that registrants will monitor and analyse adverse events. You must advise MPI of any analyses of adverse events, if the findings show that assumptions made and conclusions drawn at the time of registration may not be (or no longer be) relevant, reliable or correct.

Failure to send to MPI adverse event analyses that may be new information may be a breach of the conditions of registration and an offence that, on summary conviction, may attract a term of imprisonment of up to 2 years or a fine of up to $30,000 for an individual or $150,000 for a corporation.

5. Information required

NOTIFICATION OF A PRODUCT ALERT

The notification of a Product Alert event must be in writing. This must be on the same working day or the first working day after you becomes aware of the event so a fax (04 894 2566) or e-mail message (approvals@mpi.govt.nz) should be sent.

The notification must include:

- **registrant identification and contact information**
- **date**

- **date the event occurred**
- **trade name and registration number of the product involved**
- **brief description of the event**
- **advice on investigation and estimated reporting date.**

6. Reporting an adverse event

All adverse events reported to you as a veterinary medicine registrant should be recorded, investigated, assessed and reported to MPI, using the AER form on our website:

Adverse Event Report: Veterinary Medicines

You do not have to provide information in this format, but you should provide all the information listed.

You must investigate all adverse events that you receive for the purposes of determining whether the adverse event is related to the use of, or exposure to, the product or not. You should ensure that:

- **any AERs sent directly to any manufacturers of your products are recorded, investigated and assessed by an appropriately qualified representative;**
- **all the information required by these guidelines is submitted to MPI within the specified timeframes.**

EVALUATION AND CLASSIFICATION

MPI requests that you evaluate and classify the investigation findings for all AERs that you receive for your products. You may wish to classify the report using The Causality Assessment Algorithm[1] (section 7 below). This algorithm, which is also utilised by the Australian Pesticides and Veterinary Medicines Authority (APVMA), was established as a scientifically valid and rigorous method for assessing causality of adverse event reports. You may use an acceptable alternative method of classification, but if you use an alternative method, please provide an explanation of the causality rationale for the method used.

MPI knows that many product registrants already have in place programmes for receiving, recording, investigating, evaluating and classifying AERs. With many registrants operating internationally, reports created for other regulatory authorities are likely to fulfil our requirements. We do not wish to cause unnecessary duplication of such programmes and consider that processes and procedures consistent with the guidelines of the Adverse Event Reporting Programme would be acceptable evidence to us that you are meeting your registration condition obligations. Any inquiries regarding the level of equivalence of individual programmes should be directed to MPI.

TREND ANALYSIS

MPI points out that you have a statutory obligation to advise us of any new information about your product. This includes trend analyses for AERs you receive, if the findings indicate that the assumptions made and the conclusion drawn at the time the product was

[1] 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.

registered may not be (or no longer be) relevant, reliable or correct. If an increase or change is detected in the number of AERs received for a product, assess the significance and provide a rationale for the change. Reference to published scientific articles/papers should be provided, where applicable.

We will monitor AERs reports from you and from any third party. If we suspect a trend that would bring into question the registration of the product or the conditions imposed on the registration, we will ask to review analyses you have carried out and not reported as new information, as required.

CORRECTIVE ACTION

MPI requests that you provide us with a short narrative on what corrective action is necessary in light of the evaluation/classification and trend analysis of the adverse event information, or provide justification for why no action is required.

We will consider the adverse event information and your comments, and then determine recommendations for any corrective action required. We will write to you with a summary and a recommendation on any corrective action proposed. You will have the opportunity to provide comments on the proposed recommendations if you do not agree with the recommended corrective action required.

After taking into account all comments, we will provide our final conclusions and recommendations. You will be given a timeframe in which the corrective action is to be completed.

FEEDBACK TO VOLUNTARY REPORTER

The conclusions drawn by MPI during investigation and evaluation of each AER will be reported back to the reporting person and the registrant. This will include an explanation of whether we consider that the observed adverse effects were likely to be related to the use of or exposure to the product. Where appropriate, we will explain what these conclusions are and what corrective action, if any, will be taken in response to the information.

CONFIDENTIALITY, RIGHTS AND RESPONSIBILITIES

All information provided on suspected adverse events is treated as confidential. However, all information held by MPI is subject to the provisions in the Official Information Act 1982 and the Privacy Act 1993. Any request for information will be considered on a case by case basis under the Official Information Act 1982 and the Privacy 1993. The consideration will take into account whether the request for information relates to information that could be considered to be commercially sensitive under section 12 or Part 6 of the ACVM Act.

The Adverse Event Reporting Programme is not intended to replace a person's right or responsibility to complain to the registrant or manufacturer about an adverse event with a veterinary medicine.

7. The Causality Assessment Algorithm

As registrant, you should conduct a causality assessment for each adverse event report. The following algorithm has been adapted from published information and may be used as a guide to conduct causality assessment. If you wish to conduct causality assessment using

another method, then the results of the assessment must be consistent with MPI's requirements.

1. PREVIOUS EVENT 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

8. Causality assessment

The relationship between the use of the veterinary medicine 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 event;**
- **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). This includes discretionary and illegal off-label use.

POSSIBLE (ALGORITHM SCORE 0 TO 2)

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

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, overdosing or underdosing). This includes discretionary and illegal off-label use.

UNLIKELY (ALGORITHM SCORE –1 TO –6)

Where sufficient information exists to establish that the described adverse event 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 events where reliable data is either unavailable or is insufficient to make an assessment should be categorised as 'unknown'.

FURTHER INFORMATION

For further information about the Adverse Event Reporting Programme email us: approvals@mpi.govt.nz