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Committee for Medicinal Products for Veterinary Use (CVMP)

Concept paper for revision of the guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products

Agreed by the Pharmacovigilance Working Party	July 2012
Adopted by CVMP for release for consultation	12 July 2012
Start of public consultation	25 July 2012
End of consultation (deadline for comments)	31 October 2012

The proposed revision is the first part of a two-step revision of the guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products. Most of the revision comprises annexing two already available documents to the current guideline.

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

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1. Introduction

Directive 2001/82/EC of the European Parliament and of the Council, as amended, states that the Member States shall administer a veterinary pharmacovigilance system in order to ensure the adoption of appropriate regulatory decisions concerning the veterinary medicinal products authorised within the Community, with regard to information obtained about suspected adverse reactions to veterinary medicinal products under normal conditions of use. This system shall be used to collect information useful in the surveillance of veterinary medicinal products, with particular reference to adverse reactions in animals and in human beings related to the use of veterinary medicinal products and to evaluate such information scientifically. Likewise the obligations of the marketing authorisation holder (MAH) for recording and reporting adverse reactions associated with a veterinary medicinal product for which marketing authorisations are held are defined in Directive 2001/82/EC as amended.

In accordance with Articles 49 and 50 of Regulation (EC) 726/2004 of the European Parliament and of the Council, the holders of marketing authorisations and the competent authorities of the Member States shall ensure that all relevant information about adverse reactions to the veterinary medicinal products authorised under this Regulation is recorded in accordance with the guidance on the collection, verification and presentation of adverse reaction reports referred to in Article 51 of the Regulation.

Furthermore, Article 49 of Regulation (EC) 726/2004 of the European Parliament and of the Council states that the holder of the marketing authorisation for a veterinary medicinal product shall maintain detailed records of all suspected adverse reactions occurring within or outside the Community which are reported to him. These records shall be submitted, in the form of a periodic safety update report, to the Agency and Member States immediately upon request or at intervals specified in the Regulation. These reports shall be accompanied by a scientific evaluation, particularly of the risk-benefit balance of the veterinary medicinal product.

For the purposes mentioned above, this concept paper is the initial step in revising the existing guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products. Causality assessment is the method by which the extent of the relationship between a veterinary medicinal product and an adverse event is established. It is a combined assessment which takes into account the clinical and pharmacological or immunological aspects of the case history and the quality of the documentation of the observation. It is an important component of veterinary pharmacovigilance, contributing to better evaluation of the benefit-risk balance of veterinary medicinal products and is an essential part of evaluating adverse event reports in early-warning systems and necessary for supporting regulatory measures. Guidance on causality assessment improves the standardised approach to evaluating the likelihood of a relationship between a veterinary medicinal product and the adverse event for all concerned parties.

2. Problem statement

The guideline aims to describe how causality assessment should be performed in a harmonised way by all involved parties. After a period of more than seven years of operation a revision of the guideline on harmonising the approach to causality assessment for adverse events is necessary.

The reasons for a revision are as follows:

The Committee for Medicinal Products for Veterinary Use (CVMP) Pharmacovigilance Working Party (PhVWP-V) and MAHs previously identified a need for advice for causality assessment concerning special kinds of reports which should be addressed in a revision of the guideline and put in place

together with publication of Volume 9B of The Rules Governing Medicinal Products in the European Union.

Volume 9B changed the subdivision of one classification code for causality which needs to be adapted in the revised guideline. Additionally, guidance on causality assessment for off-label use and lack of expected efficacy (LEE) has previously been developed within the PhVWP-V with the intention to ultimately be incorporated in the revised causality guideline.

With the future revision of the veterinary pharmacovigilance legislation and use of pharmacovigilance data contained in EudraVigilance Veterinary (EVVet) there may be a need to re-consider the principles relating to causality assessment. The question of whether and, if applicable, which algorithm may help in causality assessment is still subject to consideration.

3. Discussion (on the problem statement)

Causality assessment is of primary importance for reporters and hence a good tool for promoting pharmacovigilance. Up to now a revision of the guideline on a harmonised approach on causality assessment has been postponed for several reasons. One reason is that for some of the issues to be revised the discussion is at present too premature for a decision to be taken on the future approach. Acknowledging this, it is recommended to revise the current guideline in two steps for effective use of resources.

In the first step, amendments which have already been identified by all involved parties (national competent authorities, MAHs, the European Medicines Agency) and for which a harmonised approach has already been agreed on should be included in the revision of the guideline. These are reflected in two documents developed by the PhVWP-V. One document is related to reports after off-label use and the second document describes the assessment of adverse events recorded as LEE. The document concerning LEE events has been restricted to pharmaceuticals, giving time for developing an approach for vaccines in the second step of the revision which is proposed to be undertaken at a later point in time. These documents should now be incorporated in the revised guideline.

In addition there is a need to update the guideline for consistency with Volume 9B with regard to the causality classification code “O” and its subdivision “O1” and the terminology for “adverse reactions” to “adverse events”.

It is recognised that resource intensive aspects for revision of the guideline should be addressed at a later point in time in a second revision step. These relate to the potential need for incorporation of an algorithm in the causality assessment as an additional tool, development of guidance concerning causality assessment of LEE events for immunologicals and adverse events occurring after mixing of vaccines. In addition, the concept of causality assessment as part of the procedure for surveillance of data contained in EVVet needs further in-depth consideration.

4. Recommendation

The CVMP recommends revising the guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products in two steps. For the first step of the revision, to be conducted now, it is proposed to add guidance on causality assessment of off-label use and LEE regarding pharmaceuticals by annexing to the guideline the previously agreed documents on these topics.

It is also proposed to update the guideline in accordance with Volume 9B to include the subdivision of the “O” causality classification and to update the terminology, for example, substituting “adverse reactions” with “adverse events”.

The second step of the revision should be undertaken at a later point in time to address concepts which require more in-depth consideration such as the principle of causality assessment within the process for surveillance of data contained in EVVet. Additionally the guidance should address whether an algorithm for causality assessment would be a useful additional tool, in addition to causality assessment of LEE reports for immunologicals and adverse events occurring after mixing of vaccines.

5. Proposed timetable

End of consultation of concept paper for revision of the guideline: October 2012.

First step revision of the guideline by the PhVWP-V: November 2012 or January 2013.

Adoption by CVMP: December 2012 for release for consultation or February 2013.

6. Resource requirements for preparation

The revision of this guideline will be undertaken by the PhVWP-V.

7. Impact assessment (anticipated)

The revision of the guideline will be of benefit to both regulatory authorities and industry who are directly involved in causality assessment. Introducing guidance on specific issues already identified as areas for which harmonisation is needed will improve the quality of the data on adverse events. By providing further guidance for causality assessment on specific issues such as LEE and off-label use it will at the same time help all involved parties in performing causality assessment and ensure that a harmonised approach is achieved. Causality assessment may also assist in promoting pharmacovigilance with veterinarians.

8. Interested parties

Veterinary pharmaceutical industry and regulators.

9. References to literature, guidelines, etc.

- European Commission (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
- 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 of the Rules Governing Medicinal Products in the European Union
- European Medicines Agency (2003): CVMP Guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products (EMEA/CVMP/552/03)