The essentials of veterinary pharmacovigilance

A guide to the essential elements of a basic pharmacovigilance system for monitoring the safety of veterinary medicines in the marketplace

The Essentials for Veterinary Pharmacovigilance

Surveillance System for Animal Health Products

Purpose of this document

This document explains the essential elements of a basic pharmacovigilance system for monitoring the safety of veterinary medicinal products in the marketplace. It also describes the importance of alignment with international standards to ensure that data can be shared, exchanged and pooled to enhance the power of the system and to make efficient use of resources.

Summary

- **What is Pharmacovigilance?**
  Pharmacovigilance is a process by which information is collected to detect and prevent unexpected or unwanted adverse effects following the use of medicinal products. The scope of veterinary pharmacovigilance is mainly the safety and efficacy in animals and safety in people.

- **Why is Pharmacovigilance important?**
  It is important to continually monitor the safety of a medicinal product after it moves from development into the wider population. The information collected allows the on-going assessment of the benefit-risk of the veterinary medicinal product in relation to its target population and throughout its life-cycle. The existence of a reliable pharmacovigilance system supports the benefit-risk assessment approach to licensing, and avoids the drawbacks of a zero-risk approach.

- **Why are international harmonization and standard reporting formats important?**
  - A primary benefit of working to internationally harmonized standards is to align local reporting systems with global pharmacovigilance reporting, which will allow the pooling of data and result in more accurate detection of adverse events.
  - Global alignment is particularly important because the same veterinary medicinal product may be supplied to many countries; therefore it is essential to be able to pool and share safety surveillance data on these products, both within the company marketing the product, but also between the countries where it is marketed.
  - Aligning with an internationally harmonized system is more cost effective and allows for quick implementation rather than developing a unique stand-alone national system. It makes it easier and faster for authorities to co-operate and even share the work load if they wish.
  - Having one set of international standards improves compliance by removing administrative hurdles. It avoids tasks being duplicated and the need for data to be reformatted.
  - It is important to make efficient use of resources within the competent authorities and the industry. This allows limited resources to be focused on activities that contribute to product safety and efficacy, rather than on administrative tasks.
  - International harmonization promotes global trade and the wider availability of medicines.

INTRODUCTION

An adverse event (AE) is any observation in animals, whether or not considered to be product-related, that is unfavorable and unintended and that occurs after any use of VMP (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy according to approved labeling or noxious reactions in humans after being exposed to VMP(s).

The aim of a pharmacovigilance system is to identify any changes in the benefits (including efficacy) and risks arising from the use of a medicinal product. This system can be simple or more sophisticated, depending on local needs and resources.

Independent of the system's complexity, it should function to identify important risks, ensure collection of key information (such as adverse event reports – see box) to allow for adequate assessment and be integrated to facilitate timely communication of any important new information. It should also keep the basic elements (such as key definitions and formats) aligned with international standards, but should be adapted to address the different local challenges that exist in identifying and communicating safety risks depending on the availability, scale or maturity of a medicinal product surveillance (pharmacovigilance) system.

During the product development phase, the size and scope of product evaluation under field conditions are limited. Brief product exposure durations and exclusion of sub-groups such as pregnant, old/young, those with co-morbid conditions or those receiving concomitant products create the product's initial profile, but do not indicate how the product will perform under field conditions in the wider population. Therefore it is imperative to put in place systems and procedures to collect and analyse reports from the field, to confirm or further improve knowledge about the product' safety profile in the market place.

In the rare situation of a major issue, active crisis management with appropriate, transparent communication is required to ensure that the veterinary community is informed and if appropriate, changes are made to the authorized conditions of use for the product.

Pharmacovigilance is a shared responsibility. The responsibility to monitor the ongoing safety and efficacy of veterinary medicines primarily lies with the marketing authorisation holder (MAH). However, Regulatory Authorities also have an important role to play in establishing and running a national system, and assessing pooled data. Unlike MAHs, Regulatory Authorities have the possibility to make comparisons between similar products from different manufacturers and if necessary, to decide if further regulatory measures should be implemented.

A COMMON INTERNATIONAL STANDARD FOR VETERINARY PHARMACOVIGILANCE

Multinational companies, and to a lesser extent national companies, generally supply specific products to more than one country (often 30+ countries), and therefore it is necessary to have in place systems that allow them to collect and analyse adverse event information from all countries on a particular product. Equally companies have the responsibility to fulfil any specified reporting requirements to Regulatory Authorities in each country.

In order to optimize the use of resources in both companies and Authorities, allowing appropriate focus to the areas that help to maintain the safety of products, it is essential that administrative work is minimized and duplication removed. In order to achieve this, it is important to have globally harmonized pharmacovigilance requirements - including harmonized approaches to case definition, collection, assessment and reporting - to reduce the need for duplication in systems and resources, maximize synergies, allow data to be pooled to enhance signal detection, and increase sustainability.

A common approach to data collection starts with a common set of definitions. For example on what is a veterinary medicinal product and what is an adverse reaction. An important reference for this is VICH GL 24[1].

A veterinary medicinal product (VMP) can be defined as a product with claim(s) to having a protective, therapeutic or diagnostic effect or to alter physiological functions when administered to or applied to an animal (VICH GL 24). The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function. In order to have a common scope, cooperation is critical among Authorities to ensure there are common global standards for all VMPs (e.g. pharmaceutical and vaccines), independent of how they are classified regionally.

Following exposure to a VMP, an unfavourable or unintended event might be observed. This may occur in an animal or human and is referred to as an **"adverse event"** (VICH GL 24). It is important to note that whether or not it is initially considered to be product-related, if it is regarded as unfavourable and unintended, it should be reported as an adverse event. Collection of this information is important to identify at-risk sub-populations, drug-drug interactions, prescription errors, or product related problems. A lack of expected efficacy following proper use and based on the labelling indications is also a type of adverse event.

Consistency and standardization in data collection increase the value and utility of this data and thereby contribute to a sustainable market safety surveillance system. Consistency in the way adverse event data is collected promotes accurate analysis and meaningful conclusions, particularly by using standardized terms and standardized formats, such as prescribed in the VICH guidelines. Adherence to standardized terms is a critical step in classifying and communicating adverse events data. Simple, accessible tools (which minimize regional differences) must be made available to collect core data (see below) and transmit the information in a secure, standardized format to ensure accurate, uncorrupted data. These tools should be simple, independent of language, and based on internationally defined standards. Adverse event information should be communicated directly between the stakeholders (from the customer to the marketing authorisation holder) in a format that allows alignment with globally standardized fields (VICH GL 42). Examples of standardized terms are provided in Appendix I.

CREATING A PHARMACOVIGILANCE SYSTEM

1. Developing a local Pharmacovigilance System:

Alignment of veterinary systems…

In some countries rules already exist for collection and/or reporting adverse events for human medicines. Whilst it is worth examining these, be aware that the scale of the solution and the requirements will likely differ for veterinary medicines, due to husbandry, market factors, available resources and risk-perception differences. As many active ingredients are used in both humans and animals, it is important to be aligned in some areas (e.g. standardized product information). To create operational pharmacovigilance systems, it should be identified where alignment is beneficial, where it is not necessary, and where global alignment with other veterinary systems is more important.

… adapted to local conditions

First, an analysis of the country or region's existing regulatory, social, economic, infrastructure and physical environmental factors is advisable, to discern how they may impact the design of a local pharmacovigilance system. For countries where this will be a new system or where regulations for veterinary products do not exist, it is important to assess the expected scale of the pharmacovigilance system, based on number of VMPs authorized on the market and projected sales, attitudes towards adverse events or other market factors, to match it with the national needs and national resources. Considering the expected scale will aid in estimating the number of adverse events you might expect to receive, and how these would increase year on year with wider awareness.

[1] Available at http://www.vichsec.org/guidelines/pharmacovigilance.html

Funding

Next, it is critical to establish a broad understanding of the importance of implementing a pharmacovigilance system with the decision-makers involved in dedicating initial and ongoing resources to the effort. For example, consider the resources needed to build a database to hold the collected information, to analyse the information received and to take follow-up measures if necessary. Will these be funded by the Government, and if not how will this be sustained?

Involve all stakeholders

Finally, it is important to identify and involve groups that can support and collaborate in the development of the pharmacovigilance system. These may include non-governmental aid organisations, key opinion leaders, industry members, and animal health organizations. Involving influential local players can help to mitigate resistance to adverse event collection while communicating the value and benefit of a pharmacovigilance system to those expected to provide information (e.g. customers, veterinarians, pet owners, producers, etc…). The value of collecting, collating and communicating adverse event information must be evident early in the process to gain stakeholder buy-in and result in lasting, compliant behaviour.

2. Implementing a local Pharmacovigilance System:

For the initial implementation effort, an incremental approach may be advisable, starting small and then building on this, if appropriate, and if resources permit. With this approach, building the foundational elements of the system aligned with the factors identified from the analysis described above will ensure stability for later expansion. Consider the need for legislation to provide a legal basis for reporting and follow-up measures, but avoid putting 'details' in legislation. Details should be communicated via guidelines, so that they can more easily evolve with experience and changes in available resource. It is also important to establish and maintain open lines of communication with marketing authorisation holders (MAHs) when developing legislation and guidelines, to ensure alignment and realistic timelines. If feasible, open discussions with other regional National or Regulatory Authorities to facilitate a coordinated approach and possible sharing of information and alerts.

A set of guidance documents will be needed for a pharmacovigilance system framework. The foundational elements that need to be defined are:

- **For marketing authorisation holders** (MAH): Clearly delineated responsibilities and obligations of MAHs, covering information collection format (with a minimum core set of data), language, timelines and rules concerning communication plans. The MAHs are responsible for collecting, storing and analysing the pharmacovigilance data and further communication of adverse event information, when applicable.
- **For Regulatory Authorities**: Clearly delineated responsibilities and obligations of local authorities covering information collection and storage, analysis timelines, follow-up actions and communication plans. Authorities must provide responsible stewardship for information collected, support and guidance for the local pharmacovigilance system and the processes for follow-up regulatory activity where necessary.

Alignment of the local pharmacovigilance system with internationally harmonized adverse event collection formats (i.e. VICH GL 30 and 42) enables consistent exchange of information between parties and reduces non-value-added administrative work for all parties. Ensuring language is not a barrier is also important. English is the most commonly used and recommended language for communication of adverse event information between entities. Linked to the resources available and system configuration, timelines by which adverse event information should be reported from MAHs to Authorities should also be defined. Factors that affect reporting timelines should be clearly identified and communicated to avoid confusion and risk of non-compliance.

3. Practical approach for collecting individual adverse events

A. Reception of adverse event reports

In most of the cases the veterinarian or animal owner will report adverse events directly to the MAH. In some cases they may report directly to the Regulatory Authority. Both parties must have systems in place to receive, record, collate, analyse and follow-up on these reports. The recipient of the report should assign a case number, acknowledge receipt, ensure at least the core data is complete and undertake a causality assessment.

B. Minimum core data set for an individual adverse event report

A complete set of core data is critical for the evaluation of individual adverse event reports (for an example of a standard form, please see European Medicines Agency's veterinary reporting form available at https://eudravigilance.ema.europa.eu/veterinary/089304en.pdf). Minimal data requirements for an individual case report consist of the following:

- **Identifiable reporter:** Name
    - Other contact information (address, phone number, email, etc.) if available.
- **The treated animal:** species of veterinary patient(s) should be reported. In addition, the number of animals treated/affected, sex, age and weight if known.
    - For human patients, due to confidentiality laws in some countries, identification should be limited to gender, age, and initials if permitted.
- **Identifiable Product:** VMP(s) to which the animal or human was exposed
    - Brand name, dose, administration route, and marketing authorisation number, if available.
- **Adverse event description:** Abnormal finding or clinical signs/symptoms and time to onset following treatment.
    - In order to be able to evaluate a lack of efficacy report it is helpful to have information on the dose used and method of treatment, etc.

More details (e.g. reason for use, health status prior to treatment, batch number of the product) are desirable for evaluation of a case and should be obtained via a suitable reporting form where feasible. For lack of efficacy (LOE) cases, "LOE" may be defined as the apparent inability of an authorized product to have the recognized or expected efficacy in an animal, following proper use and according to the label claims.

C. Reporting timeline for adverse event reports

Adverse events that occur in your country and are received by the MAH should be submitted to the Regulatory Authority within a defined time period (within 30 days is recommended), or all cases that occur in your country and held by the MAH should be submitted to the Authority upon request.

D. Immediately after an individual adverse event is received:

Immediately after an individual adverse event report is received several activities should be initiated.

1. Assign a case number: Firstly, a unique case-number should be allocated. This is needed to identify an individual case for further communication and possible follow-up information. This number could consist of the reporting year, an initial for the Authority or MAH and a consecutive number (e.g. 2020ABC00001).

2. Acknowledge receipt: Secondly, an acknowledgement of receipt should be provided to the sender. This should contain the allocated case-number and the date when the case was received. If the information for a case is very limited and further information is expected (for example, to complete the necessary minimum 'core' data set), a request for more information should be made, especially if a significant or unexpected adverse event is reported.

3. Causality assessment: Thirdly, for each case an attempt should be made to assess the causal relation of the adverse event to the product administration. This assessment can be quite complex and should preferably be done by a veterinarian. It should take into account the following factors:

1. Associative connection with the treatment, in time or in anatomical sites.
2. Pharmacological and/or immunological explanation, blood levels, dose-effect relationship.
3. Presence of characteristic product related clinical or pathological phenomena.
4. Previous knowledge of similar reports.
5. Exclusion of other causes.
6. Completeness and reliability of the data in the case reports.
7. Dechallenge and rechallenge assessment if available.

Further guidance on the causality assessment for veterinary medicinal products is published on the Internet, e.g. by the European Medicines Agency (Veterinary regulatory - Veterinary medicines: regulatory information).

4. Inform the MAH: If the adverse event report was received directly by the Regulatory Authority a copy should be provided to the MAH or distributor. In order to enable worldwide reporting this report should be in English.

Depending on the local legislation protection of personal data of reporter/owner may be required.

5. Filing: Finally, the report should be stored, preferably using electronic data storage that facilitates analysis, is access-controlled and protected against weather elements like fire, water etc., or data loss.

4. Practical approach for compiled (aggregated) data and regulatory action

A decision on action can very rarely be made on the basis of an individual report. Usually it is necessary to aggregate data over extended time periods to identify an unusual pattern due to either the appearance of new adverse events or a change in the severity/ frequency of expected adverse events.

The analysis of aggregated data is performed by Authorities on groups of similar products, when appropriate, as well as by MAHs on their individual product(s). A risk analysis can be used to define an appropriate periodicity for the data analysis of each product. For example, the need for data analysis of well-established products, used perhaps for several decades with a history of safe use in veterinary medicine, is lower than products containing a new active ingredient with limited experience under practical conditions of use.

The ultimate aim of such an analysis is to determine whether the observed benefits continue to outweigh the reported risks ('positive benefit-risk ratio'). The results of such analysis will be the basis for deciding the next steps, for example whether or not further information needs to be obtained and whether or not regulatory actions are needed. If an action is deemed necessary it is important to work closely together with the MAH in order to ensure all relevant data and considerations have been taken into account.

5. Promote Pharmacovigilance and encourage reporting

The promotion of pharmacovigilance is important to encourage adverse event reporting. The three first steps towards encouraging reporting are to:
(a) Explain to veterinarians and animal owners why pharmacovigilance is important;
(b) Explain how to do it (what is an adverse event, what should be reported, how to get the report form and where to submit it);
(c) Make the reporting tools (i.e. an adverse event report form) easily available, such as on a website. To avoid 'reporter fatigue' the reporting system must not be cumbersome, as this will discourage reporting.

Some useful additional approaches include:

- Pharmacovigilance presentation for all graduating vets;
- Education: module on pharmacovigilance in vet university;
- Ad-hoc presentations at veterinary conferences and Industry association meetings;
- Information leaflets and dedicated websites;
- Dedicated contact point within the Regulatory Authority.

Another important element for encouraging reporting is providing feedback to the reporter. It is motivating for reporters to realize there is a potential benefit from their efforts. Activities to achieve this include:

- Confirmation of receipt: a letter to the person who reported the adverse event (e.g. the veterinarian, the animal owner, the distributor or the MAH);
- Personal response to reporters where additional information is needed;
- Annual Pharmacovigilance report from the Regulatory Authority - on the website, in veterinary magazines or in a separate newsletter addressed to veterinarians - that highlight the Authority's activities and demonstrate the value of the product monitoring system.
    - Please note, summaries of *product specific* data should not be published due to a risk of mis-interpretation by the public, as there are numerous factors that can impact reporting. Data should always be put into context (e.g. in relation to total use or sales volume).

Overall, significant changes to the benefit-risk profile for VMPs are very rare. Communications to veterinarians and the public demonstrating that a system is in place to monitor the safety and efficacy of veterinary products not only reassures them of the good stewardship of Industry and Authorities, working together, but also gives them perspective and understanding with regard to adverse event frequency and severity.

Appendix I [2].

Commonly Used Terms (aligned with VICH definitions):

- **Adverse Event Report (AER):** a direct communication from a reporter that includes at least the following information listed below. One animal or one human being, or a medically appropriate group exhibiting similar clinical signs should be included in a single report. The basic unit of information in the pharmacovigilance system is the AER and includes the following four minimal data points:
  - An identifiable reporter
  - An affected animal (defined by species at minimum) or human being
  - An identifiable veterinary medicinal product
  - One or more adverse signs or description of the event.
- **Marketing Authorisation Holder (MAH):** the commercial party who, according to the Authority is responsible for the pharmacovigilance of the veterinary medicinal product.
- **Authority:** the national or regional authority which is responsible for authorisation of the veterinary medicinal product.
- **VeDDRA:** list of terms for reporting clinical signs in suspected adverse reactions in animals and humans to veterinary medicinal products.

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC500094802.pdf

[2] Adapted from VICH GL 24