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4 Revised recommendation for the basic surveillance of 5 Eudravigilance Veterinary (EVVet) data for centrally 6 authorised products (CAPs)

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8 This recommendation replaces the Recommendation for the basic surveillance of EudraVigilance
9 Veterinary data (EMA/CVMP/PhVWP/471721/2006)

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

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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 a 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. However, proposals are also made for minimising the administrative burden associated with PSUR preparation and submission which would benefit marketing authorisation holders (MAHs). The revised recommendation will be trialled in a pilot phase before full implementation for CAPs.

1. Introduction (background)

The recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products (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.

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 and the comments received during the public consultation are addressed in this revision e.g:

- 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 listing (LL) generated by MAH 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 benefit from signal detection on data in EVVet carried out at predefined time points according to the recommendation on pharmacovigilance surveillance and signal detection of VMPs (EMA/CVMP/PhVWP/901279/2011). Although the simplified PSUR may not be fully aligned with the presentation of PSURs as specified in Volume 9B, all the relevant information would be available to the assessors. Based on a risk-based approach a simplified PSUR format would be acceptable and could benefit MAHs and regulators by reducing the administrative burden and allowing implementation of a risk-based approach for assessment (for details see point 4 discussion).

The analysis of data in EVVet by means of DWH queries is intended solely for regulators. This recommendation is foreseen to be implemented following an initial pilot phase to gain experience with the principles proposed. The pilot phase is expected to commence in June 2017 during the public consultation period on this document, following implementation of the technical change to EVVet for re-routing non-serious reports.

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 enhance the impact of post marketing surveillance primarily by regulators by strengthening surveillance activities within the resources available and avoiding duplication of work e.g. signal detection on data in EVVet for CAPs carried out by rapporteurs at predetermined frequencies and assessment of PSURs containing – at least – partly the same data.

This recommendation is intended to be used primarily by regulators, except for simplification of the content of PSURs, which would also be applicable to MAHs.

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

4. Discussion

The aim is to have all adverse events (AEs) regardless of severity (i.e. serious and non-serious AEs) occurring in the EU/EEA within EVVet. It is important and beneficial to regulators to have access to all reports, serious and non-serious, continuously, thereby enabling ongoing access to all reports between the PSUR submission intervals, which could be up to three years. Previous experiences of pharmacovigilance issues illustrate the importance of availability of all AE reports in the database to enable early identification of new signals. All AE reports in EVVet would enable analysis across all reports and the comparison/grouping of products thereby minimising potential differences in classification of reports e.g. severity (serious/non-serious).

The time frames and route of transfer of AEs are as follows:

- serious 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 and human EU/EEA AEs received by NCAs to be sent to EVVet and the MAH within 15 days;
- serious and 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 and redirected to the NCA in the country of occurrence 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 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.

Expedited reports must still be submitted within 15 days, in line with the current legislative requirements.

The following simplification of the PSUR content is acceptable on condition of electronic transfer of all AEs:

- No LL to be provided by the MAH based on the EVVet original received date field on condition that the LL generated by EVVet DWH queries in principal is identical to the current LL prepared by MAHs (based on the original received date, sender field etc.); and
- No summary of product characteristics (SPC) attached to the PSUR (reference to “date of latest SPC” to be included, to avoid mistakes and discrepancies with “the current SPC”).

The current legislation provides for a risk-based approach to periodicity of PSUR submission as a condition of the granting of the marketing authorisation of VMPs. For example, when marketing authorisations for generic CAPs are granted, a decision should be made regarding the PSUR periodicity, possibly also including a harmonisation between data lock point (DLP) for the originator and the generic(s). A risk-based approach with regard to a simplified content of PSURs is proposed to strengthen and apply the current legislative provisions as part of the routine procedure, making best use of the resources available. The following criteria should be met to qualify for a simplified PSUR:

- product in 3-year PSUR cycle; and
- no safety issues identified (e.g. high number of reports, severe human reactions) via signal detection or otherwise (e.g. post-authorisation studies, literature reviews etc.).

The simplified PSUR must contain sales figures, estimates of exposure and incidence and an overview of the adverse events reported (which are expected to be, for example, low numbers of known adverse events) with, however, a thorough benefit-risk evaluation (e.g. critically evaluating the limited number of adverse events and justifying the benefit-risk balance), but no LL and no SPC should be included.

A full PSUR (in accordance with Volume 9B excluding the LL and SPC) is expected within 60 days after the scheduled PSUR DLP:

- if non-urgent safety issues are identified by the rapporteur/PhVWP-V; a request will be sent to the MAH no later than the PSUR DLP; or

- if non-urgent safety issues are identified by the MAH; the MAH should then inform the European Medicines Agency (EMA) in advance of submitting the PSUR.

If urgent safety issues are identified, a targeted PSUR (full PSUR presented in accordance with Volume 9B excluding the LL and SPC) must be submitted as soon as possible or within 30 days. Where identified:

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

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;
- signal detection is performed at yearly intervals on all AEs for CAPs;
- only 'well-known' CAPs (i.e. 3-year PSUR reporting cycle) will be included in the pilot; and
- it will only be accepted for CAPs with no identified safety issues.

Reference to EVVet DWH queries are currently intended for regulators, due to the limitations in MAHs access to data in EVVet. 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 rapporteurs signal detection findings, the work on in-depth analysis is performed, initially, by the MAH and not by the regulators, which would decrease their workload. 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 and agreed between the MAH and authorities (rapporteur, PhVWP-V/CVMP).

It is highlighted that regardless of the findings; the rapporteur can always request further information e.g. focus-area in an upcoming PSUR or in a targeted PSUR.

Further to justify possible simplifications of PSURs (content/periodicity) the benefit-risk evaluation provided by the MAH in every PSUR needs to be thorough and precise and actually reflect an evaluation of the AEs, literature search, post-marketing studies etc.

Signal detection is carried out by the rapporteur at predefined intervals (6 or 12 months), the findings are summarised and saved 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.

To gain experience and to be able to evaluate the usefulness of the EVVet DWH queries – which have improved significantly since the first pilot on transfer of all EVVet data – and to elaborate on further development of EVVet DWH queries, as needed, and easy ways to extract data saved in FileMaker VPhS, a pilot is planned. A representative group of CAPs will be selected, in close collaboration with the MAHs and the rapporteur and their experts on a voluntary basis, to test the proposals and to further improve the systems to:

- minimise the administrative workload;
- benefit from the periodic signal detection;

- benefit from the improved EVVet DWH queries; and
- avoid assessing the data twice (partly).

Changes to the format of the assessment report will be explored in future making best use of the electronic tools available to regulators.

As mentioned previously the EVVet DWH queries for generating the LL have been significantly improved based on experiences obtained during the first pilot on transfer of all data. A tutorial has been produced giving good explanations on the use of the EVVet DWH queries including e.g. the impact of using different terms for dates. Training has also been provided both on EVVet and on DWH.

It is highlighted that the more data included in the database, the more reliable results can be obtained by analysis of the data. During signal detection obvious 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 consultative group on pharmacovigilance systems. If this is not sufficient, the issue should be notified to pharmacovigilance inspectors via the EMA Compliance and Inspection division. Access to the data is the first prerequisite for looking at data quality.

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 recommendation will be trialled initially in a pilot phase. Based on the experience gained and as the supporting electronic systems are developed further, as necessary, implementation of the revised recommendation is expected for all CAPs. It is envisaged that the recommendation will be reviewed within a few years in light of the experience gained following implementation.

5. 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 (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)

Definitions and abbreviations

AE	Adverse event
CAP	centrally authorised product
CVMP	Committee for Medicinal Products for Veterinary Use
DLP	Data lock point

219	DWH	Data warehouse
220	EVVet	EudraVigilance Veterinary
221	EEA	European Economic Area
222	EMA	European Medicines Agency
223	EU	European Union
224	LL	Line listing
225	MAH	Marketing authorisation holder
226	NCA	National competent authority
227	PhVWP-V	CVMP Pharmacovigilance Working Party
228	PSUR	Periodic safety updates report
229	SPC	Summary of product characteristics
230	VMP	Veterinary medicinal product
231	VPhS	Veterinary pharmacovigilance surveillance