Adverse Event Reporting and Signal Detection in Veterinary Pharmacovigilance –

“EVVet Data Warehouse: current situation"
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At time of granting a marketing authorisation of a veterinary medicinal product (VMP) the drug safety information from clinical trials is incomplete

- Limited number of tested animals
- All possible adverse events (AE) identified?
- Drug interactions detected?
- What happens after long-term use?
- No 'real world' data

The risk-benefit profile must be regularly re-evaluated

Pharmacovigilance
See Art 75 (2) of Regulation 2004/28/EG amending 2001/82/EG
- Recording and reporting obligations of MAH

See Volume 9B „The Rules Governing Medicinal Products in the European Union“
- Part I: Guidelines for MAHs: Adverse event reporting
- Part II: Guidelines for CAs and the Agency: Signal detection

- **adverse reaction**
  - harmful and unintended reaction at normally used doses

- **serious adverse reaction**
  - results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly or birth defect, or which results in permanent or prolonged signs in the animals treated.
  - expedited reporting (15 days)
Definitions: directive 2004/28/EC and 2001/82/EC

**human adverse reaction**

a reaction that is noxious and unintended which occurs in a human being following exposure to a VMP

**unexpected adverse reaction**

adverse reaction, the nature, outcome and severity of which is not consistent with the Summary of Product Characteristics (SPC)

expedited reporting (15 days)


**Definitions**

**Definitions: directive 2004/28/EC and 2001/82/EC**

**Signal Detection**

Information reported on a possible causal relationship between an adverse event and a VMP, the relationship being unknown or previously incompletely documented.
also included in reporting obligations of the MAH:
- Lack of expected efficacy (after use according to SPC)
- off-lable use (use not according to SPC)
- Investigation of validity of withdrawal periods, e.g. violations of MRLs
- environmental problems arising from the use of VMPs
Adverse event reporting

Expedited reporting (15 days)

Reporting obligations apply to all authorised VMPs in the EEA

**SITUATION I**

Primary source (veterinarian or health care professional, owner, breeder) reports directly to the **NCA** on whose territory the adverse event occurred.

1. The national competent authority sends the message within 15 days to
   - EudraVigilance Veterinary Database (EVVet DB) (a)
   - the Marketing Authorisation Holder(s) (MAH(s)) of the suspect drug(s) (b)

   Primary source (Vet)
   
   National Competent Authority (NCA)
   
   MAH
   
   EVVET Database

(a) (b) (c) (d)
Expedited reporting (15 days)

SITUATION I
Primary source (veterinarian or health care professional, owner, breeder) reports directly to the NCA on whose territory the adverse event occurred.

2. The MAH checks the reports and sends acknowledgment (Ack) to the competent authority (c)

3. The NCA checks the Ack(s) received from EV vet database and MAH(s) and stores them locally (d)
SITUATION II

Primary source reports directly to MAH

1. The MAH (A) reports within 15 days (a) to NCA

2. The NCA checks the report, adds own assessment and sends report within 15 days (b) to EV Vet database where it becomes available for all CA’s of all MS

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Adverse event reporting
SITUATION III

MAH becomes aware of adverse event having occurred in a third country (suspected serious unexpected adverse events, human reactions or suspected transmission of infectious agent)

1. MAH reports within 15 days of becoming aware of the report to EudraVigilance Veterinary (a).

2. Report becomes available (c) to the Agency and all competent authorities of the Member States.
Electronic reporting of adverse events mandatory since November 2005 in EEA

EudraVigilance Veterinary Database (EVVet) has been developed
Web based user interface

Send ADRs and ACKs

ADRs → database queries

WebTrader

→ generate/load reports

EVVet Database

Data sets consisting of:

- Serious AE reports occurring within **EEA**
- Human AE reports
- Few non-serious cases on a voluntary basis
- Mix of unexpected, expected, serious and non-serious AE animal reports from third countries

?? What can we do with this data??
One of the aims of pharmacovigilance is the detection of new safety signals in relation to the use of VMPs. A signal should be considered, as information reported on possible causal relationship between adverse event and a VMP, the relationship being unknown or previously incompletely documented.
What is the task?
Analysis of AE
- In predefined time period
- for one specific VMP
- in one particular species

→ potential signal:
  - Number of AE ↑
  - Frequency of a particular clinical sign, compared with expected frequency ↑
  - New unidentified clinical sign
  - Potential impact on public or animal health
So what do we need?

A tool for

- Systematic standardised analysis of spontaneous reports with statistical methods
- Calculation of a correlation score between AE and drug
- Application of this score for the detection of safety problems
- Drug monitoring
Signal Detection: general principles

Challenge:

- Extensive data volume → Difficulty to gain overview
- Short surveillance periods given for centrally authorised products “CAPs”
- Surveillance should be reproducible, standardised and harmonised…

Goal: to extract meaningful, organised information from large complex databases

But how???
Signal Detection in the EU

Recommendations for basic surveillance

• To facilitate surveillance in a harmonised way
• Focus is first on CAPs (new substances, formulation etc).
• EVVet provides a data-processing network and database management system for the exchange, processing and evaluation of adverse events
• Use of EVVet data analysis system → EVVet DataWarehouse (DWH) for the analysis of the AE reports

Signal Detection subgroup (of PhVWP vet) was established
Signal Detection in EVVet Datawarehouse

WHEN:

• CAPs surveillance on monthly basis → responsible is rapporteur
• According to list of products and calendar for signal detection analysis available on EMA web site

WHERE:

• EVVet DWH is the central point of surveillance procedure

WHAT:

• Occurrence of specific VeDDRA terms in adverse event reports → synonyms are summarised
Short Break...
Proportional Reporting Ratio (PRR)

Disproportionality analysis to detect drug-adverse event combinations reported with a frequency that is disproportionately high with respect to some computed baseline.

<table>
<thead>
<tr>
<th></th>
<th>Event ( x )</th>
<th>All other events ( (\text{VeDDRA}) )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMP ( x )</td>
<td>( A )</td>
<td>( B )</td>
<td>( A+B )</td>
</tr>
<tr>
<td>All other VMP</td>
<td>( C )</td>
<td>( D )</td>
<td>( C+D )</td>
</tr>
<tr>
<td>Total</td>
<td>( A+C )</td>
<td>( B+D )</td>
<td>( A+B+C+D )</td>
</tr>
</tbody>
</table>

\[
\text{PRR} = \frac{A}{(A+B)} / \frac{C}{(C+D)}
\]

GUIDELINE ON THE USE OF STATISTICAL SIGNAL DETECTION METHODS IN THE EUDRAVIGILANCE DATA ANALYSIS SYSTEM (EMEA/106464/2006 rev. 1)
Signal criteria in EVVet Datawarehouse

According to Evans et al. a signal occurs if the following conditions are met:

Number of reports ≥ 3  
PRR ≥ 2  
χ² ≥ 4

Chi Square statistics for 2x2 tables:

\[
\chi^2 = \frac{(ad - bc)^2(a + b + c + d)}{(a + b)(c + d)(a + c)(b + d)}
\]

The Chi Square statistic compares the counts of categorical responses between two independent groups.


More precise definition of a signal: A relationship between a drug and event that is strong enough, using a \textit{predefined threshold or criteria set} by an analyst, to warrant further evaluation.

Almenoff et al. (2005): Perspectives on the use of data mining in pharmacovigilance. Drug Safety:28(1)
• An equivalent alternative to $\chi^2$ is to calculate a confidence interval around the PRR.

• Signal Detection in EVVet DWH $\rightarrow$ signal if PRR $\geq 2$
  (lower bound of the 95% confidence interval of PRR $\geq 1$)

• A signal occurs, if the value of PRR is greater than a predefined threshold.
  • If threshold is too low: many false positive signals
  • If threshold is too high: correct positive signals are missed
Signal Detection in EVVet Datawarehouse
## Signal Detection in EVVet Datawarehouse

<table>
<thead>
<tr>
<th>Principal ID</th>
<th>Reports and Duplicates</th>
<th>Occur Country</th>
<th>Species</th>
<th>Age of Treatment</th>
<th>Date of Event</th>
<th>Product(s)</th>
<th>Rec. Use?</th>
<th>CAUSALITY ASSESSMENT DETAIL</th>
</tr>
</thead>
</table>
| 012345       | 2                      | United States | Canine/dog | 2012-01-01       | 2012-01-01   | Yes        | Data      | MAH | Bilting,Drooling,Diarrhoea,Torticolosmus,Vertigo,Ataxia,Tremor disorder, NOS,Vertigo,Hypothermia

**Primary source**

- **Bilting,Drooling,Diarrhoea,Torticolosmus,Vertigo,Ataxia,Tremor disorder**
- **NOS,Vertigo,Hypothermia**

**CAUSALITY ASSESSMENT DETAIL**

- **MAH**
  - Bilting,Drooling,Diarrhoea,Torticolosmus,Vertigo,Ataxia,Tremor disorder, NOS,Vertigo,Hypothermia
- **NOS,Vertigo,Hypothermia**
  - Bilting,Drooling,Diarrhoea,Torticolosmus,Vertigo,Ataxia,Tremor disorder, NOS,Vertigo,Hypothermia

**Case no.:** 01 - Conclusive
Signal management: Clinical Evaluation of Signals

- Case evaluation of each case:
  - Chronological correlation
  - Dechallenge/Rechallenge
  - Pharmacological/toxicological profile of product
  - Additional data (for example: laboratory test results)
  - Known/Unknown AE
    → similar cases reported?
  - Other explanations (for example: underlying diseases, concomitant drugs)

Guideline on harmonising the Approach to Causality Assessment for adverse reactions to veterinary medicinal Products (EMEA/CVMP/552/03-Final)

A "probable"
B "possible"
O "unclassified"
N "unlikely"
Signal management: Results in VPhS database

Results and recommendation of signals are described in a filemaker-database.
Signal management: Recommendation for action

Options for signal management in DB: tick

- Cumulative review and comment request from MAH
- Issue to be addressed by MAH in next PSUR
  - No immediate action: to be monitored in the next period
  - Suspected signal not confirmed: no action required
- To be discussed at CVMP
- To be discussed at PhVWP
- None/not applicable
- Other
Summary

• Signal detection
• Signal validation
• Signal analysis and prioritisation
• Signal assessment
• Recommendation for action
• Exchange of information
Limits of Signal Detection

- Global amount of data is still limited
- Reports in DWH not complete (reporting of non-serious cases is voluntary)
- No sales volume → no incidence
- Fixed query → no individual approach
- Disregard of „N“ assessed cases
- No differentiation „suspect“ vs. „concomitant“ drug
- No signal detection for consumer safety, lack of efficacy or environmental protection
- One case ≠ one affected animal (herds)
Advantages

• Fast and global surveillance
• Easy to perform → PRR simple to calculate and interpret
Take home message

• Still under development

• Signal Detection is a procedure for CAP surveillance (at the moment)

• Analysis of data improves understanding of gathered information and allows drawing conclusions
Take home message

• Standardised method

• In veterinary pharmacovigilance a new approach for data management

• Quantity of PRR → no immediate information about the level of risk

• However: signal management measures are based on experience of assessor dealing with the information
Thank you for your attention!

Questions?

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