Pharmacovigilance Inspections of veterinary medicinal products

- Inspectors’ perspective -
Introduction

- Why and how do we conduct Pharmacovigilance (PhV) inspections?
- Is there any benefit to industry?
- Types of PhV inspections
- Current state of PhV inspections in the EEA/EU
- How could an inspection be prepared? What is inspected? How is an inspection conducted?
- Findings/Areas for improvement
- The way forward and conclusions
Why do we conduct Pharmacovigilance (PhV) inspections?

Because Competent Authorities (CAs) are expected to do so!

➢ Current legislation
  • See Art. 44 (1) of Regulation (EC) 726/2004
  • See Art. 80 of Directive 2001/82/EC
  • See Volume 9B „The Rules Governing Medicinal Products in the European Union“
Why do we conduct PhV inspections?

Current legislation

**Article 44 (1) of Regulation (EC) 726/2004**

The supervisory authorities shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the veterinary medicinal product or the manufacturer or importer established within the Community satisfies the requirements laid down in Titles IV, VII and VIII of Directive 2001/82/EC.
Why do we conduct PhV inspections?

Current legislation

Title VIII, Art. 80 of Directive 2001/82/EC

1. The competent authority of the Member State concerned shall ensure by means of repeated inspection that the legal requirements relating to veterinary medicinal products are complied with.

Such inspections shall be carried out by authorized representatives of the competent authority who shall be empowered to:

…

(c) examine any documents relating to the object of the inspection…
And how do we conduct PhV inspections?

➢ Described in current legislation

Volume 9B – The Rules Governing Medicinal Products in the European Union

- Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use -

Part I: Guidelines for Marketing Authorisation Holders (MAHs)

2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections
What is the role of the MAH?

To have

- An appropriately trained qualified person for pharmacovigilance (QPPV) at his disposal & a back-up procedure in the absence of the QPPV
  - (QPPV) Responsible for establishment and maintenance of PhV system
  - The one ultimate responsible person for all aspects of PhV in a company

- An appropriate PhV system in place
What is the role of the QPPV?

Current legislation:

- See Volume 9B – The Rules Governing Medicinal Products in the European Union
- Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use

Part I: Guidelines for Marketing Authorisation Holders (MAHs)

1. General Principles
1.2.1 The Role and Responsibilities of the QPPV

- **The QPPV should** have oversight of the PhV system in terms of structure and performance and be in a position to ensure in particular the above system components and processes, either directly or through supervision.
  - QPPV is **ultimately responsible** for all aspects of the Pharmacovigilance system of a company
  - Preferably **one person**
  - May delegate specific tasks under supervision, to appropriately qualified and trained individuals
  - QPPV should have **sufficient possibilities of decision making**
  - **Contactpoint for PhV inspections**
The oversight referred to above should cover the functioning of the MAHs pharmacovigilance system in all relevant aspects, including

– quality control and assurance procedures
– standard operating procedures, database operations
– Contractual arrangements, audit reports
– Compliance data
– Training of personnel

QPPV is link to PhV inspections
Why do we conduct PhV inspections?

The objectives of PhV inspections:

Is an appropriate PhV system in place

- To **assess** that the MAH has personnel, systems and facilities in place to meet his PhV obligations;
- To identify, record and address non-compliance which may pose a risk to public or animal health;
- To use the inspection results as a basis for enforcement action, where considered necessary?
Why do we conduct PhV inspections?

To reassure CAs that the MAHs have the resources to effectively **conduct** PhV of their authorised products!
Is there any benefit to industry?

➢ An opportunity for MAHs

- To **eliminate** fear from risks associated with medicinal products
- To **draw** attention to PhV within company
- To **revise** documents relating to PhV
- To have own PhV system audited/cross-checked from **external** point of view
- To identify gaps or missing links between PhV **units and other units of subsidiaries/affiliates/parent company**
Is there any benefit to industry?

• Address questions to CA
• Benefit from CAs experience inspecting other companies

For improving and strengthening PhV
What types of PhV inspections?

- **Routine inspections**
  - National inspection programmes
    - should be carried out on a regular basis
    - focus on the ability of the MAH to fulfil PhV obligations (previous inspection findings?)
    - Inspection of MAHs, contractors, licensing partners
  - CVMP inspection programme for CAPs:
    - will be carried out on a regular basis (3 yearly)
    - may be conducted as part of national programme
What types of PhV inspections?

- Targeted inspections
  - Based on triggers
    - May be conducted when a trigger is recognised
    - In general: non-compliance with a particular area of PhV legislation is considered a trigger
Current situation: PhV inspections in the EEA/EU

- So far about 16 MS conduct PhV inspections
- Varying number of MAHs or affiliate companies in MS (0-140)!
- Some countries unable to conduct inspections due to lack of resources at present
- Fee? No fee? Per site? Per activities?
Who conducts PhV inspections?  
For national/MR/DCP MA?

- Decision of the MS/CA. It could be:
  - CA PhV inspectors (e.g. Germany)
  - GMP/GCP inspector (e.g. France)
  - Human PhV inspector (e.g. Slovenia)
  - Sometimes part of GMP or GCP inspections or stand-alone PhV inspection
  - Other

- Example: a MS conducts PhV inspections on behalf of another
Who conducts PhV inspections for CAPs?

- MS/CA on behalf of the EMA
- CVMP inspection programme for CAPs and risk analysis criteria
- Conducted by CA in MS where QPPV resides
- Collaboration between CAs to minimise duplication and maximise coverage
- Inspectors of Rapporteur’s or Co-Rapporteur’s country may join the inspection
„An appropriate PhV system in place“
What is expected?

- The PhV system of the MAH comprises of
  - The collection, processing & reporting of adverse events (AEs)
  - The ability to process reports from different sources e.g. vets/owners, CAs, 3rd countries
  - The ability to report electronically to the CA
  - Preparation of PSURs – including benefit/risk and trend analysis of AEs (signal detection)
„An appropriate PhV system in place“
What is expected?

• Training of staff
• Storage and archiving of reports, database
• PhV arrangements with marketing companies etc.
• Quality Management: Are there written procedures? Structure? Auditing of subcontractors?

Keep calm…you nearly made it!

Foto: http://jsh-artpoint.tumblr.com
How could an inspection be prepared?

- Not much to do!
- No need to impress inspectors.
- Keep your PhV system up to date!!!

- Not a last minute activity!
- Use the guidance provided by legislation, Guidelines, QA teams
- Should be addressed as part of the Quality Management of PhV
How could an inspection be prepared?

- Continuous training of all concerned staff?
  - Documents?

- Periodic internal audits of PhV activities and systems should ensure that gaps are identified and addressed
  - Would recommend every 2-3 years
  - Anytime when there is a major change in the PhV system

- Internal audit prior to a planned inspection helpful
What happens?

*Before* inspection (MAH)

- Notice usually given by CA, a few weeks to a few months prior
- Information may be requested prior to the inspection
  - Structure of organisation & relevant names
  - SOPs and other procedures (only PhV)
  - DDPS - latest version
  - Listing of expedited cases for a given period
  - Calendars of PSURs for compliance with 60 days
  - Third party agreements
  - Product related issues
  - Agreement on logistics, participants, inspection plan
What happens?

Before inspection (CA)

- Provide MAH with draft agenda of inspection
- Ask PhV assessors for experience with MAH’s reporting, compliance etc.
- List all MAH’s current MAs
- Prepare SAR/SLEE for the audit to check database and assessment
- Choose PSURs or assessment reports to discuss with MAH
What happens?

During inspection:
What will inspectors look for/at?

➢ Opening meeting
  • Introduction of participants
  • Attendees: Inspector(s), PhV staff, QA staff, Management
  • Objectives and the remit of the inspection are agreed

➢ Inspection itself, can be a few hours to a few days
What happens? *During* inspection: What will inspectors look for/at?

5 W-questions (who, what, where, when, why)

How are

- AEs (SARs/SLEEs etc.) processed (templates?)
  - Maybe sales reps and/or other staff is interviewed as well
- AE entered in database (if approp.)
- trends and signals analysed
- interactions between products
- quality defects & AE reports identified
- PSURs created?

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What happens? *During* inspection: What will inspectors look for/at?

- **timelines met?**
- **PhV training:** is all staff, including technical, customer support, quality team, sales reps, security etc. – adequately trained?
- **Is staff aware of role in PhV and is QPPV aware of all PhV responsibilities?**
  - Be aware of national legislation
What happens? *During* inspection: What will inspectors look for/at?

- Do marketing agreements with other MAHs include PhV obligations (AE and PSURs)? Can subcontractors be audited?
- An effective computer/database system (if appropriate) to include:
  - Maintenance, Archiving, Security, Disaster recovery
What happens? *After* the inspection

- **Exit Meeting**
  - Attendees: Inspectors, PhV staff, QA staff, Management
  - Informal presentation of findings *at time of inspection*
    - Findings: non-compliant with current legal PhV obligations
    - Recommendations: Company to consider
What happens? After the inspection

- Draft inspection report submitted to MAH within 14 to 30 days
  - MAH may comment usually within 30 days
- Final inspection report with the commitment to submit an action plan
  - CA/MAH sets time limits for action as appropriate according to issue (depending on MS)
- CA will monitor the MAH’s compliance with the requested conditions
Example of key findings – problem areas

- Timelines!!!
  - Serious SAR/SLEEs are not reported within 15 days
  - Electronic reporting
  - Third country reporting

- QPPVs: Delayed response to CA requests

- QM: Gaps, missing links in SOPs or no written procedure for certain aspects e. g. PSURs

- Training: Some field staff not aware of need to report all cases including SLEEs
Example of key findings – problem areas

- Training: no tests for checking training efficacy
- PhV contracts: No PhV agreements with distributor, no auditing of distributor
- PSURs, poor literature research
- PSUR assessment reports: CA‘s comments not considered in the next PSUR
- No 24/7 Availability of local and EU QPPVs and their back-up
- Feasibility of urgent 24 hours safety restriction
The way forward

- Compliance and improvements seen as a result of inspections & better communication
- Quality & accuracy of electronic reporting improved
- Volume 9B made it easier to assess compliance
- Continuous training of EU PhV inspectors will bring further harmonisation
Conclusion

Vets, industry and CAs working together to make PhV more effective…for safe veterinary medicinal products!

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Thank you for your attention!

Questions?