THE VOICE OF THE ANIMAL MEDICINES INDUSTRY

Position paper

3rd July 2020

AnimalhealthEurope comments to the EMA advice to the European Commission on the GVP

Implementing measures under Article 77 (6) of Regulation (EU) 2019/6 as regards "Good Pharmacovigilance Practice" for veterinary medicinal products.

General comments

AnimalhealthEurope would like to thank the Commission for the opportunity to provide comments on this important document.

AnimalhealthEurope very much appreciates the reminder that is made in "Considerations and rationale for the recommendations" section that:

- Regulation (EU) 2019/6 aims to reduce the administrative burden.
- The system should be adaptable and flexible to the needs of all stakeholders.
- The recommendations made in this advice take into account the experience gained from the implementation of similar legislation relating to human pharmacovigilance. AnimalhealthEurope would like to additionally emphasise the need to adapt any guidance from human pharmacovigilance to the veterinary sector reality and needs.

Following review of the document, we identified some key points we would like to share.

Note: There may appear to be some duplication in some of these points – but this reflects the sections where they appear duplicated within the GVP document. It is also a deliberate choice to work chapter by chapter following the construction of the expert advice in order to avoid missing anything.

We believe further clarification and discussion to address these points would be beneficial to all stakeholders:

In the "Overview of recommendations" section we have noted:

- A guidance to supplement the recommendations in this document will be developed. AnimalhealthEurope would very much appreciate the opportunity to contribute to the early development of these important guidelines to ensure they will provide the necessary additional clarity for all stakeholders in a timely manner.
- Marketing Authorisation Holders (MAHs) will have to record the results and outcomes of the signal management process including a conclusion on the benefit – risk balance into the pharmacovigilance database. Given the high number of data involved for some MAHs, we would strongly recommend developing a telematics-based solution to ease the management of the data and avoid the administrative burden that a manual manipulation would generate.
- A list of "Medically important VeDDRA terms" will be established. We understand that this list should be short and maybe specific to particular product classes to ensure it will have the intended added value, and not just become an additional administrative burden.

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- According to Article 75(3) of Regulation (EU) 2019/6, the general public shall be provided with access to the number and the incidence of adverse events reported each year, broken down by veterinary medicinal product, animal species and type of adverse event. To achieve this, EMA recommends the MAHs provide an estimation of treated animals. Article 58(12) of Regulation (EU) 2019/6 also requires the MAHs to record in the Union Product Database (UPD) the annual volume of sales of each of its veterinary medicinal products.

  AnimalhealthEurope considers that sales data recording into the databases could have a major impact on administrative burden and should be studied carefully. Based on the discussion during the NVR Stakeholder meeting on 25 June 2020, AnimalhealthEurope is intending to review and update the earlier proposals made on the concept of sales data and looks forward to working with the EMA to identify solutions which will meet the needs of the regulation as efficiently as possible for all MAHs (multinational to Small and Medium Enterprises (SMEs)).

- AnimalhealthEurope strongly supports the concept of "risk-based approach" with defined key elements as this will most likely reduce unnecessary burden.

Specific Comments/Questions

1. Reporting and recording of adverse events and the signal management process

Additional clarification on the signal detection and signal management (including evaluation) process is requested for the following points:

- The roles and responsibilities of the MAH and the competent authorities in that process.
- It is important MAHs have the choice to do signal detection and signal management in the Union Pharmacovigilance Veterinary Database (UPhVD) **or in their own database**.
  - Regulation 2019/06 does not require a MAH to perform either signal detection or signal management within the UPhVD – though there clearly is a requirement to record the outcome of the MAH's signal management in the UPhVD.
  - Requiring the MAH to perform signal detection and signal management in the UPhVD could represent a dramatic increase in administrative burden for all MAHs: e.g. for large MAHs who have to conduct separate signal detection and management for Regulatory Agencies in other regions and also for SMEs where products may have very few adverse events. It needs to be taken into consideration that many MAHs have invested substantially to implement sophisticated signal management systems using their own databases. The benefits are a defined process with comparable results already available, a more consistent dataset than could be achievable with the UPhVD and all cases already available in the MAH's database for concerned products (serious and non-serious; UPhVD initially lacks non-serious cases for most products).
  - The document suggests an increase in efficiency if all parties involved use the same tools. However, for MAHs with global pharmacovigilance requirements, this would result in an increase in administrative burden as they will have to do signal detection for other jurisdictions in their own databases.
- Additional clarification on case handling is requested, for example:
  - The process for how the MAH would be made aware of cases available in the UPhVD, which have not been directly reported to the MAH, is unclear. This applies to cases reported to National Competent Authorities (NCAs) and cases reported to one MAH but involving products of other MAHs (including third country cases).
  - It is unclear how the MAH would receive all important information such as the case narrative. Further clarification on the process would be needed to understand, if the MAH would be informed automatically (as current situation) or if the MAH would need to actively search the UPhVD and import cases into their own database (e.g., via XML-file download). Feedback from

Human Health (HH) indicates that the process to actively search for cases reported for MAH's own products is cumbersome and increases the MAH's administrative burden.

- The need to request single narratives is seen as a significant burden by HH. Same uncertainty applies for follow-up information reported to UPhVD directly without involving the MAH.

- In addition, the stated intent of EMA and the NCAs to be aligned with the requirements of VICH, means that obligations which MAHs operate under on a global basis and the requirements for further reporting of EEA or third country source cases to other Regulatory Authorities, should be taken into consideration at this early stage to avoid the unintended but substantial increase in administrative burden for MAHs.

1.1.1: Minimum requirements for adverse event reports

- The document adds 'source' to the identifiable reporter criteria. It is unclear what is meant by that. A source does not equal an identifiable reporter.
- When a product involved in an adverse event is only identified by the active substance (and e.g. the dosage form), the product may not be identifiable if there are multiple VMPs from different MAHs that match the available information. MAHs are only responsible for their own products and should therefore not be required to report cases when it is not confirmed any of their products was used. The rationale for including the recommendation for reporting cases where only active ingredient of the product involved is known should be explained.

1.1.2 Veterinary medicinal product names

- To avoid an increase in the MAH's administrative burden, AnimalhealthEurope thinks that other solutions should be considered rather than maintaining a large and frequently changing list of third country product names in the UPhVD, for example modifying the EMA XML message such that MAHs include a MAH defined product group identifier "PGI" (to be precisely defined) which would link together product names in different countries that the MAH considered to be essentially similar.

1.1.3 Use of standard terminology for coding adverse events

- There is a **critical need** for the synchronised implementation of updates to internationally agreed standard lists to ensure that the latest agreed versions are used for coding adverse events. These lists include VeDDRA, species and breed list and VICH GL42 data elements guideline. MAHs do try to promptly update their systems but in practice, MAHs cannot update their systems until all worldwide agencies will be able to accept the most recent version.
- Duplicate detection is a **major concern**. It needs to be clarified which party is responsible for duplicate detection and how differences in opinion will be resolved. The experience learned from HH is that this is already a major issue.

1.1.4 Measures for ensuring data completeness

- Reasonable efforts to have comprehensive and good quality adverse event data should be done not only by MAHs but by all stakeholders including the NCAs.

1.1.5 Requirement for English language summaries of adverse event reports (case narratives) reported in languages other than English

- This is a **major concern** as it is a significant change to current practice leading to significant increase in workload for the MAH, and the rationale for such requirement is unclear. Local language data, if applicable, should be available on inspection only, as part of the source data. The practical implications of this recommendation would lead to a complete contradiction with

the general objective of the Regulation and of this document to reduce the administrative burden.

All MAHs and NCAs should use English language for reporting cases. This is consistent with the rationale section that refers to VICH GL 24 and VICH GL 29 that state:

"Requirements for translation - the VICH agreed upon language is English; however, the Pharmacovigilance EWG felt that regional requirements need to remain. No recommendations at this time for changes to VICH GLs."

- To reach good quality and consistency of adverse event data, one of the important elements is to have a description of the case in English.
- Further in the document, it is recognised that the signal detection and management process still requires expert resource and manual input, including clinical judgement, to assess the data constituting a signal, which further highlights the absolutely essential nature for English language narratives.
- If Member States revert to reporting case narratives in their official languages, it will be a major increase in administrative burden (currently only one NCA is requesting to use their local language) and translations can only be requested by the Agency or other Member States for evaluation of potential signals. MAHs increasingly have reporting obligations for EEA source cases to other Regulatory Agencies and will need to conduct routine signal management and therefore there is an absolute requirement to receive high quality English narratives for all cases involving their products (as MAH currently provide to NCAs).

1.1.6 Requirements for reporting adverse events published in scientific literature

- AnimalhealthEurope appreciates that literature searches should also follow the key principle of a risk-based approach.
- So far, in veterinary pharmacovigilance it has not been identified that adverse event reports from literature have brought major additional value or have been a significant source of otherwise unreported safety information, and therefore this needs to be addressed proportionally. Continuous evaluation of the benefit-risk balance of the VMPs is ensured by key local literature review on a regular basis.
- In addition, not every literature reference has a digital object identifier.

1.1.7 Reporting of adverse events following the use of human medicinal products

- It is AnimalhealthEurope's understanding that all recommendations in this section apply to the Agency and NCAs only.

1.2 Provision of data for calculation of incidence of adverse events reported to the pharmacovigilance database

- As currently recommended, appropriate telematics solutions need to be in place to provide the estimate of animals treated.
  - AnimalhealthEurope is concerned with the potential for increased administrative burden for MAHs associated with the provision of the total estimated number of animals treated and for each target species, presented by pharmaceutical form and strength. Additional discussion with the authorities on the best way forward on this is required to prevent a disproportionate increase in administrative burden for MAHs.
  - Alternative proposals that consider more advanced IT solutions should be investigated (e.g., updating species splits and methodology on an annual basis in the system, so that the number of treated animals can be calculated automatically). In addition, the possibility of minimising

the data to be submitted should be considered (e.g., a single figure for EEA and a single figure for third countries by species).

- Additional clarity is also needed on the information to be provided and methodology to be followed for the situation where target species differ by EU country or by third countries.
- The Data Lock Point (DLP) concept is not mentioned in Regulation 2019/06, and there are no further details provided in this recommendation. While DLPs may be attractive for NCAs in terms of spreading work throughout the year, MAHs have a requirement for continuous monitoring of the benefit-risk profile for their products and being tied to a formal DLP may substantially increase the administrative burden. If DLPs are introduced, MAHs would appreciate greater flexibility for changing DLPs.
- The provision of treated animal data by DLP appears inconsistent with the primary legislation which is that the incidence has to be provided each year (which would be usually understood to be calendar year). In addition, it should refer to article 75.3.a and not to article 81.
- It is proposed that incidence figures foreseen for publication will relate to adverse events for which a causal relationship between product use and the observed event may not yet have been established and therefore, disclaimers will be published to clarify the limitations of the data published and to highlight that no definitive conclusion on the causal association can be made on the basis of those figures alone.

  Additional clarification if and how the ABON causality will be considered for these activities should be provided.

  AnimalhealthEurope is concerned with misinterpretation of the published pharmacovigilance data. Disclaimers are not considered sufficient and are not understood by veterinarians or the wider general public.

1.3 The signal management process defined in Article 4, provided for in Article 81 and explained in Recital 63 of the Regulation

- Further clarification is needed on how this risk-based approach interacts with DLPs mentioned in 1.2. It is unclear, if these are the same DLPs that are set for PSUR work-sharing.
- If MAHs have to do signal detection / signal management in UPhVD (which is not clear) this is a dramatic increase in administrative burden with considerable downsides as explained above.
- Data and evaluations from both, the MAH and the authorities, should be considered for any regulatory measures such as changes to the SPC.
- There is a need for complete narratives in English as otherwise the signal detection / signal management process would increase the administrative burden for MAHs significantly. As stated in the scientific recommendations "*Experience from signal management for human medicinal products and for centrally authorised veterinary medicinal products has demonstrated that, despite the availability of more powerful analytic tools and access to data over the life-cycle of a product, the process still requires expert resource and manual input, including clinical judgement, to assess the data constituting a signal*."
- What is publicly visible when authorities and MAHs have entered their signal management evaluations in the UPhVD is not clear. AnimalhealthEurope requests to have a clear view on the authority's signal management evaluations for their own products.
- Medically important VeDDRA terms: We understand that this list should be short and maybe specific to particular product classes; for example, it will not be possible to evaluate signals for many vaccines nearly on a weekly basis should a term such as 'anaphylaxis' be included in this list.
- The process for generating the summary for the General Public (Art 75.3.b) is unclear (e.g., will it be the MAH or NCAs? Will it be comparable to the current Pharmacovigilance Bulletin published by the Agency?).

1.3.2 Signal management activities undertaken by marketing authorisation holders

- AnimalhealthEurope considers flexibility to be an essential key element for any signal detection /signal management activity conducted by MAHs, using either their own database or the UPhVD. Any duplication of efforts needs to be avoided as this would not comply with the key principle of the new veterinary regulation to decrease administrative burden.
- Signal detection / signal management needs to work for small companies and multinational MAHs that have already established sophisticated signal detection /signal management processes using their own database and which have to comply with global requirements. In addition, for a number of years the denominator of the UPhVD will not be stable as it is missing non-serious cases, which can result in the detection of false positive signals, but also in overlooking true signals. For these reasons, it is paramount that MAHs have the option to use their own systems.

1.3.3 Signal management related activities undertaken by competent authorities and the Agency

- This section should include liaison with MAHs ideally with the provision of a telematics solution to send such signals requiring MAH assessment to MAH databases. There is no indication that MAHs will be involved in this discussion or would even be granted access to the regulator's evaluation.
- As previously stated, AnimalhealthEurope is strongly of the opinion that the aim to minimise administrative burden can only be achieved with flexibility for MAHs on choosing the database (UPhVD or own database) and timing of signal detection / signal management.

1.3.4 Alerts related to pharmacovigilance data

- The data-processing network envisaged here suggests that there should be a telematics link between the Agency and MAH systems, which is strongly supported by AnimalhealthEurope.

2. Pharmacovigilance communication

- Lessons learnt from HH is that it is very difficult and resource intensive to implement meaningful metrics for measuring the effectiveness of communication. It is therefore seen as a disproportionate requirement for Animal Health.

2.2 Availability of a link to the electronic version of the latest summary of product characteristics in the printed package inserts

- This chapter seems to be better addressed as a packaging issue and not placed under pharmacovigilance.
- AnimalhealthEurope can see the potential benefits (the expectation is that this will reduce some of the requirements for immediate implementation of certain packaging items in some countries), but it is critical that the link does not change with SPC changes – the link must remain constant for each product / language combination to avoid unnecessary minor packaging errors.
- In order not to delay the availability of newly registered products on the market, the NCA / Agency should make available a link/QR code at the conclusion of the scientific assessment and before issuing the marketing authorisation (MA) itself. AnimalhealthEurope conceives of two different approaches: 1.) The link/QR code could point to a placeholder in the UPD. As long as there is no approved SPC available, the link/QR code should show e.g. a warning message like "The SPC for this product is not yet available". 2.) The link/QR code is pointing to a resource at the MAH. As soon as the final MA approval by the NCA / Agency is obtained, the MAH redirects to the UPD entry at the NCA / Agency.

- The transition period for VMPs placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004, as mentioned in Article 152 (2) of Regulation (EU) 2019/6, should also apply to the link/QR code to the electronic version of the latest SPC in the printed package inserts.

Conclusions

- Reduction of administrative burden seems to be achieved for NCA / Agency – but only by increasing impact and burden for MAHs, which is inconsistent with the aims and impact assessment for veterinary pharmacovigilance of Regulation 2019/06. Further discussions are required to make more progress on reducing the administrative burden for MAHs. For example:
    - MAHs need the choice to do signal management in the Union Pharmacovigilance Veterinary Database (UPhVD) or in their own database.
    - Provision of the number of treated animals needs to be discussed in sufficient detail as otherwise it will be a significant administrative burden for MAHs.
    - Sales data recording into the databases could have a major impact on administrative burden and should be studied carefully.
    - The provision of the original verbatim text and a summary thereof in English would represent a massive increase in burden and is in contradiction with the VICH GL. It is a retrograde step from current practices for all apart from one NCA.
- Functional telematics solutions are essential to reduce the administrative burden for all stakeholders in several aspects of pharmacovigilance (e.g., provision of sales data, number of animals treated, methodology of product use, reporting of signal detection /signal management outcomes, communication of Agency signals to MAHs).
- In addition, AnimalhealthEurope considers it is important to engage in a profound discussion with stakeholders on the following subjects as these could have a major impact on the efficiency of the system:
    - Signal detection/ signal management process and ensuring quality of signals at MAH and Authorities side.
    - Management of multi-MAH cases from both EEA and third countries origin.
    - Duplicate detection: who is responsible for duplicate detection and how will differences in opinion be resolved?
    - Sales data & treated animals.
    - Telematics solutions supporting the signal detection/signal management and interaction between MAHs and authorities.

We reiterate our availability to provide the EMA any required information in order to help develop the guidelines. We recognise the urgency of this work in order to fulfil the entry into force date of the Regulation 2019/6 in January 2022.