25 May 2018
EMA/CVMP/PhVWP/171122/2016
Committee for Medicinal Products for Veterinary Use (CVMP)

Revised recommendation for the basic surveillance of EudraVigilance Veterinary (EVVet) data for centrally authorised products (CAPs)

Draft agreed by CVMP Pharmacovigilance Working Party (PhVWP-V)	November 2016
Adopted by CVMP for release for consultation	16 February 2017
Start of public consultation	24 February 2017
End of consultation (deadline for comments)	31 August 2017
Agreed by PhVWP-V	March 2018
Adopted by CVMP	25 May 2018
Date for coming into effect	1 June 2018

Keywords	Veterinary pharmacovigilance, surveillance, adverse event, adverse reaction, lack of expected efficacy, side-effect

30 Churchill Place● Canary Wharf ● London E14 5EU● United Kingdom
Telephone +44 (0)20 36606000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Revised recommendation for the basic surveillance of EudraVigilance Veterinary (EVVet) data for centrally authorised products (CAPs)

Table of contents

Executive summary

This is the first revision of the recommendation for the basic surveillance of EudraVigilance Veterinary (EVVet) data. The main aim of the revision is to improve the overall pharmacovigilance surveillance process, where possible, by integrating periodic safety update report (PSUR) evaluation and signal detection processes based on EVVet data and using risk-based principles. At present the recommendation will be applicable only for veterinary medicinal products (VMPs) authorised via the centralised procedure (CAPs). The revised recommendation is primarily intended for regulators to evaluate pharmacovigilance data from marketing authorisation holders (MAHs) who elect to submit all their adverse event (AE) reports (including non-expedited) electronically. The revised recommendation was piloted during the consultation process. The experience gained from the pilot, together with the comments received during the public consultation have been taken into account to further refine the proposals outlined in this document. Further simplification of the PSUR structure, focusing on a critical evaluation of the benefit-risk balance of the product and complemented by a complete electronic dataset form the basis of this revised recommendation for continuing to improve surveillance of CAPs.

1. Introduction (background)

The recommendation on pharmacovigilance surveillance and signal detection of VMPs (EMA/CVMP/PhVWP/901279/2011) was adopted by the Committee for Medicinal Products for Veterinary Use (CVMP) in April 2015 providing an initial framework for signal management and signal detection of VMPs in the European Union (EU)/European Economic Area (EEA), irrespective of the route of authorisation. With the adoption of the above-mentioned recommendation a revision of the previous recommendation for the basic surveillance of EVVet data (EMA/CVMP/PhVWP/471721/2006) became necessary, to avoid overlap and discrepancies between the two documents. This document describes the integration of signal management with the PSUR assessment process. A concept paper for revision of the recommendation for the basic surveillance of EVVet data (EMA/CVMP/PhVWP/590073/2015) was published in November 2015. The concept paper highlighted the following principles for consideration in the revised recommendation which have been addressed as part of this revision together with the comments received during the public consultation:

- further guidance on the queries to be used in the EVVet data warehouse (DWH) and on the analysis process;
- the continued responsibility of the CVMP Pharmacovigilance Working Party (PhVWP-V) to give advice on the signal detection findings;
- exchange of data and findings with the MAH during the process;
- issues relating to inconsistencies between PSUR line listings (LL) generated by MAHs and LL generated via the EVVet DWH; and
- investigating solutions to improve access for all stakeholders to the same dataset.

This revised recommendation will replace the recommendation for the basic surveillance of EVVet data (EMA/CVMP/PhVWP/471721/2006) and is primarily intended to improve the principles of surveillance of VMPs and additionally simplify PSURs with regard to the content for MAHs as well as the assessment by regulators. Regulators will benefit from signal detection on data in EVVet conducted at predefined time points according to the recommendation on pharmacovigilance surveillance and signal detection of VMPs (EMA/CVMP/PhVWP/901279/2011). Although the PSURs presented in accordance with this recommendation (hereafter referred to as a simplified PSUR) may not be fully aligned with the structure of the PSURs as specified in Volume 9B, all the relevant information including non-serious reports would be available to the assessors. A simplified PSUR format would be acceptable for the

Agency and could benefit MAHs and regulators by reducing the administrative burden and allowing implementation of a risk-based approach for assessment (for details see section 4 discussion).

The analysis of data in EVVet by means of DWH queries is, at present, intended solely for regulators. When requested by MAHs, a copy of the output of the surveillance findings, if necessary also including description of the queries and statistical methods applied, can be provided. It is anticipated that following implementation of the updated EVVet system and the finalisation and implementation of the revised legislation, there will also be possibilities for MAHs to directly access the wider dataset through the use of the DWH. This is now already in place at the European Medicines Agency (EMA) for MAHs for medicines for human use.

The recommendation and the principles described will be implemented on a voluntary basis with the agreement of individual MAHs, particularly as it is accepted that this proposal may increase the administrative burden for some MAHs. The implementation of the revised recommendation follows a pilot phase which provided the opportunity for MAHs and regulators to gain experience with the principles proposed in this document and which has also been taken into account to make further refinements.

2. Scope

This recommendation includes guidance on surveillance processes involving PSUR assessment and signal detection within the current legislative framework. The recommendation is intended for CAPs only, due to current limitations in access to product information on VMPs authorised nationally (NAPs). The aim of this document is to improve the efficiency and enhance the impact of post marketing surveillance through combining the strengths of the signal detection and the PSUR evaluation systems which cover largely the same dataset. The overall aim is to further ensure that the limited resources available are focused on the essentials through the limitation of duplication and the reduction and simplification of the formal administrative requirements.

This recommendation is intended to be used primarily by regulators, except for the electronic submission of non-serious AE reports and simplification of the content of PSURs, which would also be applicable to MAHs who choose to implement this approach, and subject to approval by the CVMP rapporteur, for each CAP.

3. Legal basis and relevant guidelines

This recommendation should be read in conjunction with the introduction and general principles of Regulation (EC) 726/2004, Directive 2001/82/EC, Volume 9B of The Rules Governing Medicinal Products in the European Union and all other relevant EU and Veterinary International Cooperation on Harmonisation (VICH) guidelines. These include, but are not limited to the following:

- European Medicines Agency and Heads of Medicines Agency (2015) Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products (EMA/CVMP/PhVWP/901279/2011);
- European Commission (2011): Volume 9B - Pharmacovigilance for Medicinal Products for Veterinary Use Guidelines on Pharmacovigilance for Medicinal Products for Veterinary; and
- European Commission (2004): Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

4. Discussion

The statistical power of surveillance can be largely improved when using an electronic dataset comprising all AEs regardless of severity (i.e. serious and non-serious AEs) occurring in the EU/EEA and third countries if applicable. It is important and beneficial for regulators to have access to all reports, serious and non-serious, continuously, thereby enabling ongoing access to AE reports between the PSUR submission intervals, which could be up to three years. Previous pharmacovigilance experience illustrates the importance of ensuring all AE reports are available in EVVet to enable early identification of new signals. Having all AE reports in EVVet enables analysis across all reports and the comparison/grouping of products thereby minimising potential differences in classification of reports e.g. severity (serious/non-serious).

4.1. Time-frame for electronic adverse event submission

Expedited reports must still be submitted within 15 days, in line with the current legislative requirements. The time frames and route of transfer of AEs as applicable in this recommendation are as follows:

- serious animal and human EU/EEA AEs received by MAHs to be sent to the national competent authority (NCA) in the country where the event occurred within 15 days;
- serious animal and human EU/EEA AEs received by NCAs to be sent to EVVet and the MAH within 15 days;
- serious unexpected AEs in animals; all human reports and any suspected transmission of an infectious agent via a VMP in third countries to be sent within 15 days by MAHs to EVVet;
- non-serious EU/EEA AEs received by MAHs to be sent to EVVet within 60 days and no later than the time of submission of the PSUR;
- non-serious EU/EEA AEs received by NCAs to be sent to EVVet and the MAH within 60 days; and
- serious expected and non-serious (if applicable) AEs in third countries to be sent by MAHs to EVVet within 60 days and no later than the time of submission of the PSUR.

4.2. PSUR structure

The current legislation provides for a risk-based approach to periodicity of PSUR submission as a condition of the marketing authorisation of VMPs. A risk-based approach with regard to the structure of PSURs is also proposed to strengthen and apply the current legislative provisions as part of the routine procedure, making best use of the resources available.

In the scope of this recommendation the simplified PSUR structure is proposed with the aim of reducing the administrative burden for MAHs. Although the simplified PSURs are not fully in line with the PSUR requirements in Volume 9B the simplification is justified by the fact that the following conditions will apply:

- all AEs related to the CAP are in EVVet and accessible to all NCAs in the EU/EEA; and
- signal detection is performed at yearly intervals [if not more frequently] by rapporteurs on all AEs for CAPs.

The following simplified PSUR structure, with the emphasis on a thorough and critical discussion of the benefit-risk balance of the product, is acceptable on condition of electronic transfer of all AEs to EVVet:

- sales data, estimates of exposure and incidence; and
- a thorough critical discussion justifying the benefit-risk balance of the product and supporting the conclusions and any actions recommended. For this purpose, there should be a critical evaluation of any potential signal identified (e.g. regardless of whether these are serious or non-serious) also drawing on information from all pharmacovigilance fields ordinarily addressed in the PSUR including non-spontaneous AEs (e.g. from clinical trials, literature reviews). The discussion should address any potential or new/emerging signals or risks and their potential causal association with the product.

The following parts of the PSUR would no longer be necessary:

- LLs, on condition that those generated by the EVVet DWH queries, in principal, are consistent with the current LL prepared by MAHs (based on the original received date, sender field etc.);
- a summary of product characteristics (SPC) (reference to “date of latest SPC” to be included, to avoid mistakes and discrepancies with “the current SPC”); and
- summaries of AEs other than within the context of a critical discussion of signals as part of the benefit-risk evaluation referred to above.

It should be highlighted that if there are any concerns regarding the product, the MAH may be requested to forward data at any time justifying that the benefit-risk balance remains favourable.

4.3. PSUR submission

The normal PSUR submission cycle, or as agreed by the CVMP, applies. PSURs submitted in accordance with this recommendation are usually expected within 60 days after the scheduled PSUR data lock point (DLP).

If however urgent safety issues are identified, unless otherwise specified by the rapporteur, a PSUR (full PSUR presented in accordance with Volume 9B excluding the LL and SPC) should be submitted as soon as possible or within 30 days unless another time-frame has been requested. Where, on the basis or urgent safety issues, the need for a full PSUR is identified:

- by the rapporteur/PhVWP-V/CVMP, the MAH will be notified; or
- by the MAH, a notification must be forwarded to the EMA as soon as possible in advance of the PSUR submission.

4.4. PSUR evaluation

Reference to EVVet DWH queries are currently intended for regulators, due to the limitations in MAHs access to data in EVVet at present. To meet the desire expressed by industry to be involved in signal detection at an earlier time point e.g. before a signal has been confirmed, it is proposed that the MAHs are involved after discussions at PhVWP-V/CVMP meetings. By providing MAHs with reference to the rapporteur’s signal detection findings, if requested, MAHs would have the opportunity to compare their findings with those of the regulators. This would enable all parties to benefit from comparing findings in EVVet to those from the MAH’s database. If a signal is identified in both systems, a stronger indication of a possible causal relation may exist, however further investigations should be discussed between the MAH and regulators.

It is emphasised that whenever any concerns or issues are identified warranting further investigation, the rapporteur can always request further information from the MAH e.g. a focused analysis on a particular signal in an upcoming PSUR or a targeted PSUR.

To support the simplifications in PSUR content proposed with this recommendation the benefit-risk evaluation provided by the MAH in every PSUR needs to be thorough, precise and actually reflect an evaluation of the AEs, literature search, post-marketing studies etc. It should be emphasised that the MAH always has the responsibility for conducting the benefit-risk analysis for their product.

Signal detection is conducted by rapporteurs at predefined intervals (6 or 12 months), the findings are summarised and recorded in veterinary pharmacovigilance surveillance (VPhS) FileMaker database and discussed at PhVWP-V meetings. Signal detection is performed by using predefined queries in the EVVet DWH. The signal detection is based on, for the large part, the same data as presented in the PSUR. To avoid assessing the same data, the findings, if relevant, and the conclusions of the signal detection should be extracted to facilitate the PSUR assessment.

It is highlighted that the more data that is included in the database, the more reliable the results that can be obtained by analysis of the data. During signal detection important flaws in data quality should be communicated by the rapporteurs/pharmacovigilance experts at the earliest opportunity to the EMA for circulation directly to the MAH or, if considered a general problem, to the PhVWP-V. If considered appropriate (serious non-compliance issues identified or suspected), the issue should be notified to pharmacovigilance inspectors via EMA Compliance and Inspection.

The experience from the pilot enabled improvements to be made to this revised recommendation including further simplification of the PSUR structure, focusing on a critical evaluation of the benefit-risk balance of the product which will be used as a basis for continuing to improve surveillance.

4.5. Conclusions

The revised recommendation aims to improve the surveillance process for CAPs and also reduce administrative burden for both MAHs and regulators associated with the preparation and assessment of PSURs. The revised approach has been trialled initially in a pilot phase and this document incorporates recommendations for improvement identified from the pilot. The revised recommendation is applicable to all those CAPs where the MAH agrees to implement the approach described in this recommendation. It is envisaged that the recommendation will be reviewed within a few years in light of the further experience gained following implementation and as the supporting electronic systems are developed further.

5. Acknowledgements

Special thanks and acknowledgement is given to the MAHs, assessors and rapporteurs that participated in the pilot which was a valuable opportunity to gain experience for further improvement of the surveillance of VMPs.

6. References

European Commission (2004) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

European Commission (2011) Volume 9B - Pharmacovigilance for Medicinal Products for Veterinary Use Guidelines on Pharmacovigilance for Medicinal Products for Veterinary

European Medicines Agency (2016) European Medicines Agency policy on access to EudraVigilance data for medicinal products for human use (EudraVigilance Access Policy)

European Medicines Agency (2011) Recommendation for the basic surveillance of EudraVigilance Veterinary data (EMA/CVMP/PhVWP/471721/2006)

European Medicines Agency and Heads of Medicines Agency (2015) Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products (EMA/CVMP/PhVWP/901279/2011)

European Medicines Agency (2016) EudraVigilance Veterinary (EVVet) data warehouse (DWH) user manual (EMA/749712/2015)

7. Definitions and abbreviations

AE	Adverse event
CAP	centrally authorised product
CVMP	Committee for Medicinal Products for Veterinary Use
DLP	Data lock point
DWH	Data warehouse
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EVVet	EudraVigilance Veterinary
LL	Line listing
MAH	Marketing authorisation holder
NCA	National competent authority
PhVWP-V	CVMP Pharmacovigilance Working Party
PSUR	Periodic safety updates report
SPC	Summary of product characteristics
VMP	Veterinary medicinal product
VPhS	Veterinary pharmacovigilance surveillance