



## **Focus Article: Pharmacovigilance – Beyond the Yellow Form**

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Most vets will be familiar with the yellow forms found at the back of the NOAH Compendium for reporting adverse events to the Veterinary Medicines Directorate (VMD). These forms are the most visible part of the VMD's Suspected Adverse Reaction Surveillance Scheme (SARSS), and even get a mention in the RCVS Code of Professional Conduct, which states that 'all suspected adverse reactions should be reported using the yellow form' (Royal College of Veterinary Surgeons, 2012). Filling in one of these forms can feel like just another piece of paperwork to add to the "to do" pile, but this underestimates the vital role that pharmacovigilance plays in ensuring the safety and efficacy of medicinal products. In this article I hope to look beyond the yellow form to give an insight into what pharmacovigilance is, and the benefits it brings to vets, animals and owners.

#### **What is Pharmacovigilance?**

During the licensing process, drugs are assessed to ensure their safety, efficacy and quality. There are, however, limitations to the trials performed when licensing a new product, including a relatively small sample size which may not be completely representative of the population as a whole, and the relatively short duration of such trials. As a result, despite the rigours of the licensing process, the safety and efficacy profile of a drug may well evolve over time with use. Pharmacovigilance allows the real world use of a product to effectively become a large scale field trial. By recording and analysing adverse events, we are able to identify possible rare adverse events that may not be seen in smaller clinical trials, monitor known reactions (including lack of efficacy), and identify potential risk factors which may promote them. If, after further investigation, these possible associations are confirmed, then the appropriate actions can be taken to mitigate risks, thus maintaining the efficacy and safety of the product.

A great definition of pharmacovigilance can be found below. This neatly sums up the collaborative nature of the process, its relevance to the real world, and the wide reaching benefits that can be achieved.

'Pharmacovigilance is the combined efforts of authorities, industry, the veterinary profession and end-users to evaluate the safety and efficacy of veterinary medicines in practical use situations and to incorporate these findings in product availability and documentation in order to optimise animal health, welfare and public health.' (O'Rourke, 2009)

#### **What counts as an adverse event?**

As can be seen from the definition above, everyone involved with the production and use of veterinary medicines, including owners, has a role to play in reporting suspected adverse events. But what counts as an adverse event?

The VMD defines an adverse event as – 'any observation in an animal, whether or not considered to be product related, that is unfavourable and unintended and that occurs after any use of a veterinary medicine' (Veterinary Medicines Directorate, 2011).

Adverse events associated with veterinary medicines include reactions in animals which occur after use in accordance with the datasheet (on-label use) or following off-label use, suspected lack of efficacy after use in accordance with the label, and reactions in humans following exposure to a veterinary medicine or a treated animal.



This is an intentionally broad definition, and captures quite a lot of outcomes in veterinary practice which vets may not consider to be an adverse event, or feel are not worth reporting. For example, a suspected lack of efficacy, such as signs of equine influenza in a horse that is up to date with its vaccines, would count as an adverse event and so should be reported. If suspected lack of efficacy cases are not reported, then how can the product's efficacy be monitored? If adverse events are not reported, then how can we assess whether their incidence is increasing, or linked to other factors? If in doubt, then the case should be reported.

### **Who should adverse events be reported to?**

There are two ways that adverse events can be reported in the UK. The first is to report the adverse event directly to the VMD. This can be achieved either through the yellow forms, or directly via the VMD website - <https://www.vmd.defra.gov.uk/adversereactionreporting/>

The second route is to contact the manufacturer<sup>1</sup> of the product directly. Manufacturers have a legal obligation to record any information that they receive about adverse events involving their products and, where appropriate, carry out an investigation. Serious adverse events and human reactions must be sent to the VMD within 15 calendar days of receipt of the case, while non-serious adverse events are reported as part of a document called a Periodic Safety Update Report (PSUR), which are submitted to the Regulatory Authority (either the VMD or the European Medicines Agency (EMA)), on a regular basis, depending on how long the product has been licensed.

It should be noted that a serious adverse event does not just entail death; there are non-fatal serious adverse events. Non-fatal serious adverse events may be life-threatening, may result in significant disability or incapacity, may produce permanent or prolonged signs in the treated animal, or could be a congenital abnormality or birth defect. Examples of such adverse events include anaphylaxis, blindness, immediate collapse lasting longer than 10 minutes, and convulsions or neurological signs occurring within a few hours of administration of a product. Further information can be found within Veterinary Medicines Guidance Note 11 (Veterinary Medicines Directorate, 2011).

### **Isn't it easier to report cases directly to the regulatory agency?**

While reporting a case to the VMD ensures that the case is entered directly into their database, the VMD does not carry out any follow up investigation of the case. The VMD will inform manufacturers of adverse events that have been reported directly to them, but this process takes time and in some cases the reporter's contact details are not passed to the manufacturer. Investigation of a case in a timely manner is often of great importance to determining whether the product was associated with the adverse event or not, known as 'causality'. Without the ability to assess causality accurately, the value of that case for shaping the safety and efficacy profile of the product is vastly reduced. For this reason, reporting the case directly to the manufacturer, who has an obligation to investigate the case where appropriate, and the staff to support this, has major benefits.

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<sup>1</sup>Technically, it is the Marketing Authorisation Holder (MAH) who is responsible for recording and reporting suspected adverse events relating to their products to the Regulatory authorities. In many, but not all, cases the MAH is also the manufacturer. For ease of understanding, the term 'manufacturer' is used synonymously for MAN in this document.



A situation where timely investigation is important could be a suspected case of equine influenza (EI) in a horse with up to date 'flu vaccinations. Ideally, samples to confirm whether the horse is suffering from EI should be taken within the first few days of signs been seen. If these are delayed, and a diagnosis is not achieved, then it cannot be determined whether that case represents a lack of efficacy for that vaccine in that horse. As a result an inconclusive causality is likely to be assigned, which limits the value of the case in contributing to the overall picture of the product's efficacy. Of course, in such situations these samples may well have been sent to an OIE reference laboratory and so would also have contributed to the broader surveillance of EI.

While ensuring an accurate assessment of causality is of benefit to developing the safety and efficacy profile of the product, it doesn't necessarily address the fact that an adverse event is not just a record on a system, but has an animal, owner and vet attached. Although adverse events are generally uncommon, manufacturers should be the first port of call for information on adverse events. Manufacturers are well placed to understand whether clinical signs are likely to be associated with product administration, and how to manage such signs. They should be willing to provide technical assistance and support to vets, and owners, at what can be a difficult time.

Finally, for those who are concerned that apparent corporate self interest will prevail, and that reporting adverse events to the manufacturer would be akin to filing them in the bin, it is worth noting that a manufacturer's pharmacovigilance premises, records and documents may be inspected by the VMD at any time. Unannounced inspections can and do take place, and lack of compliance with reporting requirements is an offence. Of course, if you are in any way concerned that a case has not been dealt with adequately, then you may report that case directly to the VMD.

### **What happens once an adverse event has been reported?**

On receipt of a case, the details are entered into a database. This includes the details of the animal, the product involved, concurrently administered products, and a narrative of the adverse event itself. The presenting signs of the adverse event are also coded according to a standard dictionary of terminology; this allows for the signs associated with the adverse event to be analysed. Finally, on the basis of the reported information, each case will have a causality assigned to it. There are five categories - A – probable, B – possible, O1 – inconclusive, O – unclassifiable/unassessable, and N – unlikely.

Cases being input into the pharmacovigilance database are continually monitored by the manufacturer, with serious cases and those involving humans being notified to the VMD within 15 calendar days. Any concerns raised can be investigated by reviewing the data contained with the pharmacovigilance database, as well as reviewing literature and carrying out other investigations.

In addition, manufacturers regularly submit Periodic Safety Update Reports (PSURs) to the Regulatory Authorities according to a set timetable for each product. These review all the adverse events received by both the manufacturer and the Regulatory Authorities worldwide over the preceding period, looking for any trends which could indicate a relationship between a product and an adverse event. They also review the number and type of adverse events compared to the amount of product sold, allowing the overall risk-benefit of the product to be monitored on an ongoing basis.



Should a potential link be found between a product and an adverse effect then further investigations can be carried out to define the nature of any potential link. If required, then further action may be taken, ranging from alterations to the product's datasheet, through to withdrawal of the product from sale.

### **Conclusion**

Pharmacovigilance plays a key role in ensuring that the medicines on which vets, animals and owners rely on a daily basis remain safe and effective. Regulatory Authorities, manufacturers, vets and owners all have important roles in ensuring this process works effectively for everyone's benefit.