Introduction

All drugs carry the risk of adverse drug events (ADEs) so suspected ADEs are an inevitable part of veterinary practice.

This review is written with practicing NZ veterinarians in mind. The purpose is to define adverse drug events, describe the investigation of them and provide practitioners some tips from an industry technical veterinarian. In doing so I intend to make the process clearer and more efficient for veterinarians confronted with a suspected ADE. This is not a complete resource on adverse drug events. I have drawn largely on the ACVM’s documentation, Zoetis’ policy and my own experience in investigating suspected ADEs.

For more detail, I recommend readers check the ACVM materials cited in the references, which are available on the ACVM website.

What is an adverse drug event?

The Agricultural Compounds and Veterinary Medicines Group (ACVMG) of MPI is the national regulatory body that administers veterinary medicines and therefore ADEs. The MPI definition of an ADE is “...any observation in animals that is unfavourable and unintended, and that occurs after the use of a veterinary medicine”. All unfavourable/unintended events that are recognised outcomes of product use and that may or may not be identified on the product label are classified as adverse events. This definition applies equally to registered veterinary medicines and products that do not require registration in order to be sold, such as animal feeds and shampoos.

Note that the observation must occur after the use of the drug, i.e. the event in question must be temporally associated with use of the drug in question. Simultaneously, temporality alone is not proof of causation. Coincidence is a common source of suspected ADE reports.

Veterinarians should be aware that the definition also applies to veterinary discretionary off-label use; illegal off-label use (contrary to label directions without veterinary advice); and use of human drugs in animals.

The three primary stakeholders involved in a suspected ADE are the reporter, the regulator and the registrant. The reporter is anybody who reports a suspected ADE to MPI or the registrant. This may be an animal owner/manager, a veterinarian or the registrant. The registrant is the company that markets the veterinary medicine concerned.

I use the term “suspected adverse drug event” frequently in this review. That is because many ADE investigations end with causality assessments of “inconclusive” or “unlikely”. Therefore, from a practitioner’s point of view, ADEs should be regarded as “suspected” until the causality assessment is made.

---

Serious adverse drug events

These are a subset of ADEs and are any adverse event that is life-threatening or fatal or results in persistent or significant disability/congenital anomaly. They also include adverse events that interfere with disease diagnosis or control and some specific adverse events in humans (such as the transfer of human pathogens [salmonella in animal feed] or development of antibiotic resistance)\(^2\).

The table below is a guide for determining if an ADE is serious or not\(^2\).

<table>
<thead>
<tr>
<th>Companion animals</th>
<th>Horses</th>
<th>Cattle, sheep, pigs</th>
<th>Poultry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death and/or Hospitalisation and/or Welfare implications (moderate to severe pain or distress)</td>
<td>Death and/or Hospitalisation or More than one veterinary visit and/or Welfare implications (moderate to severe pain or distress)</td>
<td>Deaths and/or More than one veterinary visit and/or &gt;10% morbidity and/or Welfare implications (moderate to severe pain or distress)</td>
<td>&gt;5% increase in base mortality and/or &gt;10% morbidity and/or Welfare implications (moderate to severe pain or distress)</td>
</tr>
</tbody>
</table>

Why report adverse drug events?

To achieve registration in NZ, all veterinary medicines (except those exempt from registration) must undergo target animal safety testing. Safety studies cannot examine every possible environment and signalment and cannot test every possible combination of concurrent drug use. Low incidence conditions may not be picked up in safety studies. Registrants therefore rely on veterinarians and animal owners to inform them of any concerns picked up in the field.

If ADEs are left unreported it could take longer for emerging patterns to be noticed, which could pose risks to animal welfare, trade in primary products, agricultural security, public health, domestic food residue standards and consumer information.

Some ADEs are expected outcomes and are managed by registration or label information. However, reporting is still useful and expected, especially in recently registered products or where the ADEs are observed at an increased frequency or severity and/or are not consistent with the expected outcome described on the label.

Types of adverse drug events

Side effects and safety concerns are the first types of ADE that leap into veterinarians’ minds. Additional types are lack of efficacy, residue concerns, drug interactions and accidental human administration.

What to expect - the suspected adverse event process

A suspected ADE consists of reporting, investigation, causality assessment and outcomes (if any).

---

Reporting

Anybody can report a suspected ADE. To be accepted and actionable, reports must identify four key pieces of information (see below). The reporter may report a suspected ADE directly to MPI or to the registrant. MPI automatically notifies the registrant if they receive a report.

Reporting is voluntary for the public but compulsory for registrants. The “veterinary medicines” section of the Code of Professional Conduct for Veterinarians says:

- “When using or selling any unrestricted veterinary medicine or dispensing a restricted veterinary medicine, veterinarians must:
  - Ensure effective product management (storage, reporting adverse reactions, maintaining the integrity of product, labelling, security, safety of handling)...”

Registrants must report all suspected ADEs they receive to MPI within 20 days of completing their investigation. If the suspected ADE is serious and may require the use of the product to be stopped or restricted to prevent similar adverse events, registrants must notify MPI immediately upon becoming aware of it.

If you suspect an ADE, four minimum pieces of information are needed for an actionable report:

- Reporter’s details.
- Animal(s) affected – identification and signalment.
- Product(s) – including concurrently used products.
- A description of the event.

Investigation

The registrant and the attending/prescribing veterinarian are both responsible for investigating the suspected ADE. The registrant is responsible for reporting to ACVM within the specified time limits. Registrants may contact the animal owner and veterinarian for more information and may request further work such as veterinary examination or diagnostic pathology.

Causality assessment

The registrant is responsible for making a causality assessment, which is in turn assessed by the ACVM. The ACVM either agrees with the assessment or disagrees and imposes its own causality assessment or requests further investigation (such as engagement of an independent expert). The investigation is given one of the following causality assessments:

<table>
<thead>
<tr>
<th>Causality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable</td>
<td>There is a reasonable association between the administration of the product and the onset and duration of the reported adverse event; clinical signs should be consistent with or at least plausible given the known pharmacology and toxicology of the product; there should be no other equally plausible explanation (or contributing factors) for the clinical signs.</td>
</tr>
<tr>
<td>Probable/off-label</td>
<td>As above but the drug was used off-label (includes illegal use) such as incorrect dose rate.</td>
</tr>
<tr>
<td>Possible</td>
<td>The drug is a possible cause but there are other equally plausible causes.</td>
</tr>
<tr>
<td>Possible/off-label</td>
<td>As above but off-label (includes illegal use).</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Sufficient information exists to rule out causation.</td>
</tr>
<tr>
<td>Unknown</td>
<td>Not enough reliable information can be gathered to make an assessment.</td>
</tr>
</tbody>
</table>

The ACVM reports the causality assessment to the reporter and the registrant as well as any further comments.
Outcomes
Following the causality assessment of a suspected ADE the ACVM may require the registrant to take action. Some examples include:
- No action required.
- Education of product users (via media, clinic training etc.).
- Additional label warning statement.
- Formulation or manufacturing process change.
- Product recall.

Monitoring
Registrants perform ongoing internal pharmacovigilance for ADEs. For international companies this is performed at the local and global level. Reporting must comply with the numerous regulators such as the FDA. Registrants and ACVM both monitor for trends over time.

Advice for practitioners
As a field veterinarian for Zoetis NZ, investigating suspected livestock ADEs is one of my responsibilities. I would like to offer some advice and common findings to make things easier for practitioners.

1. Is it an adverse drug event?
Before reporting, I recommend veterinarians perform a basic investigation to rule out the obvious confounders. Remember that we are looking for causation, not association. Many of my investigations end with an “unlikely” causality assessment when we discover that the drug use was coincidental or the drug in question was not used at all. For example, compare these two cases:
- A calf was injected with an antibiotic for pneumonia and it developed an injection site lesion within 24 hours.
- A calf was vaccinated with a clostridial vaccine and was found dead 48 hours later.

Case 1 is likely to be an ADE but Case 2 is unlikely to be an ADE. It is very unlikely that a clostridial vaccine would result in the death of a calf and this calf’s death was not temporally consistent with anaphylaxis. Post mortem examination reveals that the calf died of pneumonia. In Case 1, I would expect the veterinarian to contact the registrant but for Case 2, I would expect the veterinarian to perform a post mortem to rule out the more common causes before contacting the registrant.

2. Be prepared with the information
The four minimum pieces of information (reporter, animal(s), drug(s) and description) are needed before reporting. If you report a suspected ADE, you will be asked to provide these. In the case of livestock where multiple animals could be involved, you need to identify all animals (e.g. ear tag numbers) and describe them (breed, age/parity, gender). You will also need to know when the animal(s) was/were given the drug in question, what else they got at the same time, who treated them, the dose rate and the batch number(s). The more information you provide, the more useful the report is as a reference. The main tip I would give is to obtain this information from the owner in the first instance instead of going back later, especially if the event has already turned out to be unrelated to drug use and the owner is no longer motivated to investigate it. The registrant must still report it regardless of how unlikely it is an ADE.

3. Adverse drug event investigations are mostly positive experiences
In my experience and that of others in industry, most ADE investigations are positive because the veterinarian and the registrant both show great product stewardship and customer care and it is an educational experience for all involved. These investigations often flag up areas where mistakes or misunderstandings arise.
4. Keep tabs on your customers
Many suspected ADE investigations are retrospective, sometimes by more than 12 months. This usually means that the investigation is rudimentary and the causality assessment is “unknown”. I suggest that practitioners keep in touch with their customers, especially where practitioners have prescribed a new veterinary medicine or there has been a change to the way it is used on farm.

The importance of good note keeping and record retention always becomes clear during a suspected ADE investigation when the registrant asks for the key information and the case history.

For example, a veterinarian changes a dairy farm’s dry cow therapy regime and reviews it at the milk quality review 12 months later. The farmer reports that the new dry cow therapy regime did not reduce his farm’s mastitis incidence for the season. The veterinarian contacts the registrant with a lack-of-efficacy suspected ADE. At this stage there is usually no chance to perform milk cultures and we cannot objectively assess the risk factors for peri-calving clinical mastitis.

5. Expectations and biological variation
When prescribing or administering a veterinary medicine, check that your and the animal owner’s expectations are realistic. It is unreasonable to think that any product carries no risk of causing a suspected ADE at some point. Farmers and animal owners do need to be made aware of the more common/severe side effects or at very least of the potential for such side effects to occur.

Many lack-of-efficacy investigations are based on the owner being disappointed with a result that is actually normal or a result that is worse than last year’s but still normal. Veterinarians well understand that there is significant variation between farms within a season and between seasons within a farm.

Remember that no veterinary medicine is 100% effective and safe in every animal. Furthermore, expectations are often based on median or average results from multi-site clinical trials, but there is a range or results either side of the median or mean.

6. Talk to an industry technical veterinarian
We are interested in learning of any new developments or questions related to our products. On the other hand, there is a good chance that the event you are looking at has been dealt with before. Industry technical veterinarians can offer advice and assist where necessary.

7. Be available
As the prescribing veterinarian, you have a duty of care. The “veterinary medicines” section of the Code of Professional Conduct for Veterinarians says:

- “When using or recommending any unrestricted veterinary medicine or authorising any restricted veterinary medicine, veterinarians must
- Make provision for veterinary intervention in the case of adverse effects”.

The attending/prescribing veterinarian has primary duty of care and is expected to assist with investigatory work beyond reporting the event.

Summary
Veterinarians are encouraged to report suspected adverse drug events. To do so you need the four basic pieces of information. Getting this information as early as possible will speed the process up. Keeping tabs on your customers using new veterinary medicines will make it easier to investigate a suspected ADE later on. Most suspected ADE investigations are positive experiences.
Reference