6th Cycle Regional Training Seminar for
OIE Focal Points for Veterinary Products

How to set up a pharmacovigilance system for veterinary medicinal products

Version 1, June 2019

Contents

Relation to OIE International Standards

The OIE has also addressed *pharmacovigilance* in terms of the Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicines (*OIE Terrestrial Code*, **Article 6.2.5** and *OIE Aquatic Code*, **Article 6.2.3**).

These texts are presented together in a user-friendly publication and are available at: http://www.oie.int/fileadmin/home/eng/Media_Center/docs/pdf/PortailAMR/EN-book-AMR.PDF

Concerning market monitoring of vaccines, the terminology of 'vaccinovigilance' was introduced in the *OIE Terrestrial Manual*, available at: http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/1.01.08_VACCINE_PRODUCTION.pdf

1. Introduction

The purpose of this manual is to provide information to help national competent authorities (NCAs) set up and run a national pharmacovigilance system for veterinary medicinal products (VMPs, including both animal medicines and animal vaccines). As an introduction to the topic, three fundamental questions are addressed below.

What is Pharmacovigilance?

Pharmacovigilance is a process by which information is collected and analysed 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 a veterinary medicinal product for safety, quality and efficacy after it moves from development into the wider population. The information collected through pharmacovigilance systems 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 "safe and effective" medicines through the analytical review of data arising from the use of the product.

Why are international harmonisation and standard reporting formats important?

- A primary benefit of working to internationally harmonized standards is the alignment of local reporting systems with global pharmacovigilance reporting; this allows the pooling of data and results in better detection of potential risks.
- Global alignment is particularly important because the same veterinary medicinal product may be supplied to many countries; therefore, it is essential 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, duplication of tasks and the need to reformat data.
- It is important to make efficient use of resources within the competent authorities and the industry. This allows the limited resources available to be focused on activities that contribute to product safety and efficacy, rather than on administrative tasks, for the benefit of animal health and safety in people.
- International harmonisation promotes global trade and the wider availability of medicines.
- International harmonised standards for veterinary pharmacovigilance are provided by VICH and VeDDRA (see glossary).

2. Pharmacovigilance – roles and responsibilities

Veterinary pharmacovigilance involves the collaboration of multiple stakeholders: national competent authorities (NCA), Marketing Authorisation Holders (MAH), veterinarians, animal owners, diagnostic labs, academics, etc. Each of these stakeholders has a part to play in an efficient and sensitive veterinary pharmacovigilance system:

- Efficient so that unnecessary costs are minimised for both NCAs and MAHs and that it is easy for veterinarians and animal owners to report pharmacovigilance cases.

- Sensitive so that previously unrecognised risks can be detected, assessed and appropriate risk mitigation measures can be introduced (e.g. label changes).

The responsibilities of the NCA, MAH and veterinarians need to be defined by the NCA. The roles of these stakeholders, and also animal owners, are outlined below.

The role of the National Competent Authority (NCA)

- The NCA has the overall responsibility for developing and implementing appropriate national legislation and additional guidance to ensure the smooth running of a national pharmacovigilance system (see details in section 4).

- Ideally, the NCA should also collaborate with other regional NCAs and global bodies (through such activities as VICH) to share best practice, to apply lessons learnt elsewhere to improve the local pharmacovigilance system.

- NCAs should work with academics and other bodies to ensure appropriate pharmacovigilance training modules are included in education and continuing education for veterinarians and, if possible, other stakeholders such as livestock owners, pharmacists and veterinary paraprofessionals. They should also work with national Veterinary Registration bodies to ensure pharmacovigilance responsibilities for veterinarians are embedded in local Professional Ethics expectations.

The role of the Marketing Authorisation Holder (MAH)

- MAHs have a legal responsibility to comply with local pharmacovigilance legislation and guidance and to ensure cases are reported in a timely manner (see section 4).

- MAHs should have a process for recognising and capturing pharmacovigilance cases in line with local and other (Third Country) legislation.

The role of the veterinarian

- Veterinarians play an important role in the front line of veterinary pharmacovigilance. Veterinarians have an ethical responsibility to recognise potential pharmacovigilance issues and report them to the MAH and/or NCA.

The role of the animal owners

- Animal owners have an ethical responsibility to report an adverse event to either their veterinarian or the MAH or the NCA, to ensure appropriate advice and treatment for the animal under their care and to support the on-going monitoring of authorised VMPs in the market-place.

3. Defining the scope of pharmacovigilance

It is important to first define what the pharmacovigilance system aims to achieve and how to resource the necessary systems and processes. The ambitions and scope of the system will be dependent on the available resources, and conversely, resources must be obtained to match the desired scope. Adequate resources are required to manage the respective pharmacovigilance systems within the NCA and MAH. Resource can take the form of IT/tools, people and allocated budget (funding).

Resource requirements will need to reflect the number of anticipated adverse event reports. This will depend upon a number of factors, including the number, volume and accessibility of the products on the market, the local culture of reporting and previous experience of pharmacovigilance reporting.

Considerations for the scope of the system are required in terms of:

- **What products will be in scope?**
  A pharmacovigilance system should focus on veterinary medicinal products (as defined in your jurisdiction); including other types of products may need additional reporting forms tailored to these and may be best handled using separate systems.

- **What adverse events will be in scope?**
  In addition to adverse reactions in the treated animal or the user (e.g., human exposures), will the scope include other events associated with the use of the product, such as lack of expected efficacy, residues exceeding the established safe limit, environmental issues and suspected transmission of infectious agents (for vaccines)?

- **Timing for adverse event reporting?**
  Consider the need for (a) expedited case reports and (b) periodic summary reports. The term "seriousness", as defined in VICH Guideline (GL) 24, can be used to define those adverse events that require expedited reporting. All other adverse event reporting can be done in a periodic report. Both these are discussed later.

  - Note: Some authorities are moving away from expedited case reports and periodic summary reports, in favour of a system where all reports are submitted on the same timeline and there is no periodic reporting. Instead, all reports are entered into a common database (e.g. within 30 days) and the marketing authorisation holder must analyse the database periodically for 'signals' and trends.

- **What reporting format is going to be used?**
  There is a strong preference and many advantages for both NCAs and companies to use globally aligned reporting formats so that data can be exchanged and shared regionally or globally to improve safety oversight and signal detection, while minimising non-value-added administrative burden. An example of an adverse event reporting form is given in the annex.

- **Should third country reports be included?**
  Requiring individual adverse event reports from 'third countries' should be avoided in the first instance and until the local pharmacovigilance system is up and running effectively, because:

  - Third country reporting will lead to the submission of many 1000s of cases and case updates a year

  - This will divert attention from local pharmacovigilance cases (which should be considered the most important), as the local database may be dominated by third country pharmacovigilance information which may not be locally relevant

  - The large number of third country cases requires the setup of a more sophisticated pharmacovigilance system (than would be initially required for just local country cases) to handle this information in a useful way. Significant human and IT resources will be required which may divert resources from promoting and building a local culture of pharmacovigilance and provide a poor return on investment in the first instance.

If third country reporting is requested, it will be provided in English as multiple translations of the same information in different languages is likely to result in different versions of the same case following different interpretations during the translation process. Rather than requesting individual third country reports, one approach is to request an existing, already written, the summary part of the periodic summary report from the company (without the line listings).

- **The frequency of Periodic Summary Reports (PSRs)?**
  Recommended schedules for PSRs are provided in VICH GL29. Schedules for reporting should be tailored for each product type, based on the product's risk profile, rather than a "one-size fits all" approach. For example, does the product have a long history of safe use, what is its benefit/risk profile (e.g. toxicity profile; route of administration), how widely is it used (potential level of exposure). For well-established products with a known safety profile the requirement for PSRs from the MAH can be reduced to longer intervals (for example, up to 10 years). To reduce administrative burden when PSRs are required, the PSR intervals should be aligned internationally, e.g. linked to the international product birth date (IBD) (see section 10 for more details).

These factors drive what will be required from an IT and personnel perspective. A roadmap of pharmacovigilance activities with the end goal in mind is beneficial to focus resources in the right areas.

Considerations from the MAH are also required. Many major animal health companies have the resources to accommodate global pharmacovigilance requirements; however, there will be local companies that do not have the same resources. If pharmacovigilance requirements are not carefully considered there will be disparity of what is received from the MAHs by the NCA. However, flexibility is needed, provided a minimum standard is met, as international companies will not wish to reformat their pharmacovigilance reports to meet a myriad of local requirements.

The aim is to ensure global oversight and a level playing field between the products when evaluating the benefit/risk profiles of different VMPs.

4. Drafting appropriate national legislation and additional guidance

It is important that an appropriate legal framework exists at a national level to support veterinary pharmacovigilance activities. A legal basis is needed to ensure the regulatory authority has the legal capacity to take and enforce regulatory measures, such as changing the safety warnings on a product, or suspending or revoking a marketing authorisation. In addition, the legislation should provide legal clarity on the key responsibilities of each actor (regulatory authorities, marketing authorisation holder, veterinarians, etc).

A key decision is how much detail to include in primary legislation and how much detail to defer to additional secondary guidance. The recommendation is that primary legislation should be kept high level and sufficiently flexible so that it does not need changing as veterinary pharmacovigilance develops within a country. While the necessary detail is important, if this is in the primary legislation it may be restrictive at some stage in the future as the veterinary pharmacovigilance system matures. The details should be described in additional guidelines, which are easier to update, so that the system can adapt over time to experience and changing conditions.

Legislation

Legislation should set out a legal framework that is enforceable at a high level. For example:

- Define the scope of the pharmacovigilance system (see section 3) and refer to additional guidance which may be developed to provide the necessary detail to implement the legislation.

- Define NCA responsibilities (see section 2), including but not limited to:

  - setting up the pharmacovigilance system and database,
  - have appropriately trained staff,
  - requirement to record cases in the database,
  - requirement to identify risks and undertake risk management activities including appropriate regulatory action,
  - to communicate with MAHs, to promote pharmacovigilance,
  - to conduct inspections of MAH pharmacovigilance systems, as appropriate.

- Define MAH responsibilities, including but not limited to:

  - the requirement to set up a pharmacovigilance system,
  - have appropriately trained staff,
  - reporting of adverse event cases to the NCA, including expedited notification of urgent issues (which impact the benefit:risk of a product) to the NCA
  - periodically evaluate aggregated data (e.g. through PSRs or through a signal detection and management system) as appropriate and
  - designate a Pharmacovigilance Responsible Person.

- Responsibilities for any other bodies who are key parts of the local pharmacovigilance system should also be identified in legislation (such as the veterinarian).

Guidelines

Guidelines provide the additional details necessary to implement and run the pharmacovigilance system. For example, guidelines should:

- Refer to the pharmacovigilance legislation as the legal basis.
- Provide guidance on NCA activities, such as:
  - Management of adverse event cases – process timelines, receipt and filing procedures, storage and archiving, and information exchange (for example, will adverse event cases sent directly to the NCA going to be sent to the MAH, to ensure the MAH also has a full data set)? Is feedback going to be provided to reporters?
  - Evaluation of cases – how are cases going to be assessed?
  - Communication with the MAH – timelines, methods, expectations.
  - Investigation of identified issues and subsequent risk management measures.
  - Conducting inspections of MAH systems (as appropriate).
- Provide guidelines for Marketing Authorisation Holders
  - Details on the requirements for the MAH pharmacovigilance system.
  - Details on expectations for the MAH staff training and frequency of retraining.
  - Details on reporting adverse event cases, for example case format, standard terms and pick lists, timelines for reporting cases (if appropriate, details of what is considered an expedited case).
  - As appropriate, details on requirements for analysis of aggregated data (such as periodic summary reports of non-expedited cases, or signal detection in the company database).
- Provide guidelines for any other body referred to in the primary legislation.

When drafting a legislative framework and guidelines for pharmacovigilance it is important to consult stakeholders who must be able to implement and understand the requirements (companies and vets). This is an important part of raising awareness and obtaining their support, which will facilitate the smooth implementation of the new systems.

5. Setting-up a pharmacovigilance system

The basic approach to be followed is summarised below:

- Define the intended scope of the system and the resources needed (see section 3). Secure the necessary funding and on-going funding model.
- Draft the legislative framework (avoid putting details into the legislation; keep details in the implementing guidance notes) (see section 4).
- Plan the pharmacovigilance system within the agency or regulatory authority: define responsibilities and who does what. Ensure adequate resources are allocated.
- Define responsibilities and obligations of companies.
- Consult stakeholders (MAHs and veterinarians) with the draft plans, requirements and documents.
- Establish necessary documentation and systems, including standardised formats, terminology and language (international alignment is important).

Use an incremental approach

Start with a relatively simple national system. The scope or complexity of the system can be expanded later with experience and knowledge, or adapted to changing needs or changes in funding. For example, begin with adverse events to regulated VMPs occurring within the country. Also consider how many adverse event reports you might expect from the field. 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 (there is limited value in collecting 1000s of cases when there are no resources to deal with them; consider how to prioritize cases if you DO receive thousands). 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.

Will a paper or spreadsheet-based system be sufficient (i.e. adverse event reports submitted on a paper form and data entered into a spreadsheet), or will the number of expected reports require more sophisticated IT support (e.g. XML based data exchange), and is the funding available for that?

Standardised formats, terminology and language

Alignment of the local pharmacovigilance system with internationally harmonized adverse event collection formats (i.e. VICH GLs 30 and 42) enables 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 and to ensure data consistency and quality in worldwide databases.

VeDDRA standardised terminology should be used for all terms used in the context of pharmacovigilance reporting. To accommodate local language, set up the standard terms in a database with the standard VeDDRA term in English, with the local language translation alongside each term.

Defining the responsibilities

The responsibilities of the people/organisations involved in pharmacovigilance need to be defined for legal clarity and certainty, in both the legislation (high level principles) and in detailed guidance.

National Competent Authorities

The NCA is responsible for defining the national legal basis for pharmacovigilance. NCAs also need to administer an appropriate system for the collection and evaluation of information relevant to the benefit/risk balance of products (VMPs). An appropriate system can be defined as one that can be maintained from a resource perspective. The system must enable the NCA to make decisions and take appropriate action where necessary for the VMPs within its area of jurisdiction.

Clearly delineated responsibilities and obligations of local authorities should cover information collection and storage, analysis timelines, follow-up actions and communication plans (see box 1 below). 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.

Consider the requirements and qualifications needed for pharmacovigilance professionals at the NCA. Case assessments and safety signal detection will require veterinarians or veterinary toxicologists and potentially statisticians.

Box 1: Responsibilities and obligations of the competent authority include:

- To establish a pharmacovigilance system:
  - collect information
  - scientific evaluation and product group analysis
  - collate with data on sales or use, and local epidemiology (to assess potential exposure and incidence rates, and to put the data into context of local conditions)
  - monitor compliance of companies
  - do risk-based inspections and perform controls
  - take corrective actions where necessary
- Initiate further investigation and assessment of identified safety concerns
- Implement conditions and restrictions on products
- Encourage reporting
- Make companies and veterinarians aware of their obligations

Marketing Authorisation Holder

The MAH is responsible for ensuring an appropriate system of pharmacovigilance surveillance and risk management is in place to assure responsibility and liability for its products on the market and ensure action can be taken, when necessary.

Clearly delineated responsibilities and obligations of MAHs should be defined, 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 on their products (such as signal detection) and further communication of adverse event information, when applicable.

If MAHs are required to designate a Pharmacovigilance Responsible Person, the responsibilities and accountabilities and required minimum qualification should be defined.

Veterinarian or other animal health professional

The NCA needs to consider if they want to mandate the reporting of adverse events that have been reported to or observed by the veterinarian or animal health professional. This mandate would increase the visibility and obligations of the profession with regards to the collection of adverse events, but must be supported by easy access to the tools of reporting (guidance and reporting forms).

Establish necessary documentation and systems

To ensure the transparent and consistent implementation of the system, the necessary documentation must be put in place and published. This will include the necessary operating procedures, guidelines and reporting forms or templates. When establishing this documentation, the following factors should be considered:

- Align with international definitions (see VICH g 24)
- Consult draft plans with stakeholders – companies and vets
- Reporting form for adverse events; minimum core data set; reporting timelines
- A system for reception and filing system of adverse event reports:
  - Paper system or a small electronic system or a functional database
- Assignment of case numbers and filing procedures
- Template for acknowledgment of receipt letter, for feedback communication and for informing the MAH
- Procedure for causality assessment
- Data input management system and follow-up for missing essential data
- Establish tools for analysis of data; aggregation of data, signal detection; trend analysis; trigger thresholds. It is also possible to analyse across substances, products and species.
- Procedures for decisions on regulatory action.

Plan training of internal staff

The staff assigned responsibilities for pharmacovigilance activities must be appropriately trained to ensure the correct and consistent implementation of these procedures and duties. Systems and training materials need to be in place for initial training and refresher training as necessary. Staff assigned for support and back-up also need to be trained.

Prepare a communication and awareness plan with stakeholders

It is necessary to make companies and veterinarians aware of their obligations, and this requires an effective communication plan. This is particularly important to ensure companies can plan and meet the deadlines by when they must implement in-house systems and procedures, and be compliant.

A communication plan is also necessary to spread the pharmacovigilance awareness to veterinarians/users/animal owners (see also chapter 6 'How to promote pharmacovigilance and encourage reporting' and chapter 13 'What and how to communicate pharmacovigilance outcomes'). It is important that they understand the importance of adverse event reporting, and where they can access the standard reporting forms. These should be made easily available on the NCA website and/or in paper packs, together with dedicated telephone numbers.

Distributor and retailers of VMPs should also be recruited for spreading the awareness of pharmacovigilance reporting and the distribution of information sheets and the reporting forms.

Regional cooperation

An important consideration when setting up a pharmacovigilance system is the benefits of regional cooperation. Not only is aggregated pharmacovigilance data more useful, particularly if your own market is small or reporting levels are low, but also work-sharing between authorities is highly beneficial for ensuring limited resources are used to the best advantage.

6. How to promote pharmacovigilance and encourage reporting

Veterinary pharmacovigilance involves collaboration of multiple stakeholders: NCAs, MAHs, veterinarians, animal owners, diagnostic labs, academics, etc. Each of these stakeholders has a part to play in an efficient and effective veterinary pharmacovigilance system.

The NCA has the prime responsibility for promoting veterinary pharmacovigilance. This must be considered a long term and permanent activity, as it involves changing or influencing human behaviour.

Education

The prime targets for education activities should be veterinarians and veterinary technicians, and particularly the next generation of veterinarians currently in veterinary schools:

- Trainee veterinarians and veterinary technicians: a main focus of training should be trainee veterinarians and veterinary technicians. These groups are not as 'set in their ways' as experienced individuals and can act as catalysts to change behaviour once they finish their training period. In addition, after 5 or 10 years a significant number of practising individuals will have gone through this training which will reduce the resistance to change in the wider veterinary community.

- Continuing education: Efforts should be made to engage qualified veterinarians / veterinary technicians at conferences and other events where they are gathered with a training focus.

Initially such training will focus on the importance of veterinary pharmacovigilance and why it has a role to play in ensuring the safety of veterinary medicines and vaccines. Over time the focus should increasingly turn to case histories and success stories.

Publicity and feedback

Publishing an annual report on activities is an important way of providing feedback to veterinarians / veterinary technicians and encouraging reporting. While it is difficult and not especially appropriate (because generally a group of reports will lead to risk management activities) to provide specific feedback on individual reports, it is important that reporting isn't seen as a one-way street and everything goes into a 'black hole'. Descriptive statistics, as well as summaries of actions taken for pharmacovigilance reasons, help promote the importance of reporting.

Developing publicity materials that encourage reporting will help remind stakeholders of the value of reporting. Such materials can be used on websites and at stakeholder or public meetings.

Make it easy to report

Both the NCA and MAHs have a responsibility for making it easy to report veterinary pharmacovigilance cases.

- NCA and MAH websites or apps should make it very clear how a veterinarian or any other actor can report an adverse event. Web forms and apps should be simple and easy to use.

- Other means of contact, such as telephone numbers, should be clearly identified and adequately staffed. Reply to calls the next working day. A failure to follow up a request for assistance demotivates the caller and will discourage reporting.

The NCA will have a number of responsibilities either defined within the legislation and/or defined in guidance documents that it develops to add operational details to the basic legislative framework.

- NCAs should check and ensure that MAHs do record and report all adverse events reported to them, according to local legislation. Taking no action at all will discourage reporting.

- NCAs should ensure that MAH websites, apps and telephone systems are clear, easy to use and operational.

- The NCA should have an active and ongoing outreach program to engage MAHs and ensure they understand their responsibilities. This can include:
  - Training courses for company staff
  - Joint NCA-MAH working groups to collaboratively work on improving veterinary pharmacovigilance. In many countries these have proved to be extremely successful and have allowed a very open dialogue where win-win solutions are identified to problems.

While the prime targets for educational and outreach activities is likely to be veterinarians, veterinary paraprofessionals, veterinary technicians and MAHs, consideration should be also given to direct outreach to animal owner associations, such as livestock producer groups and pet owner groups, to educate them about both the importance and limitations of veterinary pharmacovigilance.

7. Submission, reception and processing of spontaneous reports

Both MAHs and NCAs need to have procedures in place for the reception and processing of spontaneous reports. An essential starting point is to ensure the reports use standard terminology and definitions (see VICH GL 24). It is also important to harmonize the contents of adverse event reports, to set the minimum data that is essential for a report to be of any use, and to facilitate the exchange of data.

Commonly Used Terms

- A Veterinary Medicinal Product (VMP) is any medicinal product with approved claim(s) to having a protective, therapeutic or diagnostic effect or to alter physiological functions when administered to or applied to an animal. The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function.

- An adverse event (AE) is any observation in animals, whether or not considered to be product-related, that is unfavourable 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 labelling or noxious reactions in humans after being exposed to VMP(s).

- A serious adverse event is any adverse event that results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event.

Standard content of an adverse event report (AER)

An AER is the basic unit of information in the pharmacovigilance system and consists of a direct communication from an identifiable first-hand reporter that includes at least the following four minimal data points to constitute a valid individual case report:

- An identifiable reporter, including name and/or contact details
- An identifiable animal (defined by species at minimum) or human being
- An identifiable veterinary medicinal product
- One or more adverse signs or description of the event

However, many more details are desired to enable a correct case analysis and the reporting form should include the possibility to enter this additional important data (see chapter 10 box 2).

In order to ensure consistency and accuracy of collected data, the content and the structure of any nationally approved AER should follow the internationally defined standards (VICH GL 30 – Controlled list of terms; VICH GL 35 – Electronic Standards for Transfer of Data; VICH GL 42 – Data Elements for Submission of AE Reports). An example is provided in the annex.

Acceptable languages

To enable worldwide reporting, the data collected should be recorded in English which is the common language for pharmacovigilance. A second local language is acceptable for transmission of local reports to the national authority. When required, global reporting is done in English in order to avoid the need for translation into multiple local languages, and thus reducing the risk of losing consistency and accuracy of data.

Giving access to AER for the people willing to submit

The reporting tools (i.e. an AER form) must be easily available, such as on an official website (regulatory authority, animal health association, veterinary professional organisation). The AER form should be simply printed and filled in under paper format, or uploaded and electronically completed. Guidance should be provided on how to complete the AER form via information leaflet or on-line assistance directly from the website. The contact point within the regulatory authority should be clearly detailed (physical address where to send paper version, e-mail to send electronic document, phone hot-line).

For regulatory authorities with a more mature pharmacovigilance system the reporting tool could consist of an AER form being filled directly via the website of the regulatory authority and connected to the national pharmacovigilance database.

The promotion of these reporting tools should be done during initial and continued education of veterinarians, during ad-hoc presentations at veterinary conferences and industry association meetings (see chapter 6).

Data process for spontaneous reports

An adequate organisation must be in place within the regulatory authority to ensure the data in the AERs are correctly processed. Four steps are identified as follows:

- Reception of the AER
    - Assignment of a case number needed to identify an individual case for further communication and possible follow-up information.
    - Confirmation of receipt either via a letter or an e-mail or a SMS to the person who reported the adverse event (e.g. the veterinarian, the animal owner, the distributor or the MAH);
    - Personal response to, and follow-up with, reporters where additional information is needed.

- Handling and storage of source documents
    - AER forms received under paper format or printed must be kept as source documents in a physical or electronic archive
    - Storage of the electronic documents received via e-mail or from dedicated website needs to be under a structured organisation allowing the detection and management of duplicates and follow-up as needed
    - Storage needs to be secure to prevent loss or theft, and to protect personal information (see chapter 9).

- Recording of data
    - The data from AERs needs to be entered into a computer system to facilitate analysis of aggregated data. The data entry needs to be verified or validated. The complexity of the computer system can vary as described in section x (ranging from an Excel spreadsheet to a validated database). Whatever the record system in place, the fields designed to capture the data should follow the internationally defined standards (GL30 – Controlled list of terms; GL35 – Electronic Standards for Transfer of Data; GL42 – Data Elements for Submission of AE Reports).
- Coding and assessment
    - This is discussed in more detail in chapter 8 below. A medical review of the AER and evaluation of the causality assessment will be required by a suitably qualified and trained person; the causality assessment and comments must then be sent to the regulatory authority with the case reference.

8. How to record the data

Adequate resources should be in place at the MAH and the NCA ensuring that reports are documented in the pharmacovigilance database as soon as possible after receipt, and in order to ensure:

- timely coding, assessing and reporting as per local legislation,
- adequate and timely review and analysis of the data.

Submission of individual AERs

Current legal requirements vary depending on the country/region. The timeline requirement for an individual AER is important – if it is too short, a MAH will be frequently reporting incomplete information and this will lead to a lot of follow up reports that increase the administrative burden on MAHs and NCAs.

Historically, some NCAs required that serious AERs are submitted expedited within 15 calendar or working days after the minimum information (four minimal data points) has been received (Date of First Receipt) and non-serious cases as part of the next PSR. Alternatively, an increasing number of regulatory authorities employ a 30 calendar day reporting timeline for all reports as this gives the NCA a complete view of all reports in a timely manner (the distinction between serious and non-serious is not being considered for the submission of individuals AERs). This 30-day requirement allows time to go back to the reporter to collect the necessary full information to make a meaningful interpretation of the reported case.

Independently from the above-mentioned legal timelines, MAHs should notify authorities as soon as possible of any report (or group of reports) that identify a significant safety concern, followed-up with a completed AER submitted within the legally required timeframe.

VeDDRA Terms

The free text description (report narrative), or its translation, of the sequence of events that occurred after the exposure to the VMP should closely reflect the wording that was used by the person who initially reported the case. In addition, each report should be coded using VeDDRA terminology for animal and human adverse events. VeDDRA is the clinical dictionary used to describe adverse clinical manifestations under a standardized format, later allowing structured data query and trending analysis of the electronic records.

VeDDRA terminology is described by VICH guideline 30 and is maintained by an international group within the framework of VICH.

Causality assessment

For each case, an assessment should be made of the causal relation of the adverse event following the administration of a VMP, taking into account the following factors:

- Associative connection with the treatment, in time or in anatomical sites.
- Pharmacological and/or immunological explanation, blood levels, dose-effect relationship.
- Presence of characteristic product-related clinical or pathological phenomena.
- Previous knowledge of similar reports.
- Exclusion of other causes.
- Completeness and reliability of the data in the case reports.
- De-challenge and re-challenge information if available.

Causality scoring algorithms can be used to assess either at

- The clinical sign level, e.g. modified-Kramer system (used by FDA)
- The case level, e.g. ABON system (used by EU[1]) whereby causality is classified as A-probable, B-Possible, O1-Inconclusive, O-Unclassifiable/Unassessable, or N-Unlikely.

In Annex:
Veterinary Suspected Adverse Reaction Report Form for Veterinarians & Health Professionals

[1] Recommendation on harmonising the approach to causality assessment for adverse events to veterinary medicinal products, EMA/CVMP/PhVWP/552/2003

9. How to store and archive pharmacovigilance data

Data Storage

Storage requirements will depend to some extent on the chosen system (i.e. a paper-based system, small electronic system or a functional database system). The following points should be considered:

- Adverse event reports should be stored, preferably using electronic data storage that:
  - facilitates analysis
  - is access-controlled and prevents unauthorised access
  - is protected against
    i. elements like fire, water, etc.
    ii. data loss (data security; electronic longevity)
    iii. theft (data privacy)

- A simple (vet-specific) pharmacovigilance database compatible with international standard format is preferable
  - MAH: facilitates easier reporting
  - NCA: facilitates exchange of data between countries and regulatory authorities

- Operating procedures should be in place for storage and archiving, including the storage of the analysis output, such as identified signals and trend analysis reports.

- Ensuring operational capacities:
  - MAH: capacities may be local, regional or global
  - NCA: in addition to legislation and regulatory framework, financial support to build a functional and sustainable pharmacovigilance system is needed

Archive periods

Records retention periods are sometimes specified in regional legislation.

For the MAH

It is recommended that pharmacovigilance data and documents relating to individual authorised VMPs should be retained for a period of 2 years after the *expiration date of a product* or longer as international obligations or individual company retention policies (whichever is longer).

For the NCA

It is recommended that pharmacovigilance data and documents relating to individual authorised VMPs should be retained as long as the product is authorised and for at least 3 years after *the marketing authorisation* has expired (or as long as the product is still within expiry).

10. Standardised periodic summary reports

A Periodic Summary Report (PSR) is intended to provide an update of the worldwide safety experience of a VMP at defined time points post-authorisation, such as every 3, or 5 or 10 years. International guidance on the scope, frequency and content of PSRs is given in VICH GL 29.

This section provides guidance for a standardised approach to the presentation of the data for submission in a PSR. A consistent set of data will contribute to a harmonised approach for the detection and investigation of adverse events for VMPs and thus help to increase public and animal health. To achieve this goal, the scope, timing and contents of the PSR should be consistent and aligned between different agencies and companies.

International Birth Date (IBD)

Each VMP has an International Birth Date (IBD). The IBD is defined in VICH GL 24, and can be designated as the last day of the same month for administrative convenience, if desired by the MAH. The IBD is the basis for harmonizing MAH periodic reporting dates, and the Data Lock Point (DLP) for PSRs needs to be based on this IBD. The DLP is the date designated as the cut-off date for data to be included into a particular PSR.

PSR frequency

The frequency for PSR preparation and submission should be based on the time the product has been marketed, as the safety profile of the product becomes more established over time. In the early years of commercialisation of a product, limited information is available on the product safety profile. Therefore, more frequent preparation and submission of PSRs is appropriate to collect more information on the safety profile of the product.

A standardised global PSR schedule is recommended:

- Every 6 months for the first two years, after first marketing anywhere in the world in a country that has PSR requirements.
- After the first two years of marketing following the IBD, PSRs should be required no more frequently than yearly for the next 4 years of marketing.
- Beyond the sixth year of marketing, PSRs should be submitted no more frequently than every 3 years.

For a product that has already started on a global PSR schedule based on the IBD, new authorisations for that product in a country where the product was not authorised before, should not restart or change (i.e. increased frequency) the global PSR schedule. The country for which this product is a newly authorised VMP will receive the next global PSR that is prepared according to the global PSR schedule. Existing global PSRs should be made available to the regulatory authorities, which will provide an overview of the product safety profile to date for that VMP.

PSR language

Considering the global scope of the PSRs, the language of a global PSR should be English. If a NCA requires information in the local language, the submission timeline should be extended to 90 calendar days to allow for translation of the global PSR conclusions.

In case a translation is required by a NCA, this requirement should be limited to the PSR document conclusions. There should not be a requirement for translation of third country individual case reports (AERs).

PSR contents

The PSR contents are described in this section and a summary of the PSR contents is shown in the box below. Each PSR should cover the period of time since the last PSR and should be submitted within 60 calendar days after the DLP. Gaps and overlapping of data should be avoided.

Box 2: Summary of the PSR contents (see VICH GL 29)

a. MAH name and address

b. Product names and MA numbers of all products covered by the

c. The period covered by the PSR and the IBD

d. All AERs since the last PSR from anywhere in the world (see VICH GL 42 for data elements)

e. Bibliography following a bibliographic search

f. Estimated exposure and incidence rates

g. Summary of any regulatory actions taken anywhere in the world

h. Critical analysis and review of the benefit-risk assessment

a. The name and address of the marketing authorisation holder should be provided.

b. The VMP(s) covered by a PSR should be clearly identified in the PSR (including same and similar products). This includes an overview of the trade names, MA numbers and associated MAHs (name only) in all countries globally, for the product(s) covered by the PSR at the time of the DLP of the reporting period covered by the PSR.

c. The reporting period (including DLP) and frequency (e.g. first full 6-month PSR, second annual PSR, etc) of the PSR based on the global PSR schedule should be clearly indicated in the PSR. It should also be clearly indicated what the IBD for the VMP is, and in what country the first global authorisation was granted.

d. Details of all adverse events received anywhere in the world should be included in the PSR. Include a line listing of any AERs received but not yet submitted to the NCA (see box below). The main focus of the PSR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSR, providing a basis for conclusion whether there is a change in the safety profile of the VMP.

Adverse event information to be included in the line listing includes:

- Unique Adverse Event Report Identification Number (also referred to as the World Wide Number) (see VICH GL 42, paragraph A.4.1)
- Country of occurrence
- Local agency reference number (if available)
- Seriousness
- Product administration start date
- Product administration end date
- Adverse event start date
- Reacting animal species
- Reacting animal age
- Number of animals exposed
- Number of animals reacting
- Number of animals died
- Use of the product (on label, off label, unknown)
- Case narrative
- Other products administered concomitantly
- Clinical signs reported (as VeDDRA terms)
- Causality assessment (e.g. Kramer ratings or ABON classification)
- Reason for the causality assessment

e. A bibliographic listing of scientific articles that address AEs found published during the time period of the PSR that pertains to the VMP(s), and a brief statement assessing the relevance of these articles to the VMP(s); the bibliographic listing is generated using a widely accepted search engine and a search on the product name in peer-reviewed journals. Additionally, a bibliographic listing of the studies that address AEs and the MAH has sponsored for the VMP(s) should be included.

f. The PSR should address the relationship of distributed volume of the VMP(s) covered by the PSR to the number of AERs, i.e. an incidence rate expressed as the number of AERs per unit of sales. Distribution data should be provided by country if necessary. This is explained in the next sub-section.

g. An overview of regulatory and MAH actions taken anywhere in the world for safety or efficacy reasons (e.g. follow-up measures, specific obligations and variations) since the last period covered in the PSR indicating scope, status and date should be given.

h. The PSR should include a concise critical analysis and opinion on the risk/benefit profile of the VMP(s). The main focus in the data review should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSR, e.g. related to:

   i. Evidence of previously unidentified concerns
   ii. Changes in frequency of AEs
   iii. Drug interactions
   iv. Human AEs

The analysis of the adverse events reported may be supported by tables or tabulations summarising the main findings. It may be helpful, especially for PSURs which contain a large number of adverse events, to introduce summary tabulations and prepare separate tables e.g. on basis of seriousness, causality assessment or VeDDRA categories on organ level (e.g. System Organ Class (SOC) or Preferred Term (PT) level).

The evaluation should indicate whether the data remain in line with the cumulative experiences to date and the approved labels, and if necessary suggest proposed actions or follow-up measures.

Calculating the incidence reporting rate

Since the exact exposure of animals to a VMP is not directly available to MAHs, sales data is generally used as an indication for distribution data to provide an estimation of exposure. Also, there is known under-reporting of adverse events. Thus, any incidence reporting rate is not "true incidence" but an estimate of the incidence of those events reported based on available data and provides guidance to the Regulatory Agency on which events occur most frequently and which are rarer. The reasoning for the calculation assumptions should be justified in the PSR.

Clear assumptions for the calculation of the estimated number of animals treated should be provided in the PSR and should be based on the recommended use of the VMP. Where animal weight is required for calculation of the estimated number of animals treated, the selected animal weight should be justified in the PSR. The following standard weights are recommended for use in these calculations:

Species and subpopulations	Standard weight (kg)
Horse	550
Dog	20
Cat	5
Cow	550
Beef calf	150
New-born calf	50
Sow/boar	160
Finishing pig	60
Weaner pig	25
Sheep	60
Lamb	10
Poultry, broiler	1
Poultry, layer hen	2
Poultry, turkey	10
Rabbit	1.5

In situations where a VMP is indicated for multiple target species, additional information to explain how the distribution of proportional use in different species is estimated should be provided.

The reason for standardizing the calculations is to allow for comparison between similar products. A consistent approach in the calculations for estimated exposure for a specific VMP will also allow for comparison over time. Changes to an established calculation for estimated exposure for a specific VMP should therefore be justified.

An overall incidence reporting rate can be calculated for all spontaneous adverse reactions with causality coded, for example Kramer ratings or as A, B, O or O1 if the ABON system is used, that occur after recommended or non-recommended (off-label) use in the target species. Adverse reactions from laboratory or clinical studies should be excluded from the calculation for spontaneous reports. In addition, an incidence for lack of efficacy reports with causality A, B, O or O1 that occur after recommended use in target species should be calculated, when relevant.

In situations where a VMP is indicated for multiple target species, estimated incidences should be calculated for each target species.

However, the overall incidence reporting rate is only a very rough estimate indicating only 'high' or 'low' numbers of reports in relation to sales, with no information on type, severity or causality. Therefore, it is recommended to also calculate the 'A, B' incidence reporting rate (and compare to the overall ABON rate).

If the number of AERs are very low calculating the incidence reporting rate may not be helpful and it might be more meaningful to apply medical judgement to all cases (instead of statistics).

Please also refer to the subsection "Putting data into context" (see below).

11. How to analyse aggregated data

Ways of data analysis

The collated adverse event (AE) reports should be analysed in meaningful intervals and for comparable periods for the product or a product group, as appropriate. Methods to analyse the data depend on the numbers of AEs in the reviewed period. In case of low numbers of AEs in the reviewed period, the analysis may be done during the individual case handling or by analysis of the AEs aggregated in a line listing.

Spreadsheets can be used for products / product groups with mid-size AE numbers in the reviewed period, to allow for further evaluations. For example, the AEs can be separated according to affected species, differentiation of serious versus non-serious AEs, affected system organ classes, differentiation of cases after on-label versus off-label use, etc.

A more complex analysis can be done using a database and/or statistical evaluations for products / product groups with large AE numbers (e.g. >200 cases in the review period), comparing the above-mentioned parameters in different periods, or with different products /product groups.

There are various methods of data analysis available to detect trends or potential signals, each having its pros and cons. For animal health products in general the AE numbers for the products are much lower than for human products and therefore a flexible approach allowing a variety of different methods to data analysis is important for the animal health sector.

Clustering of similar products into a group should be possible to increase sample size (e.g. same product but different strengths, same active ingredient etc.).

Timeframes/periodicity; risk-based approach

Trending and signal detection should be done in a risk-based approach, and thus primarily focus on more serious and/or new as-yet unknown unintended effects. The safety profile for new active ingredients and/or products may not be completely established after authorisation. With post-authorisation experience the safety profile of a product becomes better known. Although safety surveillance should be ongoing, for all products, the formal review periods for *new* active ingredients/products should be shorter (e.g. half yearly for first 2 years post authorisation) but can be extended with accumulated experience (e.g. yearly for the next 2 years and 3-yearly or more thereafter when the safety profile of the active ingredient/ product is established).

Putting data into context

The relevance of a detected potential signal needs to be validated as a variety of factors may lead to more or differing AE reporting (e.g. additional sales channel, marketing campaigns, increased awareness due to discussion in internet fora or publications, additional product launches, increase in sales, re-imbursement policy, product pricing, etc.). Furthermore, there are changes in reporting frequency possible over time, which is why it is recommended to compare the reviewed period with equal previous periods.

An increase in the number of reports over time for a particular product or a particular sign/VMP pair should be interpreted in the context of the evolution of the product's sales during the same period, and of any action that could have increased reporting (such as publications) for this product.

Raw data on potential signals without relation to the product sales may not be meaningful. As in general the numbers of AEs in a given country are limited, worldwide incidence reporting rates should be considered in the signal validation to provide a more reliable basis, particularly prior to decisions for risk mitigation measures.

All AE reports independent of the assessed product relation should be analysed (reporting rate) and compared with those considered probably or possibly product related and/or unclassifiable (incidence calculation).

For products with low numbers of AEs, simple analysis methods, such as comparing individual cases in a period with those of previous periods, may be employed.

For products with large numbers of AEs the evaluations can be more stratified (e.g. on country level, SOC or HLT level, on-label versus off-label use, serious versus non-serious), as appropriate and meaningful.

Signal management

A 'signal' is typically the detection of a new AE or a change in the rate of a known AE. A more comprehensive definition is provided by CIOMS (see 'Glossary and definitions').

Tools and expertise for analysing the data should be available for both signal detection and trend analysis.

Signals should be prioritised based on their potential severity, to enable focus on important risks first. All detected potential signals need to be validated, evaluated for their relevance and possible relation with the product, impact and likelihood of occurrence, preferably in a multi-disciplined team (e.g. clinical, toxicological, regulatory and pharmacovigilance).

A confirmed signal is considered a risk. It is categorised as

a. either a potential risk when there is no clear proof of product relation (assumption) and further investigations are necessary before definitive measures can be taken,
b. or as identified risk when there is scientific proof/clear scientific base of product relation.

The risk level is defined based on its severity as

a. either low risk where no risk mitigation measures are considered to be necessary and routine pharmacovigilance monitoring is sufficient
b. or important risk when for an identified risk mitigation measures are considered necessary. The time frame for implementation of the measures should reflect the level of risk (i.e. be risk-based).

Sometimes, in the case of a significant animal safety issue, or human safety issue, precautionary measures are taken before the product relationship is definitely established (e.g. temporary suspension of the marketing authorisation while investigations are carried out).

12. Risk management and follow-up regulatory measures

Risk management measures and their time frames for implementation should be risk based, depending on the level of risk (low or important/high) and whether it is a potential risk or an identified risk (risk-based approach). The focus of any actions should be on important risks and should be science based.

For a signal categorised as a potential risk, further investigations are necessary before measures can be decided.

For an identified low risk, either no risk mitigation measures besides routine pharmacovigilance measures are considered to be necessary or there is no urgency for implementation of mitigation measures.

For an identified important risk, mitigation measures are considered necessary to return to a positive benefit-risk balance. When the identified risk is important, urgent measures are necessary.

A variety of risk mitigation measures are possible depending on the level of risk. For example, education/training/information to stakeholders, warning statements via websites/product folders/letters to stakeholders, changes to the label and summary of product characteristics (SPC),, additional studies, withdrawal or suspension of the MA.

The timeframes for implementation of measures should be based on the severity of risk. For important risks the measures should be implemented without delay and within 1 year. In case of low risks, the measures should be implemented with the next planned variation for a label change.

Close cooperation between NCA and MAH for risk management and risk mitigation is important to achieve the best outcome and appropriate handling of the issue. The MAH should be involved and informed prior to any decision being taken by the NCA for risk mitigation measures.

Measures should be the same where the product characteristics are the same/similar (e.g. for copycat or same/similar products, including generic products), to ensure the safety statements are harmonised, and the handling of safety issues is the same.

13. What and how to communicate pharmacovigilance outcomes

Communication on pharmacovigilance and safety issues to veterinarians and other health professionals and the general public is an important part of pharmacovigilance activities and the risk management process. Careful considerations must be made when developing guidance for industry on this topic. Providing pharmacovigilance data to the public without sufficient context to interpret the data does not provide useful information on the safety of veterinary medicinal products The outcomes (i.e. the validated risks put into context) of the analysis of the pharmacovigilance data should be communicated.

Provision of information about the safe and effective use of VMPs, and any important changes to the product information, supports appropriate use and should be considered as a public health responsibility.

Risk communication needs to be considered throughout the risk management process. The overriding principle should be to ensure the right message is delivered to the right person at the right time. In principle, significant new or emerging information should be brought to the attention of veterinarians and other health professionals before the general public, in order to enable them to take action and respond accordingly.

Effective communication on safe and effective use of VMPs entails:

i. Cooperation between all parties
ii. Coordination between MAH and NCA (or relevant Ministry/official body)
iii. A strategy that meets the urgency to communicate and an understanding of the impact or effectiveness of that information to the veterinarian, other health professional and the general public

Any communication to health professionals and the public needs to be agreed between the NCA and MAH. Communications need to be carefully considered and not cause undue burden to the prescriber/veterinarian. There is a wide portfolio of products available to prescribers and we need to consider the information provided to aid and assist in the safe use of VMPs.

NCAs along with the MAH need to determine which pharmacovigilance outcomes to communicate, not just how to communicate them. Whenever possible and appropriate such outcomes should be based on the global patient experience.

Label or package safety warnings

If changes to the label or package safety warnings are justified then spontaneously reported ADE data should be listed separately from clinical trial data with appropriate language/caveats. The use of international classification of frequency of adverse events on the label, such as CIOMS classification, is recommended (see glossary and definitions) when appropriate. If CIOMS classification is utilized, the source of the estimates (spontaneous or clinical trial) should be indicated and it must be recognized that when the estimate is derived mainly from spontaneous reports, the statistics represent *reporting frequencies*.

Risk mitigations beyond that of label changes should be considered where appropriate; e.g., safety bulletin, Dear Healthcare Professional letters, Training program etc. These must be agreed between the NCA and MAH.

There is an abundance of options available to MAH and NCAs with regards to communicating pharmacovigilance information. As already articulated, careful consideration needs to be made about the pharmacovigilance outcome and risk mitigation to be communicated. The forum or media of communication and the intended impact of the communication should also be determined. Where possible the effectiveness of the communication should be measured to determine if further activities are required. This is not an exact science and the communication of each pharmacovigilance outcome needs to be determined on a case-by-case basis.

14. Inspections and ensuring compliance

When implementing a pharmacovigilance system, a key responsibility of the NCA is to perform pharmacovigilance inspections and ensure compliance. Adequate resources should be made available for this activity. The NCA should implement a risk-based approach to inspection frequency and scope.

NCAs may choose to combine pharmacovigilance, product quality surveillance, routine inspections, and control of advert and promotion into a single unit ensuring most efficient use of resources. International/regional collaboration in regulatory activities can also help to reduce duplicative activities.

Types of inspections

a. **Routine inspections:** Routine pharmacovigilance inspections are scheduled as part of the inspection program. There is no specific trigger for these inspections, although a risk-based approach to prioritising them should be taken

b. **For cause inspections**: For cause inspections are undertaken in response to specific triggers where a pharmacovigilance inspection is the appropriate way to examine the issues.

c. **Announced and unannounced inspections:** a MAH is expected to be continually compliant and ready for an inspection at any time. However unannounced inspections need a reasonable justification, as they are a less effective use of the inspector's and company's time. Announced inspections allow the company to ensure that all relevant personnel are available on the day, and that all documentation is retrieved and assembled for inspection.

d. **Re-inspections:** these may be necessary to follow-up an inspection where serious or multiple non-compliant issues were identified.

e. **Desktop/Paper inspections:** Remote inspection of a pharmacovigilance system and documentation through a request for specific documentation.

Internal audits

Responsibilities of MAH

a. Internal audits of the pharmacovigilance system should be performed, preferably by the quality department, at regular intervals or risk based
b. Corrective and preventative actions (CAPAs) described in the final audit report should be documented and completed in a timely manner.

Responsibilities of NCA

a. Ensure that an adequate internal pharmacovigilance audit program is in place
b. Internal audit reports are confidential and not subject to authority inspection.

Glossary

AE	Adverse Event
AER	Adverse Event Report
CAPA	Corrective and Preventive Actions
CIOMS	Council for International Organizations of Medical Sciences
DLP	Data Lock Point
GL	Guideline
HLT	High Level Term
IBD	International Birth Date
IRR	Incidence reporting rate
MA	Marketing Authorisation (also known as a product licence or registration)
MAH	Marketing Authorisation Holder
NCA	National Competent Authority
PSR	Periodic Safety Report
PT	Preferred Term
SPC	Summary of Product Characteristics
SOC	System Organ Class
VeDDRA	Veterinary Dictionary for Drug Regulatory Activities – list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products
VMP	Veterinary Medicinal Product
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products VICH guideline
VICH GL	VICH guideline

Definitions

1. The WHO definition of pharmacovigilance: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
2. The CIOMS definition of signal management: information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.
3. CIOMS frequency grouping of AE: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); Frequency not known (cannot be estimated from the available data).

Annex: Veterinary Suspected Adverse Reaction Report Form

Form to be sent to (Name and address of the relevant Regulatory authority)		**IN CONFIDENCE** For official use only Ref. Number: **Initial report** ☐ / **Follow-up report** ☐
Fax:	Phone:	
E-mail:	Website:	

IDENTIFICATION	**NAME AND ADDRESS OF SENDER**	**NAME & ADDRESS / REF. OF PATIENT**
Safety issue in animals ☐ in humans ☐ Lack of expected efficacy ☐ Withdrawal period issues ☐ Environmental problems ☐	Veterinarian ☐ Pharmacist ☐ Other ☐ Name: Address: Phone: Email:	(according to national law) Name: Address: Ref.:

PATIENT(S) Animal(s) ☐ Humans (for humans fill only age and sex below) ☐

Species	**Breed**	**Sex**	**Status**	**Age**	**Weight**	**Reason for treatment**
		Female ☐ Male ☐	Neutered ☐ Pregnant ☐			

VETERINARY MEDICINAL PRODUCTS ADMINISTERED BEFORE THE SUSPECTED ADVERSE REACTION

(if more products are administered concurrently than the number of boxes available, please duplicate this form)

	1	2	3
Name of the veterinary medicinal product (VMP) administered			
Pharmaceutical form & strength (ex: 100 mg tablets)			
Marketing Authorisation number			
Batch number			
Route/site of administration			
Dose / Frequency			
Duration of treatment / Exposure Start Date End Date			
Who administered the VMP? (veterinarian, owner, other)			
Do you think that the reaction is due to this product?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Has the Marketing Authorisation Holder (MAH) been informed?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐

Suspected adverse reaction date ___/_____/____	**Time between administration and event** (in minutes, hours or days)	Number treated: Number reacted: Number dead:	Duration of the adverse reaction in minutes, hours or days

DESCRIPTION OF THE EVENT (Safety issues in animals or Safety issues in humans/Lack of expected efficacy/Withdrawal period/environmental problems)
Please describe:

Indicate also **(a)** indicate the medical condition of the animal prior to the product administration; **(b)** if the reaction has been treated, how and with what and what was the result; **(c)** if the product(s) have been withdrawn and what happened (dechallenge) or if the animal(s) have been retreated with the product(s) and what happened (rechallenge) and if the reaction has been treated, how and with what and what was the result?"

OTHER RELEVANT DATA (ATTACH FURTHER PAPERS IF NECESSARY e.g. investigation carried out or ongoing, a copy of medical report for human cases)

HUMAN CASE

If the reported case refers to a human being, please also complete the details of exposure below

Contact with treated animal ☐
Oral ingestion ☐
Topical exposure ☐
Ocular exposure ☐
Injection exposure ☐ finger ☐ hand ☐ joint ☐ other ☐
Other (deliberate...) ☐

Exposure dose:

If you do **not** agree that your complete name and address are send to the MAH if further information requested, please tick the box. ☐

Date: **Place:** **Name and signature of sender:**

Contact point (Phone):
(if different from the number on page 1)

Prepared by **HealthforAnimals** in support of the OIE 6th cycle focal point training for veterinary products and in alignment with VICH guidance and international standards