Workshop session 7
Safety surveillance in the market: Pharmacovigilance

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Global Animal Health
Workshop 2017
Good Regulatory Practice for the Marketing Authorisation of Veterinary Products in an African Context

Organising Committee:
Session objective:

- Discuss the essential elements of a basic PhV system
- Share experiences on the development of PhV systems and processes:
  - What challenges are encountered
  - Recommendations for successful implementation
Pharmacovigilance has been defined by the World Health Organization as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.” The aims of pharmacovigilance (PhV) are to enhance patient care and patient safety in relation to the use of medicines; and to support public health programmes by providing reliable, balanced information for the effective assessment of the risk-benefit profile of medicines.

(WHO definition)

In VICH GL 24, pharmacovigilance of VMPs is defined as “the detection and investigation of the effects of the use of these products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products.”

The aim of a pharmacovigilance system is to monitor medicine safety and efficacy on an ongoing basis and to identify any changes in the risks and benefits (including efficacy) arising from the use of a VMP.

Changes might include:
• A new adverse effect (previously unknown) in the target species or user
• A change in the rate of incidence of a known adverse effect (product sales volumes are required to calculate the rate of incidence)
• A change in the rate of efficacy.
In VICH GL 24, an adverse event (AE) is defined as “any observation in animals, whether or not considered to be product-related, that is unfavorable and unintended and that occurs after any use of a VMP. It is important to note that whether or not it is initially considered to be product-related, if it is regarded as unfavorable and unintended, it should be reported as an AE.

The scope of the reporting system includes, as standard:
- reports of lack of expected efficacy (effectiveness) of a VMP
- adverse effects associated with ‘off-label’ use or misuse
- harmful and unintended effects in humans exposed to VMPs.

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In VICH GL 24, an adverse event (AE) is defined as “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)”. It is important to note that whether or not it is initially considered to be product-related, if it is regarded as unfavorable and unintended, it should be reported as an AE.

The scope of the reporting system includes, as standard:
- Adverse effects experienced by an animal following the use of a product
- Reports of lack of expected efficacy (effectiveness) of a product when used in line with the label recommendations
- Adverse effects associated with ‘off-label’ use or misuse
- Harmful and unintended effects in humans exposed to VMPs.

Other definitions presented in VICH GL 24 include:
- **Serious Adverse Event**: A serious adverse event is any adverse event which 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.

- **Unexpected Adverse Event**: An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labeling or approved documents describing expected adverse events for a VMP.
Why is PhV important?

It is important to continually monitor the safety of a VMP after it moves from development into the wider population.

During product development, pre-authorisation studies (for example, target animal safety studies, field studies) may identify common AEs.

However, the size and scope of the safety evaluation under field conditions is typically 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 important to put in place systems and procedures to collect and analyze reports from the field, to confirm or further improve knowledge about the product’s safety profile in the market place.

In addition to gathering safety information on the wider target population when the product is administered in accordance with the authorised conditions of use, the pharmacovigilance system also facilitates the collection of safety information associated with off-label use (for example, use at overdose, use in a different species) or misuse of a product.
What are the benefits of an effective pharmacovigilance system?

To ensure the health and welfare of animals and humans by:
- Continued monitoring
- Providing assurances on the continued safety
- Increased knowledge of the safety profile
- Updated and improved label warnings
- If necessary, removal from the marketplace of VMPs (or a batch)
What are the essential elements of an effective PhV system?

An effective pharmacovigilance system should function to:
- ensure collection of key information (adverse event reports), its safe storage and retrieval
- allow for adequate assessment of PhV data, by product and by groups of similar products
- allow for good, open communication (between regulatory authority (RA) and the marketing authorization holder (MAH), between RA and the reporter),
- identify important risks in a timely manner (for example, by systematic monitoring), and
- facilitate timely communication of any important new information.

In the rare situation of a major safety issue, active incident/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. It is also necessary to have a system to be able to recall a product or a batch from the marketplace.
Developing a PhV system

• Draft legislation for PhV: It is necessary to provide a legal basis for reporting and follow-up measures (taking appropriate regulatory action in the case of an identified risk).

• Plan PhV-system in regulatory authority: responsibility, level of ambition, cooperation in region, practical work, etc

• Define responsibilities and obligations of regulatory authority and of companies, so it is clear who is responsible for what: collecting, storing and analyzing the pharmacovigilance data and communication of adverse event information, when applicable.

• Align with international definitions/practices: Alignment with internationally harmonized definitions and adverse event collection formats (i.e. VICH GL 24, 30 and 42 - http://www.vichsec.org/guidelines/pharmacovigilance.html) enables consistent exchange of information between the RA and the MAH or between different RAs and reduces 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.

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• Consult draft plans with stakeholders: 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 organizations, 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...).

• Establish necessary documentation and systems
  • Reporting form for adverse events (AE)
  • Filing system for AE-reports:
    Paper → small electronic system → database
  • Tools for analysis of data; signal detection; trend analysis; trigger thresholds
  • Operating procedures
  • Feedback communication.
Basic PhV requirements in legislation:

- Definitions of adverse events, scope of PhV, surveillance, timelines
  - Definitions – see VICH GL24
- Obligation for companies to
  - receive AE-reports from vets/users/owners
  - analyse the AE-reports and survey their products in general
  - inform authorities.
- Possibility for authorities to
  - receive AE-reports from vets/users/owners (must communicate reports to MAH)
  - inspect to evaluate company compliance
  - analyse data from PhV or other sources
  - take necessary actions based on PhV data.
- Exchange of AE-reports between authorities and companies

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• Possibility for authorities to
  • receive AE-reports from vets/users/owners (must communicate reports to MAH)
  • inspect to evaluate company compliance
  • analyse data from PhV or other sources, such as published literature
  • take necessary actions based on PhV data, e.g.
    • Require a new safety warning in the product literature
    • Communicate to the veterinary profession of other end-users
    • Require follow-up studies
    • Require more intense PhV surveillance
PhV guidelines:

- Keep legal requirements at a high level.
  - 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 or advances in information technology.

- Details communicated via guidelines:
  - Guidance for marketing authorisation holders (MAH):
    - Need for a named PhV contact point
    - Information collection format (and language)
    - Format and timelines for transmission of reports to authority (see http://www.vichsec.org/guidelines/pharmacovigilance.html)
    - Rules relating to communication to the customer or wider public.
  - Guidance for Authority:
    - Information collection and storage
    - Timelines for processing of reports
    - Approach to causality assessment and data analyses
    - How decisions on the need for action are taken
    - Communication with reporter, MAH and wider public
    - Evaluating MAH compliance (including on-site inspections).
Individual adverse event report

A valid report will require at least the following core details:

- An identifiable reporter
- Animal/human details
- Suspect product
- Event details

For a full scientific evaluation, further information is desirable and should be provided, if available.

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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 EMA CVMP Reporting form available at https://eudravigilance.ema.europa.eu/veterinary/089304en.pdf).

- A valid report will require at least the following core details:
  - An identifiable reporter (such as a veterinary practitioner, other retailer or animal owner). Other contact information (address, phone number, email, etc.) if available.
  - Animal/human details: Number, species, age, sex
  - Suspect product: Name and authorisation number
  - Event details. 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.
For a full scientific evaluation, further information is desirable and should be provided, if available:

- Reason for use
- Health status prior to treatment
- Dose administered
- Batch number of product
- Laboratory findings
- Post mortem examination findings.

See also slides 2 and 3 in annex for additional information on processing AE reports and analyzing AE data
Questions to consider:

▶ What practical steps need to be taken to successfully implement a PhV system in the regulatory authority?
  • What challenges have been encountered?
▶ What is the approach to processing reports?
▶ What systems are in use to ‘house’/analyse data?
▶ Are there opportunities for regional cooperation? What are the potential benefits? How is it being achieved?
▶ Promoting PhV – how is this being done?

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Notes
See also slides in annex relating to these questions
Access to further information

- Directive 200182/EC (Title VII)

- Eudralex, Volume 9B – guidelines on pharmacovigilance for medicinal products for veterinary use

- VICH Guidelines [www.vichsec.org](http://www.vichsec.org)
  - GL 24: definitions, basic PhV process
  - GL 29: management of periodic safety updates
  - GL 30 and 42: adverse event collection formats.

- The Essentials of veterinary pharmacovigilance
ANNEX – additional information

In relation to the questions, the following additional information is provided in this annex:

1. Practical steps to successfully implement a PhV system
2. What is the approach to processing reports?
3. What systems are in use to ‘house’/analyse data?
4. Are there opportunities for regional cooperation?
5. Promoting PhV – how is this being done?

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1. Practical steps to successfully implement a PhV system

- Define PhV-responsibility (who does what)
- Realistic ambitions

- Communication and awareness plan
- Training?
- Make companies and vets aware of their obligations
- Set deadline for companies to implement in-house systems and procedures (compliance)
- Spread the PhV-message to vets/users/owners (use key opinion leaders, local animal health organisations, local industry representatives)
- Standard reporting form available on website, paper, by telephone, on conferences, etc
- Start analysing across substances, products, species
- Consider using a risk-based approach, where the surveillance intensity is proportional with the expected risk level.

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2. What is the approach to processing reports?

- Immediately after AE-report is received:
  - case-number and acknowledge receipt
  - causality assessment by Agency-vet:
    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.
  - decision on action/no-action, or request more information, etc

- PhV-report forwarded to Company
  - NB: Protection of personal data of reporter/owner may be required

- Filing for future retrieval/analysis

- Routine surveillance (risk based approach).

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3. What systems are in use to ‘house’/analyse data?

- From paper → small electronic system → database
- Simple (vet-specific) database with international compatibility is preferable
- Tools for analysing data in the database are important
- There are hurdles for a large regional/international database, for example:
  - IT-compatibility for existing national databases
  - Product database (same product with different names must be "linked")
  - Who is responsible for analysing data
  - "Access to data"-agreements.

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4. Are there opportunities for regional cooperation? What are the potential benefits? How is it being achieved?

► Aim for regional cooperation if possible, but requires a harmonized approach
  • Language
  • Need for common definitions
  • Need for standardization of terminology/reporting format
  • Align with international standards.

► Benefits
  • Allows for quick implementation.
  • Easier for competent authorities to co-operate/share the work.
  • The same VMP may be supplied to many countries; allows pooling and sharing of safety surveillance data.
  • More efficient use of resources (competent authorities and industry). Avoids duplication of tasks and reformatting of data.
  • One set of international standards improves compliance by removing administrative hurdles.

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5. Promoting PhV – how is this being done?

- Receipt letter to vets/users/owners, (and companies) who have reported AEs
- Personal response to a few reporters if additional information is needed
- Annual PhV-report in Vet magazine
- PhV-presentation for all graduating vets
- Education: module on PhV in vet university
- Ad-hoc presentations at vet conferences and Industry association meetings
- AE-reporting form easily available.

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