Establishing a signal management process – experience to date with new procedures

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Topics

1) What is signal management?

2) What MAH signal management is in place under current procedures?

3) Thoughts for the future - MAH perspective

What is signal management?

- Why signal management?
  - **Are there <u>new</u> risks associated with an active substance or a veterinary medicinal product, or have known risks <u>changed</u>?**
- <u>Context</u>:
  - First step is signal detection, using:
    - ✓ statistical formulas – requires approx 500 cases on a product

      And/or
    - ✓ "manual" analysis of data – for example comparison with previous summary reports (PSURs) and ongoing case review.

What is signal management?

- Once a potential signal is detected, signal management requires further steps:
  - validation and confirmation of the signal
  - analysis and prioritization
  - signal assessment
  - recommend action
  - track the steps taken.

What MAH signal management is in place under current procedures?

- Activities vary greatly among different MAHs, dependent on the MAH size/portfolio (number of cases per product) and database tools.
- Currently MAHs do not have access to Eudravigilance data so using own database
- Validated veterinary specific PhV signal detection concepts and methods are still under development. No current detailed guidance available.
- Many MAHs have insufficient cases to use complex statistical tools
- MAHs may detect potential signals, or receive information/questions from regulatory authorities (for example following analysis in Eudravigilance)
- *Eudravigilance does not contain all cases from MAH (usually only expedited)*

What MAH signal management is in place under current procedures?

Some other aspects to consider:

- Overall data quality
- Number of animals reacting per case and not per clinical sign
- One ABON code per case
- Limitations of Trending & Signaling tool (e.g. no interface with sales)
- Automated signal detection algorithms can save time and identify signals earlier but if setup inappropriately will generate enough false signals to overwhelm resources for the detection of “true” signals.

Thoughts for the future - MAH perspective

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- **Overall aim:**
  - **Ensure the benefit-risk balance of the products is monitored:**
    - ✓ **Are there new risks associated with an active substance or a veterinary medicinal product?**
    - ✓ **Have known risks changed?**
    - ✓ Surveillance to be **Risk* based**
  - The vision for veterinary pharmacovigilance in European Union (EU) as foreseen in the legislative proposal is **the use of signal management processes** to achieve the aim.

*Risk = severity of hazard x probability (or frequency if known)

Thoughts for the future - MAH perspective

- All adverse events - *no distinction between serious (expedited) and non-serious* - will be sent to a single Union database.

  As more data is available in a single place, this should increase the statistical power.

- The MAH will continue to record all adverse events in the MAHs database; MAH can use own database and/or single Union database for signal detection.

- Surveillance will be performed by signal management processes , using a risk based approach.

- This risk based approach will eliminate purely administrative documents and replace them with a targeted approach, using resources more effectively (both MAHs and Competent Authorities)

Thoughts for the future - MAH perspective

- MAH will determine their monitoring frequency on a risk basis.
- The trigger level for further investigation must be defined.
- Possible criteria for risk:
  - New product
  - Type of product (e.g. active ingredients with higher toxicity profile)
  - Higher incidence rate of adverse events
  - Type of adverse events (seriousness)
  - New target species/new indication/new administration route/new formulation/ delivery device
  - Products with potentially higher risk for user or environmental safety
  - Vaccines (live/modified live vaccines, “modern technologies vaccines”)
  - ***…***

Thoughts for the future - MAH perspective

- Activities by the MAH can be tailored to meet the MAHs own portfolio rather than being driven to generate reports to the same cycle regardless of risk.

- Validated signals with important animal or public health impact or those which may significantly affect the benefit-risk profile of the VMP require urgent attention and will be prioritized for further management.

- Signal assessment evaluates a validated signal to identify the need for additional data collection or for any regulatory action.

Thoughts for the future - MAH perspective

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- MAHs and Competent Authorities will communicate validated signals that may pose a serious risk for animal or public health or environment and that may change significantly the benefit-risk profile of a product immediately as an Emerging Safety Issue.

- The MAH must be involved in signal assessment - this requires information concerning the number of doses which needs to be provided by the MAH within a reasonable timeframe (timings established using a risk based approach).

- The MAH should be consulted on the outcome and proposals for regulatory action, if any, before final decisions are taken and communicated.

Thoughts for the future - MAH perspective

- The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned active substance/VMP may also need to be communicated to the public including health care professionals.

- To avoid administrative burden (e.g. variations, labelling), a single assessment and single outcome by the Competent Authorities is a deliverable from the signal management process.

Next steps

- The new legislative proposals should be high level to allow for further technical development over the next 10-20 years

- The implementation of signal management to meet the proposals of the new legislation will require detailed guidance to be developed. This guidance should be developed in collaboration between the Competent Authorities, the Agency and MAHs, beginning as soon as possible and with built in flexibility for modifications to meet technical advances.

- IFAH-Europe is firmly convinced that this system will function to increase the level of true pharmacovigilance in the best interests of animal and human health and would welcome the opportunity to contribute to the development of detailed guidance

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Thank you for your attention!

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