



The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

EMA/CVMP/345/98-Rev.1-FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS
(CVMP)

GUIDELINE ON
PROCEDURES FOR COMPETENT AUTHORITIES FOR PHARMACOVIGILANCE
INFORMATION FOR VETERINARY MEDICINAL PRODUCTS

DISCUSSION IN PHARMACOVIGILANCE WORKING PARTY	12 June 1998
ADOPTION BY CVMP	8 July 1998
TRANSMISSION TO INTERESTED PARTIES	9 July 1998
DEADLINE FOR COMMENTS	9 January 1999
DISCUSSION AND ADOPTION BY THE PHARMACOVIGILANCE WORKING PARTY	16 April 1999
FINAL APPROVAL BY CVMP	12 May 1999
REVIEW BY PHARMACOVIGILANCE WORKING PARTY	16 March 2004
ADOPTION BY CVMP	15 April 2004
DATE OF COMING INTO EFFECT	16 April 2004

Public

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GUIDELINE ON PROCEDURES FOR COMPETENT AUTHORITIES FOR PHARMACOVIGILANCE INFORMATION FOR VETERINARY MEDICINAL PRODUCTS

LEGAL BASIS AND PURPOSE

The legal framework for recording and evaluating pharmacovigilance data on veterinary medicinal products in the Community is contained in Directive 2001/82/EC of the Council and the European Parliament and in Council Regulation (EEC) No. 2309/93. Pharmacovigilance obligations apply to all authorised veterinary medicinal products.

Reports of suspected adverse reactions, frequently observed misuse and abuse of veterinary medicinal products as well as data on use (consumption) must be collated and scientifically evaluated by Member States of the Community.

Moreover, suspected human reactions following use of veterinary medicinal products and suspected adverse reactions following extra label use are also routinely transmitted to competent authorities and must be evaluated. Furthermore, for products with known side effects, the evaluation must take into account whether there is an increased incidence of such effects.

Epidemiological surveillance schemes and reports from authorisation holders may provide competent authorities with useful information on changes in resistance patterns. Reports of lack of efficacy should be taken against this background.

Potential environmental problems and reported violations of approved residue limits are aspects of post-authorisation surveillance, which are also considered within the scope of veterinary pharmacovigilance.

Following the notification of individual reports either from companies directly or from another concerned party to the competent authorities of suspected adverse reactions (SAR) to veterinary medicines, it is necessary to record and evaluate the report. Basic information on the SAR will have been established from the individual report. These details must be validated by checking the particulars with the reporter and/or other parties involved. In checking with the reporter, it is important to ensure consistency in scope and quality of the information gathered. Therefore, the accuracy of the particulars should be reaffirmed and omission of any details queried.

In addition, periodic safety update reports (PSURs) must also be reviewed by Competent Authorities during the first years following the grant of the product authorisation and at time of renewal of the authorisation. Specific advice on the evaluation of PSURs is given in chapter 3 below.

The following sub-headings may be useful in the evaluation of a report:

1. Details and particulars;
2. Causality assessment;
3. Action required.
4. Documentation of decision taken and notification of that decision to the MAH and, when necessary, to the European Agency for the Evaluation of Medicinal Products (hereafter referred to as the Agency) in accordance with the requirements laid down in Article 91 of Directive 2001/82/EC.

1. DETAILS AND PARTICULARS

To assist in the validation and assessment of the SAR, the format of particulars outlined in section 5.3 of the Guideline on Pharmacovigilance for veterinary medicinal products - Guidance on procedures for Marketing Authorisation Holders (EMA/CVMP/183/96) or as included in Volume 9 of The Rules Governing Medicinal Products in the European Union, Part II (using whichever is the most recent version of the document) should be followed. Where complete information on a report is submitted by the marketing authorisation holder (MAH), the Competent Authority (hereafter referred to as the Authority) may be in a position to evaluate the information without need for further clarification. In these cases the Authority should verify the record(s) by a system of random checks on records. In those cases where the report is notified by the veterinarian, pharmacist or other professional, directly to the Authority and not indirectly via the MAH, the information should always be verified by the Authority.

1.1 PRODUCT DETAILS

Details of the composition of the product including vehicle and excipients should be recorded together with the batch number(s) of the relevant product if available. Where the product has a marketing authorisation, it is necessary to establish whether the product was used within the terms of the authorisation. In many cases, it will also be useful to clarify the immediate previous use of the product itself or batch, and whether other drugs (including feed additives) were administered, prior to or together with the suspected product. Where more than one product was used, full particulars of each product (active ingredients, vehicles and excipients) should be documented.

1.2 ANIMAL DETAILS

While details of the number of treated animals, the number reacting and the number of deaths will be established from the original report form, it may be necessary to obtain further details on the report including information on the condition of the animal before treatment, the reason for treatment, the pregnancy state, recovery details and any other pertinent information available to facilitate assessment of the case. Where an animal has died, information from post mortem reports should be obtained if available. Reports of laboratory or other investigations should also be sought where appropriate.

To ensure that the same report is not duplicated, it is necessary that the specific address of the farm/location where the suspected adverse reaction occurred and/or the reporter of the reaction be documented. However, as many criteria as possible should be used to check for duplicates.

1.3 HUMAN REACTIONS

Where reactions in humans following use of a veterinary medicinal product are reported, it may be necessary to contact the investigating doctor or national poison/ toxicology investigation centre to clarify details of the report. Whilst recognising that it may be difficult to obtain medical information concerning a patient it is nevertheless important to capture the minimum details outlined in section 7 of the Guideline on Pharmacovigilance for veterinary medicinal products - Guidance on procedures for Marketing Authorisation Holders (EMA/CVMP/183/96) or as included in Volume 9 of The Rules Governing Medicinal Products in the European Union, Part II (using whichever is the most recent version of the document).

2. CAUSALITY ASSESSMENT

An assessment of causality should be made on each report submitted. Various approaches to assigning causality are possible. However, in order to exchange data for European Community purposes four conclusions can be made:

Category "A": Probable

Category “B”:	Possible
Category “O” ¹ :	Unclassified (cases where insufficient information was available to draw any conclusion)
Category “N”:	Unlikely to be drug related (cases where sufficient information was available and where investigation has established this beyond reasonable doubt).

In assessing causality the following factors should be taken into account:

1. associative connection, in time which may include dechallenge and rechallenge following repeated administration or in anatomic sites
2. pharmacological explanation; blood levels; previous knowledge of the drug.
3. presence of characteristic clinical or pathological phenomena
4. exclusion of other causes
5. completeness and reliability of the data in the case reports
6. quantitative measurement of the degree of contribution of a drug to the development of a reaction (dose-effect relationship).

For inclusion in category “A” (probable) it is recommended that all the following minimum criteria should be complied with:

1. There should be a reasonable association in time between the administration of the drug and onset and duration of the reported event.
2. The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the drug.
3. There should be no other equally plausible explanation(s) of the case. (If such are suggested - are they validated? What is their degree of certainty?). In particular, concurrent use of other drugs (and possible drug interactions) or intercurrent disease should be taken into account in the assessment.

Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information) then such reports can only be classified as “B” (possible), “N” (unlikely) or “O” (unclassifiable/not assessable).

For inclusion in category “B” (possible), it is recommended that this be applied when drug causality is one (of other) possible and plausible causes for the described event but where the data does not meet the criteria for inclusion in category “A”.

In cases where sufficient information exists to establish beyond reasonable doubt that drug causality was not likely to be the cause of the event then such reports should be classified as “N” (unlikely).

Where reliable data concerning an SAR is unavailable or is insufficient to make an assessment or causality then such reports should be classified as “O” (unclassifiable/not assessable).

The causality assessment made by the Authority may differ from that of the MAH. If this is the case the Authority should when possible communicate its conclusion and the reasons for the decision to the MAH.

More detailed guidance on causality assessment is given in a separate guideline on causality assessment (EMA/CVMP/552/03)

¹ Where there is a possibility that an SAR could be related to treatment but present data is not enough to draw a conclusion, it has proved to be useful to create working subcategories for O: O1 – inconclusive (cases where other factors prevent a conclusion being drawn, but a product association cannot be discounted) and O2 – unclassified (cases where insufficient or unreliable information did not allow to draw any conclusion).

3. PERIODIC SAFETY UPDATE REPORTS (PSURs)

PSURs of world-wide experience, provided at defined times post authorisation, must be evaluated to ascertain whether further investigations need to be carried out and/or whether changes should be made to the Summary of Product Characteristics, labelling or packaging.

From the information on volume of sales provided, the incidence of adverse reactions will have been documented in the report. The Authority should note that where a veterinary medicinal product is indicated for more than one species, it is clearly not possible to calculate individual species incidence of reactions.

However, theoretical calculations for single species, though arbitrary, may be of some value.

The Authority should cross-check that:

1. All individual serious reports previously notified to them are included in the PSUR.
2. Reports sent directly from veterinarians, pharmacists and other healthcare professionals, who indicated that the information would also be sent to the MAH, are included in the PSUR.
3. All relevant bibliography known to the Authority is included.
4. An overall safety evaluation of the risk/benefit profile of the product has been provided by the MAH.

The Authority should evaluate the data provided and verify whether the information provided remains in line with risk benefit analysis conducted at time of authorisation. If the evaluation of the information provided in the PSUR leads to a change in the risk benefit ratio, the Authority should clearly document this in an addendum to the original assessment report.

4. ACTION REQUIRED FOR INDIVIDUAL SAR REPORTS

The date of receipt of the report should be logged by Officer(s) of the Authority. Following the validation of the report, it should be recorded and a letter of acknowledgement sent to the reporter.

The Officer should clarify whether the authorisation holder has been informed and if not, notify the holder within 15 days that a report has been received. While the primary responsibility for any action to be taken rests with the MAH, nevertheless, depending on the nature and frequency of the reaction, the Authority will decide on a course of action. In the case of reports which have been assigned a causality 'A' or 'B' this may include:

- (a) To discuss with the MAH the nature, frequency and, if possible, the mechanism of the SAR (e.g. allergic, toxic, microbiological), and establish what action might be taken.
- (b) To await the result of the MAH investigation including, where relevant, details of batch analysis. In this regard, it is most useful to record the name of the qualified person or other appropriate person of the MAH together with relevant telephone and fax numbers.
- (c) If appropriate, to carry out independent analysis on the suspect product and/or a product from the same batch.
- (d) To subject the product to more frequent monitoring by requesting the MAH to provide, at regular intervals, a periodic safety update on the product.
- (e) To request the MAH to carry out a risk/benefit analysis on the product with particular reference to the adverse reaction experience and the volume of sales of the product or unit treatments given for the period under review.
- (f) To transmit to the Pharmacovigilance Working Party, Committee for Veterinary Medicinal Products information about regulatory action to be taken or envisaged.

- (g) To transmit to the Agency all cases related to veterinary medicinal products authorised through the centralised procedure, in no case later than 15 days following the receipt of the information.
- (h) After informing the MAH of the reasons for the action, and after discussion with the authorisation holder whenever possible,
 - to issue or to instruct the MAH to issue a mail shot or notice to veterinarians or other users with data concerning a side effect,
 - to instigate a rapid alert procedure,
 - to effect a batch or product recall via the MAH.

It should be noted that also reports of serious SARs to nationally authorised and mutually recognised products must be notified to the Agency immediately or latest within 15 days. As long as not data-processing network to facilitate the exchange of pharmacovigilance information is available, it is acceptable that only reports, which have been assigned 'A' or 'B' causality are transmitted. However, with the implementation of electronic reporting all serious SARs and human adverse reactions will require transmission to the Agency.

5. DOCUMENTATION OF DECISION TAKEN AND NOTIFICATION OF THAT DECISION

All decisions taken and the reasons for those decisions should be documented. Where a decision is made to withhold, withdraw or suspend authorisation to manufacture, import or market a product the party concerned shall be notified and informed of the remedies available to him under current legislation and the time allowed for seeking such remedies. The Agency shall also be informed of such decisions, together with the reasons on which the decisions are based.

6. STIMULATING REPORTING OF SARs

While, in order to respect the confidentiality of product information, the generic name of the active or inactive substance contained in the veterinary medicinal product should be used in any report intended for the public, nevertheless, when justified in the opinion of the Authority, the proprietary name of the product linked to the SAR may be given. In order to encourage the voluntary notification of SARs, it is useful to collate and summarise the reports validated as probable or possible and to make this information available to the professions in a relevant manner. Direct contact with practising veterinarians, pharmacists and veterinary investigative laboratories, as well as organisations representing these individuals is advocated. Other means of encouragement, e.g. by placing advertisements in relevant journals or participating in discussions at Veterinary Colleges and targeting new graduates in particular, as well as stimulating research in the area of veterinary pharmacovigilance are also useful. Ongoing encouragement of reporting is necessary and annual reporting of the experience of authorities to the professions is desirable.