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Veterinary Medicines and Product Data Management

Summary from the workshop - Veterinary pharmacovigilance question time: better regulation for electronic reporting and periodic safety update reports (PSURs)

24 November 2010, European Medicines Agency, London

Executive summary

- The aim of the workshop was to convene regulatory and industry experts in pharmacovigilance to reflect on the veterinary pharmacovigilance system in the European Union (EU), with specific focus on electronic reporting and periodic safety update reports (PSURs), in light of the review of the current legislation for veterinary medicinal products.
- Key issues raised during the discussion included the following:
    - PSURs place a significant administrative burden on marketing authorisation holders (MAHs) and national competent authorities (NCAs) which could be reduced in the future if a more flexible and proportionate approach to PSUR requirements would be possible;
    - development of a comprehensive, functional EU product database is necessary to achieve a fully operational electronic reporting system for adverse events;
    - electronic reporting, signal detection and PSURs are inter-dependent and need to be considered in synchrony to improve the pharmacovigilance system;
    - further consideration and development of the concept of a risk-based approach is required to enhance the approach and methodology for adverse event surveillance; and
    - concerted efforts and collaboration are required by stakeholders to develop approaches for effective adverse event surveillance, making optimal use of resources as part of a proportionate veterinary pharmacovigilance system.
- The workshop was considered fruitful and a welcomed opportunity for industry and regulators to exchange views and experiences. The discussions highlighted areas where further consideration is required for development of the pharmacovigilance system in future.

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Introduction

A workshop took place on 24 November 2010 at the European Medicines Agency, entitled veterinary pharmacovigilance question time - better regulation for electronic reporting and periodic safety update reports (PSURs)[1].

The aim of the meeting was to convene regulatory and industry experts to reflect on the veterinary pharmacovigilance system in the European Union (EU), with specific focus on electronic reporting and periodic safety update reports (PSURs), in light of the review of the current legislation for veterinary medicinal products.

Fifty-two delegates attended the workshop. Participants represented veterinary pharmacovigilance experts from industry (including qualified persons for pharmacovigilance, QPPVs), industry associations (Association of Veterinary Consultants, International Federation for Animal Health Europe and Syndicat de l'Industrie du Médicament Vétérinaire), the Federation of Veterinarians of Europe (FVE) and EU national competent authorities (NCAs).

The workshop comprised short presentations from industry and regulatory authorities to set the scene, followed by panel and open discussion sessions, primarily based on questions submitted by participants in advance on the two key topics: electronic reporting and PSURs. This document summarises the presentations and discussions that took place. For some of those questions that were not selected for discussion at the workshop, it was possible to give appropriate responses and these have been collated in a separate document (Doc. Ref. Id. EMA/838435/2009) [2] and circulated for information to participants.

Summary of the presentations, panel and open discussion sessions

1. Setting the scene: the European Commission public consultation on better regulation

a) On behalf of IFAH Europe, B. Cornez (Huvepharma N.V) presented the key challenges for industry highlighted in the 'IFAH-Europe impact assessment data package' focusing on the current administrative burden of veterinary pharmacovigilance for marketing authorisation holders (MAHs). Approximately half of the workload comprised PSUR handling, principally involving compilation, preparation and management of data for analysis. Spontaneous adverse event report management and development and maintenance of the pharmacovigilance system, respectively, made up the remaining workload for MAHs. A more flexible and less bureaucratic approach to PSUR handling could represent a major improvement to the current pharmacovigilance system. This would enable MAHs to focus on the core objectives of pharmacovigilance i.e. adverse event report management and provision of support to product users.

b) The European Medicines Agency Secretariat presented an overview of the CVMP proposals for the revision of the veterinary legislation on pharmacovigilance, which was part of the CVMP's response to the European Commission's initiative for stakeholder consultation and review of

[1] Veterinary pharmacovigilance question time: better regulation for electronic reporting and periodic safety update reports (PSURs) - 24 November 2010 – Programme (Doc. Ref. Id. EMA/433980/2010) http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2010/11/event_detail_000342.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c3

[2] Answers to questions not addressed at the workshop: Veterinary pharmacovigilance question time (Doc. Ref. Id. EMA/730943/2010)

the current veterinary legislation[3]. The presentation provided an overview of proposals for future legislation on the following areas: reinforcing the responsibility of MAHs for surveillance of veterinary medicinal products; strengthening the potential legal options to enforce compliance with pharmacovigilance requirements; tailoring the approach to surveillance; rationalising the approach to electronic reporting, PSURs and renewal procedures, signal detection; the extended scope of pharmacovigilance; Article 78 of Directive 2001/82/EC[4] procedures; and communication with the public and healthcare professionals.

c) ***Panel discussion: question 1: Is a stand-alone pharmacovigilance master file a possibility?***

The panel discussed the concept of the pharmacovigilance master file for veterinary medicinal products. Although the concept is not within the framework of the current legislation, there was general support for the development of the pharmacovigilance system master file for veterinary medicinal products in future. A potential future master-file would entail the detailed description of the pharmacovigilance system being linked to the MAH, rather than the marketing authorisation for a veterinary medicinal product. This could minimise the amount of product-specific information included in the marketing authorisation application itself. Where appropriate, product specific information could be included in an addendum, for example, which would be available to competent authorities upon request.

It was recognised that whilst the pharmacovigilance master file concept may not address all the current problems experienced with the detailed description of the pharmacovigilance system, it may alleviate unnecessary administrative burden experienced by MAHs and competent authorities. Controlled and transparent processes would, however, be required for updates to the pharmacovigilance system, when appropriate.

d) ***Open discussion on the legal framework***

Participants reflected on the existing legal framework for veterinary pharmacovigilance. The requirements for veterinary pharmacovigilance under the current legislation were considered to be too complex, which was attributed to the fact that the veterinary legislation mirrors the one for human pharmacovigilance. It was proposed that future legislation should be developed in a more proportionate way, to address the needs of veterinary pharmacovigilance, which were not considered to be identical to those for human pharmacovigilance. Future revisions of Volume 9B (when available) would require development of the guidelines in parallel with the future legislation.

2. Electronic reporting: reporting routes, time to report; proposed Member States and MAH reporting obligations

a) K. Quine (Elanco Animal Health) presented IFAH Europe's perspective of electronic reporting for the future. A proposal for single step reporting was presented, whereby one adverse event report would be submitted by MAHs within VICH[5] regions, for example, to a single central EU database containing all EU reports, and enabling adverse event data to be exchanged between VICH regions. The proposal provided the basis for a potential global adverse event database, in the long-term.

[3] Commission consultation on Better regulation for Veterinary Pharmaceuticals - CVMP analysis of the functioning of current veterinary legislation and proposals for its evolution and comments on the Commission paper http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/07/WC500094747.pdf

[4] European Parliament and Council (2001) - Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products as amended by Directive 2004/28/EC and Directive 2009/9/EC. http://eur-lex.europa.eu/en/index.htm

[5] VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

Alternative timeframes for electronic reporting of adverse events occurring within the EU were suggested as follows: 15 days for serious adverse events and 90 days for all other EU reports, or by the next PSUR data lock point (DLP). It was proposed that third country reports would be accessible to Member States via an EU database connected to other VICH regions and for MAHs, via their regional agencies and databases.

Concerning analysis of adverse event data, it was suggested that competent authorities would likely use the central EU database for signal detection (prior to the development of a global database), whilst MAHs would continue to use their own databases for signal detection. Global coordination was encouraged, which highlighted the need to ensure appropriate global standards and to establish a single global database which should address all electronic reporting requirements. To achieve this, positive interactions between competent authorities and industry would need to be maintained and enhanced.

b) C. Ibrahim (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit) gave a presentation on electronic reporting from a regulatory perspective. The current electronic reporting system was considered dependent on the quality of the data contained within the system and consequently quality assurance was considered fundamental for ensuring robust and reliable data for surveillance.

The availability of a fully operational EU product database was highlighted as a priority for electronic reporting. The central EU database, EudraVigilance Veterinary (EVVet), contained all adverse events reported expeditedly for centrally authorised products. However, the need to populate the database for non-centrally authorised EU products was considered fundamental and the primary constraint preventing the accomplishment of a fully functional EU-product database and fully operational electronic reporting system in the EU.

For surveillance, the principle of understanding the nature of adverse event data was considered key to enable meaningful conclusions to be drawn from analyses. Attention was drawn to the forthcoming surveillance procedure for adverse events for centrally authorised products, to be implemented by the Committee for Medicinal Products for Veterinary Use (CVMP)[6]. The procedure would be based on signal detection queries from the EVVet Data Warehouse (DWH) and was developed to enhance the harmonised approach to surveillance using electronic tools.

The key elements for a successful electronic reporting system for veterinary pharmacovigilance were identified as the functionality of EVVet, data quality and adaptation of data analysis methods for signal detection.

c) ***Panel discussion question 2*** **- What would be the benefit for a) MAHs and b) NCAs if all adverse event reports (including non-serious, suspected lack of expected efficacy (SLEE) etc.) were to be submitted electronically?**

It was considered that electronic submission of all adverse events may be beneficial for MAHs if accompanied by a corresponding reduction in the current requirements for PSURs. However, the success of comprehensive electronic reporting would be dependent on an effective, user-friendly and fully automated system. It was suggested that a potential reduction in some of the PSUR requirements (as a consequence of complete electronic reporting) could only be feasible after establishment of a functional system for signal detection, using a risk-based approach for surveillance.

[6] European Medicines Agency standard operating procedure: Safety monitoring of centrally authorised products (SOP/V/4032)

For competent authorities, electronic reporting of all adverse events was also considered beneficial as it would facilitate reporting and management of adverse events. However, secure transmission of reports and development of the veterinary medicinal product dictionary (to include non-centrally authorised products) would be required to ensure the system would be fully functional. It was also suggested that there would be a need to clarify roles and responsibilities for electronic reporting and subsequent surveillance of non-centrally authorised products to ensure smooth operation of the system.

d) ***Panel discussion question 3 - Should the MAH send reports directly to the EudraVigilance Veterinary (EVVet) central database?***

Differing views regarding the concept of a single reporting point were expressed amongst the panel and also participants. Generally, industry representatives expressed that a single reporting point to the central database could provide a simpler approach compared to the current electronic reporting system. However, different views were expressed between representatives from the NCAs. Some NCA representatives favoured a single reporting point, in view of the potential decrease in administrative burden of adverse event report handling. Other NCA representatives felt that it would be important for MAHs to send adverse event reports to the NCAs before submission to EVVet to ensure validation of reports, identification of duplicates and for addition of the NCAs' causality assessment.

e) ***Panel discussion question 4 - If all adverse events (serious, non-serious etc.) were submitted electronically, would line listings in PSURs and PSURs in their present format still be appropriate?***

It was generally considered that PSURs could be simplified if all adverse events were available via a central database, provided the corresponding benefit-risk assessment was also submitted by the MAH. Additionally, it was suggested that submission of PSURs could be adapted in accordance to experience gained following use of products in the field. For example three potential 'risk' categories were described as follows for, 1) 'new products and high potential risks'; 2) 'well known products and low risks'; and 3) 'well known products and some potential risks'. The opportunity to further discuss and elaborate the basis for such risk categories was considered a useful future prospect for development of the approach and methodology for adverse event surveillance.

3. Periodic safety update reports (PSURs): frequency, content and assessment

a) C. Torres (Ceva Santé Animale) gave a presentation on behalf of IFAH-Europe on the frequency, content and assessment of PSURs. It was reported that in general industry supported the idea of a risk-based approach to surveillance to make best use of available resources in order to focus on safety monitoring. It was proposed that PSURs should only be submitted after products had been on the market for 10 years or less. PSUR submission frequency was proposed as annual for the first 4 years after initial placing on the market and thereafter every 3 years. After ten years, no PSURs would be required unless requested by competent authorities for safety reasons. Also it was suggested that PSURs should not need to be submitted with renewal applications, where the concept of renewals is to be maintained. However, if changes to the product safety profile would be identified, it was suggested that the renewal application could be accompanied by a statement from the QPPV proposing the update of the summary of product characteristics (SPC) and product literature concerning adverse reactions and safety warnings, where appropriate. The need to decrease the administrative

burden of PSURs would allow MAHs to target resources to evaluation of safety data and signal detection. The value of sharing experiences between industry and regulators was emphasised for continued improvement of the pharmacovigilance system. Finally it was felt that it was important to keep an open mind and to adapt to the pharmacovigilance system as it continues to evolve.

b) A. Werner (Bela-pharm GmbH) gave a presentation on PSURs from the perspective of generics companies with a view to optimising resources for MAHs and NCAs. The key issues focused on were: 1) harmonisation of DLPs; 2) the reduction of PSUR submission frequencies (particularly for 'well-known' substances), supported by the submission of all adverse events electronically; and 3) rationalisation of the safety information included in SPCs. It was proposed that safety information included in the SPC and product literature should be limited to specific substance-related information, supported by adverse event or clinical data. Updates to SPCs and product literature should reflect changes in the safety profile of products, without the need for separate variation procedures to implement the changes.

c) P. Ekström (Läkemedelsverket) gave a presentation on PSURs from the regulatory viewpoint. The importance of provision of feedback to MAHs on the preparation and presentation of PSURs according to the current requirements in force was highlighted. The use of electronic tools developed for analysing EVVet data to facilitate signal detection was described. In addition an approach for signal detection was outlined, with the aim of targeting rare and serious adverse events. Reflections on possible future PSUR submission requirements included an approach adapted to the perceived 'risk' of the product, whilst maintaining the provision for competent authorities to request PSURs when safety concerns or potential signals arise. Electronic reporting of *all* adverse event reports by MAHs to a single central database was supported. MAHs were encouraged to use EVVet, and associated data analysis tools, for surveillance and to take the lead for signal detection for their products, allowing NCAs to fulfil their supervisory role whilst alleviating the administrative burden for Member States.

d) Open discussion on PSURs

Other PSUR-related topics raised during the open discussion amongst participants included the following:

- *PSUR synchronisation and worksharing initiative*

  Industry representatives reported that a more systematic and pragmatic approach to PSUR management and assessment was welcomed. Whilst acknowledging that the PSUR synchronisation and worksharing initiative provided a valuable learning experience, it was suggested that efforts should be concerted to further streamline the process. The consideration of PSUR harmonisation at VICH level was also suggested as a possible future prospect.

- *Current PSUR requirements*

  The constraints of the current legislation to allow for different approaches for PSUR submission were considered as it was reported that there was often a lack of flexibility with the application of legislation at national level in some Member States e.g. submission of PSURs according to the international birth date of the product. However, no firm proposals were made to address this issue at the current time.

4. General/open discussion session - signal detection and adverse event surveillance approaches

During the workshop there was extensive discussion on signal detection and adverse event surveillance. An example of a two-step approach to signal detection was described comprising: 1) initial screening of adverse events; followed by 2) in-depth assessment of signals to determine the potential causal relation with the product. This in-depth evaluation would entail review of the case report narrative and application of clinical knowledge and judgment. It was therefore highlighted that further consideration would be required in relation to the proposals for MAHs to use EVVet for signal detection and to place the responsibility for signal detection on companies, in light of the forthcoming EVVet access policy, whereby the MAH would not have access to the narrative field of adverse event reports associated with their products. Taking into account resource availability, it was suggested that it would be more efficient for MAHs to continue to use their own databases for signal detection and for NCAs to use EVVet, which would allow for analyses at active-substance level. The opportunity was also taken to highlight the additional value for MAHs provided by the EVVet access policy which foresees that electronic tools would be made available for MAHs in future to query data within EVVet. This provision was considered a useful facility for MAHs as it could enable validation of signals detected in their own database against the EVVet dataset. Finally, it was emphasised that there still remained a need to gain experience using the electronic tools already available and to further develop and refine the methodology for signal detection.

There were initial reflections on the concept of a 'risk based approach' in veterinary pharmacovigilance. For example, one industry representative suggested that a product could be categorised on the basis of the number of adverse events reported per year e.g. a product for which 15 adverse events (or fewer) were reported in one year could be classified as 'low risk' and in such cases, a schedule could be assigned such that adverse event surveillance would be based on spontaneous reports only, without the need for PSURs. It was also proposed by another industry representative that for 'well-known' substances, the PSUR submission frequencies could be reduced. Although the proposal was supported by some of the panel members, one NCA representative stressed that such an approach may not account for the potential role of excipients in adverse events and that such a proposal would therefore require further consideration. It was, however, generally agreed by industry and regulatory representatives that further development of criteria and corresponding guidance for a risk based approach to surveillance would be needed.

Conclusion

The workshop provided an opportunity for regulators and industry to reflect on the current veterinary pharmacovigilance system and consider improvements for the future for effective regulation and surveillance of adverse events. Key issues that arose during the discussion for improvement of the pharmacovigilance system included the following:

- future legislation should be proportionate to ensure effective safety evaluation of veterinary medicinal products with optimal use of resources;
- creation of a veterinary pharmacovigilance master file;
- systematic, flexible and a less bureaucratic requirements for PSURs;
- simplified and fully automated electronic reporting process for adverse events with the potential for a global system in future;
- completion of a fully functional EU product database to include non centrally authorised products;

- development of a risk based approach for adverse event surveillance and enhancing signal detection;
- further development and gain of experience using electronic tools and validation of signal detection; and
- sharing of experiences and continued dialogue and collaboration between stakeholders for evolution of the pharmacovigilance system.

In general, the workshop was considered fruitful and a welcomed opportunity for industry and regulators to exchange views and experiences. The discussions highlighted areas where further consideration is required for development of the pharmacovigilance system in future.

List of participants

Chair: Kornelia Grein, European Medicines Agency.

Panel: Marie-Odile Hendrickx, Pfizer Limited; Roel van Lieshout, Eurovet Animal Health; Fabia Dyer, Veterinary Medicines Directorate; Lisbet Vesterager-Borge, Danish Medicines Agency.

Speakers: Bob Cornez, Huvepharma N.V.; Peter Ekström, Läkemedelsverket; Cornelia Ibrahim, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit; Karen Quine, Elanco Animal Health; Cecilia Torres, Ceva Santé Animale; Andreas Werner, Bela-pharm GmbH; Raquel Gopal (on behalf of Jos Olaerts), European Medicines Agency.

Regulatory participants: Frédéric Klein, Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Agence Fédérale des Médicaments et des Produits de Santé; Lionel Laurier, Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Agence Fédérale des Médicaments et des Produits de Santé; Alia Michaelidou-Patsia, Ministry of Agriculture, Natural Resources and Environment; Eleni Vatamidou-Petrou, Ministry of Agriculture, Natural Resources and Environment; Vladimir Brychta, Ústav pro státní kontrolu veterinárních biopreparátů a léčiv; Karoliina Laine, Lääkealan turvallisuus- ja kehittämiskeskus Fimea; Elisabeth Bégon, Agence Nationale du Médicament Vétérinaire - Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du travail; Katrin Kirsch, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit; Angelika Schadewinkel-Scherkl, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit; Klaus Cussler, Paul-Ehrlich-Institut; Elke Schönborn, Paul-Ehrlich-Institut; Helen Amenta, ΕΘΝΙΚΟΣ ΟΡΓΑΝΙΣΜΟΣ ΦΑΡΜΑΚΩΝ; Edit Nagy, Central Agricultural Office Directorate of Veterinary Medicinal Products; Hazel Dunphy, Veterinary Medicines Department; Lisa Woods, Veterinary Medicines Department; Rita Quondam Giandomenico, Ministero della Salute; Hanne Bergendahl, Statens Legemiddelverk; Agnieszka Rogowska Jaśkowiak, Urząd Rejestracji Produktów Leczniczych, Wyrobow Medycznych i Produktów Biobójczych; Inês Filipa Martins de Almeida, Direcção-Geral de Veterinária; Henrique Ramos da Costa, Direcção-Geral de Veterinária; Robert Soldan, Institute for State control of Veterinary Biologicals and Medicaments; Katarina Štraus, Agency for medicinal products and medical devices of the Republica of Slovenia; Ramiro Casimiro, Agencia Española de Medicamentos y Productos Sanitarios; Remedios Ezquerra Plasencia, Agencia Española de Medicamentos y Productos Sanitarios ; Susanne Stenlund, Läkemedelsverket; Baukje Schat, Veterinary Medicines Unit College ter Beoordeling van Geneesmiddelen; Marjan van Hooft, Veterinary Medicines Unit College ter Beoordeling van Geneesmiddelen; Gillian Diesel, Veterinary Medicines Directorate.

MAH representatives (Qualified Persons for Pharmacovigilance or their replacements): Marie-Hélène Grillet, AB Science; Sandra Nicoll, Abbott Animal Health; Jordi Puig, Andersen SA; Dietmar Kretzdorn, Bayer Animal Health GmbH; Serge Carel, Biokema Anstalt; Dirk Hörstemann, Böringher Ingelheim Vetmedica GmbH; William Drury, Cyton Bioscience Ltd; Amrit Chohan, Dechra Ltd; Mathilde Louwerens, Dopharma Research; David Sylvester, Eco Animal Health; John Tasker, Eco Animal Health; Marcel Horlings, Intervet/Schering-Plough Animal Health; Johan Vanlerberghe, Janssen Pharmaceutica NV; Rosa Calonge, Laboratorios Dr. Esteve, S.A.; Lidia Serarols, Laboratorios Hipra SA; Susanne Heidemann, Merial S.A.S.; Rae Knight, Novartis Animal Health; Dominique Portsmouth, Novartis Animal Health; Laure Gardey, Virbac SA.

Association representatives: Declan O'Rourke, Association of Veterinary Consultants (AVC); Despoina Iatridou, Federation of Veterinarians of Europe (FVE); Jan Vaarten, Federation of Veterinarians of Europe (FVE); Sylvie Meillerais, International Federation for Animal Health Europe (IFAH); Marie-Anne Barthelemy, Syndicat de l'industrie du Médicament Vétérinaire

European Medicines Agency: Isaura Duarte; Pedro Oliveira; Dean Tripoli, Esther Day, Anna Vecellio.