Veterinary Medicines Pharmacovigilance Programme: Adverse Event Reporting and ACVM Act Risk Area Notifications

ACVM guideline for registrants (March 2026)

Contents

PURPOSE

The Veterinary Medicines Pharmacovigilance Programme is a quality assurance programme developed by New Zealand Food Safety, which is part of 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.

The programme enables ongoing confirmation that the conditions of registration for individual and groups of veterinary medicines remain appropriate to prevent or manage the following risks associated with the use of veterinary medicines:

- risks to public health
- risks to trade in primary produce
- risks to animal welfare
- risks to agricultural security.

It also enables confirmation that:

- the use of agricultural compounds does not result in breaches of domestic food residue standards and
- sufficient consumer information is provided when agricultural compounds are sold so people can use them without causing harm.

The programme includes Adverse Event Reporting and ACVM Act Risk Area Notifications components.

SECTION A: ADVERSE EVENT REPORTING

1. Introduction

Adverse Event Reporting is the component of the Pharmacovigilance Programme that manages observable unexpected or unintended incidents in animals that are reported as having occurred with a possible relationship to the use of a veterinary medicine.

2. Additional guidelines

- VICH GL24: Pharmacovigilance of veterinary medicinal products: management of adverse event reports
- Risk Management under the Agricultural Compounds and Veterinary Medicines Act 1997: Overview

3. Definitions

3.1 Adverse event: veterinary medicine

An adverse event is any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any on-label or off-label use of a veterinary medicine.

Classes of adverse event:

- any negative physiological or pharmacological side effect
- target and non-target animal safety issue
- residue issue (violative residue detections or inhibitory substance [IS] grades)
- lack of efficacy
- transmission of infectious agents
- interactions with other registered veterinary medicines or substances including compounded veterinary medicines and human medicines (specifically their possible impact on the reported veterinary medicine's risk profile)
- veterinary discretionary off-label use of products resulting in an adverse event
- human adverse symptoms following exposure to a veterinary medicine.

3.2 Serious adverse event: veterinary medicine

A serious veterinary medicine adverse event is any adverse event that:

- results in death
- is life-threatening
- results in persistent or significant disability/incapacity
- results in a congenital anomaly or birth defect
- results in issues in humans that may extend beyond the affected individual (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 group is considered a serious adverse event.

This table is **a guide** to help determine if an adverse event should be regarded as serious:

Cattle, sheep, pigs	Poultry
• Deaths and/or • More than one veterinary visit and/or • Increased morbidity above base and/or	• Increase in base mortality and/or • Increase in base morbidity and/or

• New or worsening clinical signs	• New or worsening clinical signs

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 intra-arterially. 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;
- a report of the death of a dog due to accidental monensin exposure. While the exposure resulted in the death of an animal, if the required label warnings were in place the exposure would not have implications on the continued use of the product.

3.3 Product Alert: veterinary medicine

A Product Alert is the immediate notification to MPI of a serious adverse event where immediate cessation or restriction of product sales and/or use is warranted to prevent additional serious events from occurring.

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

4. 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 condition of registration imposes an obligation to advise MPI of adverse events related to the product. Compliance with this condition of registration is your responsibility as registrant of the product.

The condition is:

Condition 64

- 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.

4.1 Statutory basis for reporting new information related to adverse events

Another condition of registration imposes an obligation to advise MPI of any new information about the product. Compliance with this condition of registration is your responsibility as registrant of the product.

The condition is:

Condition 65

- 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.

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

This includes adverse event information reported in overseas countries for a product that is identical (i.e. same formulation, manufacturing process, batch formula, and final formulation) to that registered in New

Zealand. Note: the adverse event reports (AERs) themselves do not need to be submitted but the information about them must be reported to MPI.

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.

5. Statutory obligations

5.1 Immediate notification of Product Alerts

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 use of the product may need to be stopped or restricted as a consequence of a decision by MPI.

Immediately means you must notify us 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 us. The subsequent reporting of the investigation of a Product Alert event is the same as for any other adverse event (see below).

5.2 Adverse event report

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 as a final report as soon as the investigation is completed, but no later than 20 working days after receipt.

If the investigation cannot be concluded within this timeframe, the event, scope of investigation and any interim conclusions must be reported to MPI as an interim report within 20 working days. This report must clearly state that further information is expected and provide a timeframe for completion of the investigation. Once the investigation is completed, the conclusions and causality assessment must be reported to MPI immediately and identified as the final report.

Failure to immediately notify us 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.

5.3 Advice on new information obligation

It is expected that registrants will monitor and analyse adverse events. You must advise us 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 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.

5.4 Change in product registrant

The responsibility for the assessment and reporting of adverse events lies with the registrant on record at the time that the event is notified, irrespective of who was the registrant at the time the event occurred. Registrants must ensure that sufficient information is obtained to enable finalisation of any open AERs at the time that the product ownership is transferred.

6. Notification of a Product Alert

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 become aware of the event, so an e-mail message should be sent to: ACVM-adverseevents@mpi.govt.nz

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.

7. Reporting an adverse event

All adverse events reported to you as a veterinary medicine registrant should be recorded, investigated, assessed, and reported to us, 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, and
- all the information required by these guidelines is submitted to MPI within the specified timeframes.
- It is expected that adverse events are reported to MPI within the defined timelines (see appendix one) as they are received. The only exception is for adverse events that occur during post authorisation studies. Under this scenario, adverse events that, upon investigation, are not considered to be adverse product reactions or which do not challenge the acceptability of the conditions of registration (including the approved label statements) may instead be summarised and provided in a single report upon completion of the trial. Any adverse events that indicate that the conditions of registration may no longer be appropriate, Product Alerts and new information must be reported as per standard process.

7.1 Report content guidance

- The description of the event (or narrative) must be detailed enough to enable MPI to independently assess the relevance of the event. Avoid simplistic summaries and ensure accurate timelines are reported.
- If additional information is expected, ensure that this is clearly stated at the end of the narrative included on interim reports.
- If information is lacking, the reason must be clearly stated in the narrative (e.g. reported by a third party, reporter did not return calls).
- As the collection of adverse event report information is required to ensure the risks managed under the ACVM Act are managed, there is no New Zealand legislative barrier to the contact details of the reporting party being provided to MPI. There are occasions when direct contact with the reporting party is deemed necessary, so the reporter details should be provided.
- If due to individual registrant preference reporter contact details are not provided as routine practice, the reporter's contact details must be made available to MPI immediately upon request if required.
- If the reporter refuses to share their details with MPI this must be clearly stated on the first report form submitted. Inclusion of the term "Withheld" in the reporter contact details would suffice.
- The location (at minimum the region, postcode or city) where the event occurred must be disclosed with all reports filed.
- If supportive information such as images or laboratory results have been provided by the reporter, attach these with the reports sent to MPI. If these cannot be provided in full, the following must be included in the event summary:
  (i) a detailed description of the findings for all images, and

(ii) a true and accurate electronic copy of all abnormal laboratory measurements (whether you consider them relevant or not) along with reference ranges, and

(iii) a true and accurate electronic copy of all diagnostician interpretation comments in full.

- If deemed necessary MPI will request full copies.

7.2 Evaluation and classification

We request that you evaluate and classify the investigation findings for all AERs that you receive for your products.

We expect all registrants to provide a causality assessment based on the ABON algorithm (appendix 3)

We know 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 us at ACVM-adverseevents@mpi.govt.nz

7.2.1 Causality ruling guidance

The causality ruling justification provided must be detailed and adequately address all issues of relevance to the ruling selected with reference to the causality algorithm used.

- If a possible ruling is based on the potential that other causes were not ruled out, specifically identify at least one of these causes and state the reasons why it is considered to be equally plausible.
- If the “O1” inconclusive or the “O” unclassifiable/unassessable rulings are selected, these must be adequately justified. If a product association cannot be discounted but other factors prevent a possible ruling, the correct causality ruling is O1. If information is insufficient or unreliable, the correct causality ruling is O.

7.3 Trend analysis

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 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. Provide reference to published scientific articles/papers, if 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.

Trends that are considered by MPI to indicate the need for additional investigations include (but are not necessarily limited to):

- an increased number of events beyond that previously observed for the product or class that cannot be explained by an increase in sales volumes
- a cluster of events
- off-label events relating to a specific use pattern not explained by an increase in sales volumes for that purpose
- multiple events characterised by sudden loss of efficacy for products used over prolonged periods where that is not stated on the label as a possibility.

7.4 Corrective action

We request 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.

7.5 MPI outcome report

7.5.1 Standard Process

For most AERs, MPI will provide email notification of our ruling. If it differs from yours, justification for the difference will be provided.

Registrants may request corrections to event summaries included in MPI's outcome email if they contain inaccurate information. MPI rulings are final and will only be reviewed if new information is provided.

Where case updates are provided after the event has been closed by MPI and the email notification sent, an additional notification of our ruling will be provided only if there is a change from our initial ruling.

7.5.2 Flea Products

Most flea product inefficacy reports received are characterised by one or more of the following features that indicate that efficacy is not as expected, or that the product is likely to be as efficacious as expected, or causality is unable to be confirmed with confidence:

(i) Improper use (e.g. collar applied too loosely or underdose);
(ii) Break in treatment prior to product use resulting in environmental parasite infestation;
(iii) Inefficacy reported within 3 months of 1st treatment (where fleas are already present);
(iv) No or few fleas seen (pruritus is the primary clinical sign);
(v) Dead fleas seen;
(vi) Source of reinfestation confirmed;
(vii) Insufficient information to make an assessment.

For the same product class, many adverse safety reports describe on-label adverse effects. It is important that all inefficacy and adverse safety reports continue to be sent to MPI, however if the assessment is straightforward and MPI agrees with your causality assessment, an outcome email will not be provided for individual cases.

Once a month, a summary email of all relevant flea inefficacy and safety cases will be provided for your records to acknowledge our agreement.

7.6 Feedback to voluntary reporter

If an adverse event has been filed directly with MPI by a non-registrant person associated with the adverse event, the conclusions drawn by MPI after the registrant has investigated and provided their report, and MPI has assessed and classified the AER will be reported back to the reporting person and the registrant.

The feedback 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. If appropriate, we will explain what these conclusions are and what corrective action, if any, will be taken in response to the information.

The feedback to the voluntary reporter will be sent no less than ten working days following the registrant outcome to allow for any post-ruling narrative clarifications deemed necessary by the registrant.

7.7 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 2020. Any request for information will be considered on a case-by-case basis under these two Acts. 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 contact the registrant or manufacturer about an adverse event with a veterinary medicine.

SECTION B: ACVM ACT RISK AREA NOTIFICATIONS

1. Introduction

New Zealand is an exporting nation that places emphasis on animal welfare and has a geographical remoteness that means animal diseases endemic in many parts of the world remain exotic to our shores. In consequence, there is a need to proactively respond to information relating to the use of a veterinary medicine that has not resulted in an adverse event but may result in unacceptable ACVM Act risk area management outcomes if not appropriately managed. The sharing of such information is the focus of ACVM Act Risk Area Notifications (RMNs).

The ACVM Act risk areas are discussed in the overview document referenced in section two. The majority of RMNs are likely to be related to potential residue violations but reports of uses that contravene conditions of registration and/or label directions (e.g., the use of phenylbutazone in food producing animals) and any other use that could significantly jeopardise ACVM Act risk management should also be reported.

2. Additional guidelines

Risk Management under the Agricultural Compounds and Veterinary Medicines Act 1997: Overview

3. Definitions

Risk mitigation notification: veterinary medicine

A report submitted in relation to the use of a veterinary medicine that has the potential to result in unacceptable outcomes for any of the ACVM Act risk areas.

Issues that should be notified include:

- potential residue issues
- illegal off-label use (that is, contrary to label directions associated with conditions of registration that prohibit the use).
- uninformed off-label use (that is, contrary to label advice in the absence of an appropriate risk: benefit assessment).

Issues that are serious and should be notified with urgency include any that:

- may result in residues that pose a risk to food safety. This includes any overdose/inappropriate dosing event that is likely to result in a residue violation.
- have resulted in interference with disease diagnosis or control (e.g., inappropriate use of a product that may negatively impact on a national disease monitoring program).

4. Information requirements

- Risk Mitigation Notifications can be reported in the same format as an adverse event report or alternatively via an e-mail message sent to: ACVM-adverseevents@mpi.govt.nz
- Notifications that relate to possible residue risks or interference with disease diagnosis or control should be notified to MPI as soon as possible but no later than 5 days after receipt of the report to enable regulatory confirmation of the acceptability of the proposed risk management strategy.
  Other notifications should be made once communications with the reporter are closed or earlier if deemed appropriate.
- Unless considered unwarranted by the registrant, in the first instance Risk Mitigation Notifications are expected to contain a summary of the information provided by the reporter and

any risk management advice provided to the reporter. A causality ruling is not expected to accompany Risk Mitigation Notifications.

- Reporter contact details should be provided if permission has been obtained. If not supplied with the notification, the reason must be stated.

5. Further information

For further information about the Veterinary Medicine Pharmacovigilance Programme email us:

ACVM-adverseevents@mpi.govt.nz

6. Document History

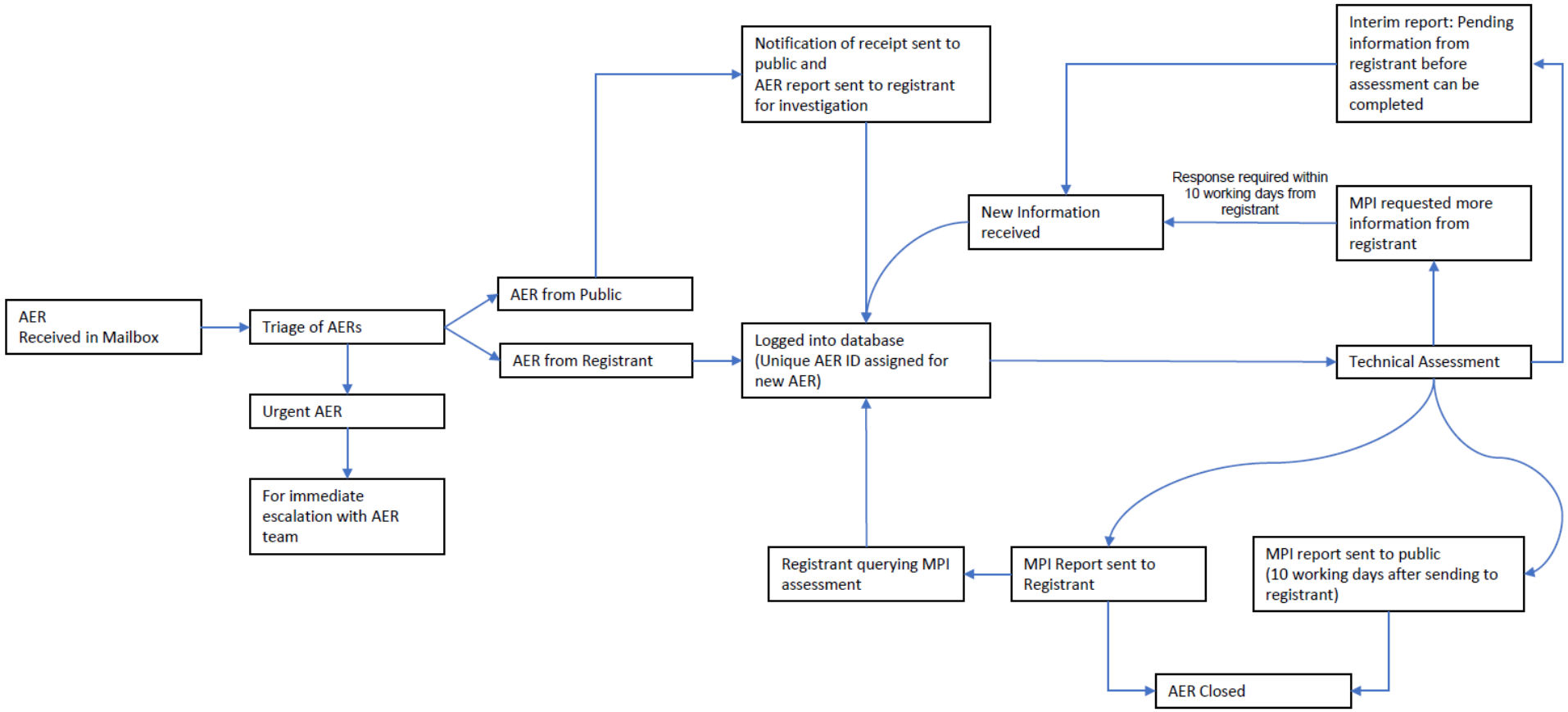
Version Date	Key Sections Changed	Description of Changes
March 2026	Section 7.1 and Section 7.5	Clarification of location data reporting requirements Updates to standard process and new process for flea product reporting.

APPENDIX 1: Reporting Timelines

Timeframes for categories marked with an asterisk are mandatory.

Category	Timeframe
Product Alert*	Initial report: Within 1 working day Final report: Immediately upon completion of investigation. Any additional timeframes will be conveyed based on the specific event as deemed appropriate
Adverse Events*	Interim report (if necessary): Within 20 working days Final report: Immediately upon completion of investigation, but within 20 working days if no interim report filed and within 90 working days if an interim report is filed. Notification (with justification) is expected if an extension is required
Risk Mitigation Notification – Residue and Interference with Disease Diagnosis or Control Issues	Notification and closure report: within 5 working days. If necessary due to ongoing investigation: Interim summary notification within 5 working days with a closure notification to follow immediately upon completion of investigation, but within 20 working days
Risk Mitigation Notification – Other	Immediately upon closure or with urgency depending on the circumstances of the issue and potential significant impact on ACVM Act risk areas
Response to MPI Request for Information	10 working days Notification (with justification) expected if extension required
Request for Review of MPI Record of Assessment	10 working days (response to any party who reported the event directly to MPI will be sent on working day 11)
New Information	Interim report (if necessary): Within 20 working days Final report: Immediately upon completion of investigations or as agreed

APPENDIX 2: Adverse Event Process Flowchart



APPENDIX 3: ABON Causality Algorithm

Detailed guidance is provided in the following sections regarding causality assessment of adverse safety, inefficacy and residue violation events.

SECTION A: QUESTIONNAIRE – SAFETY

The determination of causality requires six main factors to be taken into account: associative connection, pharmacological and/or immunological explanation, clinical or pathological phenomena, previous knowledge, other causes and reliability of data. The following questionnaire compiles guiding questions for each aspect, which are meant as examples and not intended to be exhaustive. They facilitate finding the answer to the main and conclusive question, which is listed at the end of each section. Within the first four factors "yes"-answers to the conclusive questions point towards A and B coding, whereas for the last two factors "yes" answers point away from A.

1. Associative connection

a) in time (including de-challenge and re-challenge)

b) with anatomical site

1.1. Is the observed event associated with the administration of the VMP? Is the chronology in good accordance with treatment? Is there a reasonable association in time between the administration of the product and the onset and duration of the adverse event?

- Is there a reasonable association in time between the administration of the product and the onset of the adverse event?

Yes	No	Not known
Reasonable association	No reasonable association	Unknown
A, B	**N**	**O1 or O**

1.2. Has there been any improvement after stopping treatment or giving an antidote (de-challenge)?

- What happened after de-challenge - recurrence, no recurrence or no re-challenge done?

Yes	No	Not known
Improvement	No improvement	No de-challenge performed
A, B	**O, N**	**A, B, O1, O, N**

1.3. Did the adverse event reappear after re-challenge (same or related animal)? Is a similar event known in that patient from previous exposure?

- What happened after re-challenge - recurrence, no recurrence or no re-challenge done?

Yes	No	Not known
Recurrence	No recurrence	No re-challenge performed
A, B	**N**	**A, B, O1, O, N**

1.4. Could the location/distribution of signs be caused by the treatment?

Yes	No	Not applicable
Associative anatomical connection	No anatomical connection	
A, B	**N**	**A, B, O1, O, N**

Main question for section 1

- Is there a reasonable association in time and/or anatomical site?

Yes	No	Not known
Reasonable association	No reasonable association	Unknown
A, B	**N**	**O1 or O**

2. Pharmacological and/or immunological explanation

a) known pharmacology, toxicology of the product (active substance and/or excipients)

b) VMP concentrations in blood

c) dose-effect relationship (degree of contribution of a product to the development of a reaction).

2.1. Does the reported event fit into the toxicological profile or allergic potential of the product? Does the pharmacological/toxicological knowledge of the product fit the signs? Is the adverse event, the description of the clinical phenomena, consistent with or at least plausible, given the known pharmacology and toxicology of the product?

Do similar compounds cause events of this type?

- Does the reported event fit into the pharmacological/toxicological profile or allergic potential of the product?

Yes	No
A, B	**O1, O, N**

2.2. Has the product been overdosed? Did the product concentration in blood exceed the therapeutic concentration? Are concentrations in plasma known? What dose was used - overdose, correct dose, low dose, unknown dose? Did the adverse event show a dose-effect relationship?

- Did the adverse event show a dose-effect relationship (e.g. overdose)?

Yes	No	Not known
A, B	**A, B, O1, O, N**	**A, B, O1, O, N**

Main question for section 2

- Is there a reasonable association with the known pharmacological/toxicological profile, the allergic potential of the product and/or a dose-effect relation?

Yes	No
A, B	**O1, O, N**

3. Presence of characteristic product or treatment related clinical or pathological phenomena

Are characteristic clinical or pathological phenomena present, which are related to the product or treatment?

Are there any measurable criteria to confirm the adverse event objectively, are confirming factors known (postmortem results, laboratory results)?

- Are additional data (laboratory tests, pathological findings) confirming clinical plausibility?

Yes	No	Not applicable/not available
A, B	**N**	**A, B, O1, O, N**

4. Previous knowledge of similar reports

a. from literature

b. from adverse events reported before

Are there any reports of this event known from literature? Is the event known and expected (described in SPC)? Have there been previous reports with these kinds of signs? Was this type of event reported before in an adverse event? Is the adverse event (generally) known to be potentially related to the product or treatment mentioned? *('adverse event' in this respect is the single pathological sign or the [majority of the signs in the] complex. 'Known' means published in literature or reported before and classified as A (probable) or B (possible)).*

- What about consistency of the reported event - is it already described in literature or SPC, has it been reported before?

Yes	Yes	No	No
Described in literature or SPC, described in case record	Observed before, but not fitting pharm/tox profile	Never observed before, but fitting pharm/tox profile	Never observed before, not fitting pharm/tox profile

A, B	**B, O1, O, N**	**B, O1, O, N**	**O1, O, N**

5. Exclusion of other causes

Are there possible other causes for the adverse event? Is there another (also) likely cause? Is there another obviously more likely cause? Is this adverse event, to my best knowledge, unrelated to treatment? Use of combination of products/other products used?

Is the present disease contributing to signs? Is the health status of the animal contributing to signs? Are predisposing factors known? Are there other confirmed causes known (post mortem results, laboratory results, re-/de-challenge, other products used with pharmacological-toxicological potential to cause event)?

- Is there any other explanation (confirmed, possible, no other explanation)?

Yes	Yes	No
Confirmed	Possible	None
N	**B, O1, O**	**A**

6. Completeness and reliability of the data in the case reports

- Is the reported information insufficient? Is there reason to doubt the reporting source/ information?

Yes	No
O1, O	**A, B, N**

SECTION B: CAUSALITY ASSESSMENT - SAFETY

1. For inclusion in category A (probable)

Associative connection in time (**4.1 = yes**) and

Adverse event fits the pharmacological/toxicological profile of the product (**4.2 = yes**) and

No other equally plausible explanation (**4.5 = no**) and

No indication of insufficient/unreliable information (**4.6 = no**).

2. For inclusion in category B (possible)

Associative connection in time (**4.1 = yes**) and

Adverse event fits the pharmacological/toxicological profile of the product (**4.2 = yes**) and

Other equally plausible explanation possible (**4.5 = yes**) and

No indication of insufficient/unreliable information (**4.6 = no**).

or

There have been reports of the adverse event before (**4.4 = yes**) and

No indication of insufficient/unreliable information (**4.6 = no**) and

Associative connection in time (**4.1 = yes**) or adverse event fits the pharmacological/toxicological profile of the product (**4.2 = yes**).

3. For inclusion in category O1 (inconclusive)

Category O1 is for events where at least one of the answers from the questionnaire point to a causal relationship to the product or the treatment (A or B) but overall information is not sufficient to draw a conclusion. As some of these O1 classified events will recur and due to sufficient information in subsequent reports turn out to belong to B or even A category, they present an interesting issue for surveillance. For pharmacovigilance surveillance purposes O1 classified events can be seen as kind of interesting “precursors”.

Associative connection in time (**4.1 = yes**) and/or

Adverse event fits into the pharmacological/toxicological profile of the product (**4.2 = yes**) and/or

No other equally plausible explanation (**4.5 = no**) and

Inconclusive, unreliable or insufficient information (**4.6 = yes**).

4. For inclusion in category O (unclassifiable/unassessable)

Inconclusive, unreliable or insufficient information (**4.6 = yes**) which cannot be used to answer questions 4.1 to 4.5.

5. For inclusion in category N (unlikely)

Sufficient information exists to confirm that the product or treatment did not cause the adverse event (**4.5 = yes**) and

No indication of insufficient/unreliable information (**4.6 = no**).

SECTION C: QUESTIONNAIRE – INEFFICACY

Assessment is intended to confirm whether inefficacy is apparent. The following approach compiles guiding questions for each aspect, which are meant as examples and not intended to be exhaustive. The overall interpretation of the answers point towards A (probable), B (possible), O1 or O (inconclusive or unclassifiable/unassessable) or N (unlikely).

1. Was the VMP used in accordance with the label?

- Were the therapeutic indications respected?
- Were the characteristics of the animals to which the VMP has been administered in compliance with the label recommendations (species, age etc.)?
- Was the dose administered correct or at least the minimum dose (in compliance with the label recommendations)?
- Were the treatment length and the therapeutic regimen correct or in compliance with the label recommendation?

Yes	No	Not known
Efficacy expected	Efficacy not expected	Unknown
A	**N, O1**	**O**

- Was the administration route used in compliance with the label recommendation?

Yes	No	Not known
Efficacy expected	Efficacy may be compromised	Unknown
A	**B, O1, N**	**O1, O**

- Is there a clear medicinal contra-indication related to efficacy for the products administered concurrently?

Yes	No	Not known
Efficacy not expected	Efficacy expected	Not known if contra-indicated
N	**A**	**B, O1, O**

2. Did the onset of the clinical signs occur after the treatment period necessary to establish efficacy and during the period of the efficacy of the product? [onset and evolution of the clinical signs and/or presence of the pathogens in absence of specific clinical signs (presence of parasites etc.)]?

- Was the LEE identified during the efficacy period of the product?

Yes	No	Not known
Efficacy expected	Efficacy not expected or may not yet have been achieved	Lack of information
A	**N, O1**	**O**

3. Did the clinical signs fit the condition for which the product is indicated?

- Is there a reasonable consistency between clinical signs of the adverse event recorded and those of the indications mentioned in the label? Are the clinical signs recorded specific to or in line with the condition treated?

Yes	No	Partial	Not known

Signs would not be present if product was efficacious	Signs indicate disease is due to a different cause	Some of the signs could be caused by inefficacy	Lack of information
A	**N**	**B, O1, O**	**O**

4. Are there any measurable criteria to explain the event objectively?

- Is confirmatory objective data available? (e.g. post-mortem results or laboratory results to confirm the diagnosis made before or after treatment of the animals or observations)?

Yes	No or Unknown
A	**A, B, O1, O, N**

5. Is there any information available concerning the environment that could explain the pathology (illness) despite animals having received treatment (if applicable)?

- Was the animal health status good?
- For vaccines, was the challenge pressure high?
- Is there any information related to concomitant pathology and the medical history of the breeding/ farming and/or of the animal?
- Were zoo-technical and environmental measures taken? Were the hygiene conditions satisfactory? Were the farm management practices acceptable?

Yes	No	Not known
Expected efficacy may be reduced	Efficacy expected	Lack of information
B, N, O1, O	**A, B**	**B, O1, O**

6. For topically applied ectoparasiticides, is there any information available concerning the environment that could explain the pathology (illness) despite animals having received treatment (if applicable)?

- Was the animal health status good?
- Was the infestation pressure high?
- Does information suggest that the length of protection may have been adversely affected?

Yes	No	Not known
Expected efficacy may be reduced	Efficacy expected	Lack of information
B, N, O1, O	**A, B**	**B, O1, O**

- Has there been a sudden loss of efficacy after a period of good parasite control?

Yes*	No, N/A or not known
A, B	**B, O1, O**

* If yes, and all other responses include A or B, an inconclusive ruling is not appropriate as true product inefficacy is one of the equally plausible causes

7. For anthelmintics with claims limited to sensitive strains, was resistance confirmed as the cause of ongoing parasitism?

Yes	No	Not known
Efficacy not expected	Efficacy expected	Lack of information
N	**A, B**	**B, O1, O**

8. Is there any indication to confirm that the event is due to another cause that could explain the clinical signs recorded?

Yes	Maybe	No	Not known
Another cause more likely	Other equally plausible causes are identified in the narrative	No plausible cause exclusive of inefficacy	Lack of information
N, O1, O	**B**	**A, B**	**B, O1, O**

9. Is a quality problem suspected?

Yes	Maybe	No	Not known
Quality defect identified (e.g. expired batch, batch failure)	Quality defect suspected (e.g. storage conditions not respected)	Quality defect excluded or no reason to suspect failure exists	Lack of information (e.g. batch number not known)
N	**O1, O**	**A, B**	**B, O1, O**

10. Previous knowledge of similar reports concerning the inefficacy

- Are there similar reports for the product or other scientific data supporting the potential for inefficacy under the use circumstances?

Yes	No or Unknown
A, B	**B, O1, O, N**

11. Is the reported information insufficient? Is there reason to doubt the reporting source/ information?

Yes	No
O	**A, B, N, O1**

SECTION D: CAUSALITY ASSESSMENT - INEFFICACY

1. For inclusion in category A (probable)

All answers to the questionnaire are “A” selections (stand-alone or one of the options)

2. For inclusion in category B (possible)

All answers to the questionnaire are a mixture of “A” or “B” selections (stand-alone or one of the options).

3. For inclusion in category O1 (inconclusive)

Category O1 is for events where at least one of the answers from the questionnaire point to a causal relationship to the product or the treatment (A or B) but overall information is not sufficient to draw a conclusion. As some of these O1 classified events will recur and due to sufficient information in subsequent reports turn out to belong to B or even A category, they present an interesting issue for surveillance. For pharmacovigilance surveillance purposes O1 classified events can be seen as kind of interesting “precursors”.

4. For inclusion in category O (unclassifiable/unassessable)

One or more of the answers to the questionnaire generates a stand-alone “O” selection.

5. For inclusion in category N (unlikely)

One or more of the answers to the questionnaire generates a stand-alone “N” selection.

SECTION E - RESIDUES

For residues, the causality assessment refers to the presence of unacceptable levels of residue in harvested produce despite compliance with the approved label (including directions for use and withholding period). Investigation of the event must seek to confirm whether the product has been used on-label and if so whether there were any extenuating circumstances that may have contributed to

unacceptable residue levels. Where unacceptable milk residue levels are suspected based on inhibitory substance grades, the quantity of residue is expected to be confirmed where possible.

Causality assessment is as follows:

A – Probable: The product was used on-label and residues exceeding the applicable maximum residue level have occurred in produce harvested from the treated animal. There are no contributing factors.

B – Possible: The product was used on-label and residues exceeding the applicable maximum residue level have occurred in produce harvested from the treated animal, but there are contributing factors (e.g. very small number of contributing cows).

O1 – Inconclusive: Residues exceeding the applicable maximum residue level have occurred in produce harvested from the treated animal, but the product was used off-label, or the available data suggests there may be an alternative explanation (e.g. biologically impossible but verified milk residue levels).

O – Unassessable: There is insufficient (e.g. only IS grading for milk residue) or unreliable data.