

# Guidance for Industry

## Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AER's) - VICH GL24

### DRAFT GUIDANCE

*This guidance document is being distributed for comments only*

This draft guidance document describes a system for the management of adverse drug event reports following the use of marketed veterinary medicinal products.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 00D-1632.

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U.S. Department of Health and Human Services  
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Center for Veterinary Medicine  
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**PHARMACOVIGILANCE OF  
VETERINARY MEDICINAL  
PRODUCTS:  
MANAGEMENT OF  
ADVERSE EVENT REPORTS (AER's)**

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Recommended for Consultation  
at Step 4 of the VICH Process  
on 15 June 2000  
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

# Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AER's)

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***This draft guidance represents the agency's current thinking and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.***

## **I. Introduction**

Pharmacovigilance of veterinary medicinal products (VMP's) can be defined as the detection and investigation of the effects of the use of these products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products. This document will only deal with the spontaneous reporting system for identification of possible adverse events following the use of marketed VMP's.

Within all regions involved in the VICH process there are certain legal obligations for the pharmaceutical industry, the commercial party responsible for the products, with regard to adverse events reported to them. Those legal obligations relate to the acceptance of adverse event reports and the storage and submission of those reports to the authorities.

It is of importance for all parties, the Marketing Authorization Holders (MAH's), the Regulatory Authorities and the users of VMP's to develop harmonized and common systems, common definitions and standardized terminology within pharmacovigilance. Harmonization of those elements between the regions facilitates the reporting responsibilities for the MAH's, many with worldwide activities. At the same time harmonization of systems and requirements facilitates the inter-regional comparison of data and exchange of information, thereby increasing the general knowledge of a product's general performance and safety profile.

## **II. Scope**

The scope of pharmacovigilance in this VICH document is the management of the detection and investigation of the clinical effects of marketed VMP's mainly concerned with the safety and efficacy in animals and the safety in people exposed to these products. While pharmacovigilance in its broadest sense may entail a wide range of activities, this document only deals with the spontaneous reporting system for the identification of possible adverse events following the use of marketed VMP's.

## **III. Definitions**

The terms and definitions in this document are intended to harmonize other previously used terms referring to similar concepts. Within the scope of this document the following definitions of items or actions have been developed.

### **III.1 Veterinary Medicinal Product (VMP)**

Any medicinal product with approved claim(s) to having a protective, therapeutic or diagnostic effect or to alter physiological functions when administered to or applied to an animal. The term applies to therapeutics, biologicals, diagnostics and modifiers of physiological function.

### **III.2 Adverse event (AE)**

An adverse event is any observation in animals, whether or not considered to be product-related, that is unfavorable and unintended and that occurs after any use of VMP (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy or noxious reactions in humans after being exposed to VMP(s).

### III.3 Serious adverse event

A serious adverse event is any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect.

For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event.

### III.4 Unexpected adverse event

An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labeling or approved documents describing expected adverse events for a VMP.

### III.5 Adverse Event Report (AER)

An adverse event report is a direct communication from an identifiable first-hand reporter that includes at least the following information:

- an identifiable reporter
- an identifiable animal(s) or human(s)
- an identifiable VMP
- one or more adverse events

### III.6 Marketing Authorization Holder (MAH)

The Marketing Authorization Holder is the commercial party who, according to the national or regional regulations, is legally responsible for the pharmacovigilance of the VMP.  
See 21 CFR 51.300

### III.7 Regulatory Authority (RA)

The Regulatory Authority is the national or regional authority which, according to the legislation, is responsible for the issuing, adaptation or withdrawal of marketing authorizations/licences of VMP's and for pharmacovigilance activities.

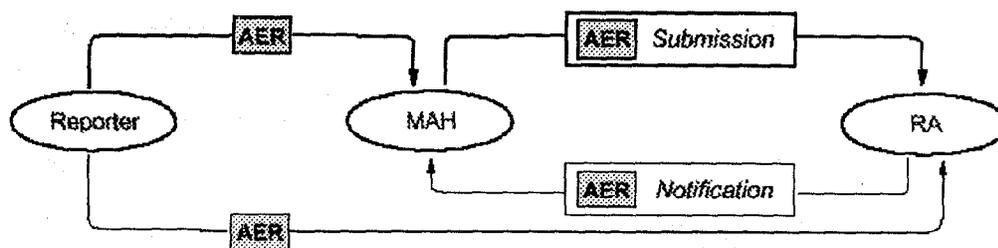
### III.8 Periodic Summary Update (PSU)

The document submitted to the RA at set intervals to support the continued marketing and the adequacy of the approved labeling of the VMP. This document should include an analysis of all AER's received during the interval and may include a bibliographical listing of articles published that pertain to the safety or efficacy of the VMP. The analysis should include a summary and review of the type, severity, and frequency of the AER's received related to the quantity sold, and a review of resulting actions.

## IV. The Pharmacovigilance Process

### IV.1 Information flow in the Pharmacovigilance System.

The flow of information is illustrated below:



Information flow in the pharmacovigilance system.

Data preferably flows as shown in the upper half of the figure, where the reporter communicates with the MAH and the MAH submits AER's it has received to the RA. An alternate path is shown in the lower half, where the reporter communicates with the RA and the RA notifies the MAH of AER's it has received.

## **IV.2 Informational unit**

The basic unit of information in the pharmacovigilance system covered by this document is the AER.

## **IV.3 Recording AER's**

The MAH should record each AER received and store it in a manner which allows easy access to the data. The receipt, acknowledgement or recording of an AER by the MAH or the RA does not necessarily have any implication regarding the veracity or authenticity of the AER nor implies any degree of causality.

## **IV.4 Submitting AER's**

The MAH submits an AER to the regional RA where the adverse event purportedly occurred as provided by the relevant requirements, either as an expedited submission or as a periodic submission. The submission of an AER does not necessarily imply an endorsement or agreement with its content, unless regional or national regulations require differently.

## **IV.5 Expedited AER submissions**

The expedited submission of certain AER's may be required (21 CFR 510.300), related to the seriousness or unexpectedness of the reported event or because of the urgency of its implications regarding the safety of animals or man. If, based on these expedited submissions, the regional RA decides on a regulatory action, the MAH should immediately inform all relevant regional RAs about this action.

## **IV.6 Periodic AER submissions**

At regular intervals, the MAH should submit all AER's not previously submitted.

## **IV.7 Reporting source**

Although reporting via the attending veterinarian is encouraged, an AER may be initiated by anyone directly involved with the purported adverse event. Preferably, an AER is communicated by the reporter directly to the MAH, but the AER may also have been routed through an agent. A communication through an intermediate agent should be considered an AER only if the agent has been authorized by the reporter and provides sufficient information to allow direct contact between the reporter and the MAH.

## **V. Data elements for the transmission of adverse event reports**

The format for submitting information about an AER should include provisions for transmitting all the relevant data elements useful to assess an AER. The data elements should be sufficiently comprehensive to cover complex reports from most sources, different sets and transmission situations or requirements. In many, if not most, instances a substantial number of data elements will not be known.

Data elements, as defined in this document, are recommended for electronic transmission. Other items recommended for electronic submission are:

controlled vocabularies  
relationships between data elements

procedures for electronic submission  
These items will be addressed in the future.

The specific data elements are described below. User guidances are presented in italics and notes for the transmission format are included as SMALL CAPITALS.

## **A. Administrative and identification information**

### **A.1 Regulatory Authority**

Business name  
Street address  
City  
State/county  
Mail/zip code  
Country

*User guidance:*  
*RA where the AER is sent.*

NOTE CONCERNING TRANSMISSION:  
TEXT

### **A.2 Marketing Authorization Holder**

#### **A.2.1 MAH information**

Business name  
Street address  
City  
State/county  
Mail/zip code  
Country

#### **A.2.2 Person acting on behalf of MAH**

Title  
First name  
Last name  
Telephone  
Fax  
e-mail

*User guidance:*  
*The person acting on behalf of the MAH is the contact person for this AER and its contents.*

NOTE CONCERNING TRANSMISSION:  
TEXT

### **A.3 Persons involved in the AER**

#### **A.3.1 Attending veterinarian**

Title  
First name  
Last name  
Business name  
Street address  
City

State/county  
Mail/zip code  
Country  
Telephone  
Fax  
e-mail

*User guidance:*  
*Veterinarian or other health professional.*

NOTE CONCERNING TRANSMISSION:  
TEXT

### **A.3.2 Animal owner**

Same as in A.3.1.

*User guidance:*  
*Animal owner or tender of the animal(s).*

NOTE CONCERNING TRANSMISSION:  
TEXT

### **A.3.3 Primary reporter category**

*User guidance:*  
*The individual/organization providing the primary information for the AER.*

NOTE CONCERNING TRANSMISSION:  
LIST: VETERINARIAN, ANIMAL OWNER, PHYSICIAN, PATIENT, OTHER HEALTH PROFESSIONALS, UNKNOWN

## **A.4 AER information**

### **A.4.1 AER identification number**

*User guidance:*  
*Unique identifier for the AER, designated by the MAH, to be referred to in future follow-ups.*

NOTE CONCERNING TRANSMISSION:  
TEXT

### **A.4.2 AER submission status**

NOTE CONCERNING TRANSMISSION:  
LIST: INITIAL, FOLLOW-UP

### **A.4.3 Date received by MAH**

*User guidance:*  
*Date initial AER received.*

NOTE CONCERNING TRANSMISSION:  
DATE FORMAT: DAY, MONTH, YEAR

### **A.4.4 Date of submission**

*User guidance:*  
*Date current AER submitted to RA.*

NOTE CONCERNING TRANSMISSION:  
DATE FORMAT: DAY, MONTH, YEAR

#### **A.4.5 Type of submission**

NOTE CONCERNING TRANSMISSION:

LIST: EXPEDITED, PERIODIC

### **B. Description of the AE**

#### **B.1 Animal data**

*User guidance:*

*Except for B.1.1, data relates to the affected animals only.*

##### **B.1.1 Number of animals exposed**

*User guidance:*

*(Estimated) number of animals exposed/treated.*

NOTE CONCERNING TRANSMISSION:

INTEGER

##### **B.1.2 Number of animals affected**

*User guidance:*

*(Estimated) number of animals affected in the AER.*

NOTE CONCERNING TRANSMISSION:

INTEGER

##### **B.1.3 Species**

NOTE CONCERNING TRANSMISSION:

LIST (TO BE DETERMINED)

##### **B.1.4 Breed**

NOTE CONCERNING TRANSMISSION:

LIST (TO BE DETERMINED)

##### **B.1.5 Production type**

NOTE CONCERNING TRANSMISSION:

LIST (TO BE DETERMINED)

##### **B.1.6 Sex**

NOTE CONCERNING TRANSMISSION:

LIST: FEMALE, MALE, UNKNOWN

##### **B.1.7 Physiological status**

NOTE CONCERNING TRANSMISSION:

LIST: INTACT, NEUTERED, PREGNANT, UNKNOWN

##### **B.1.8 Weight**

*User guidance:*

*(Estimated) weight in kilos of the animal(s) affected.*

NOTE CONCERNING TRANSMISSION:

NUMBER (2 DECIMALS)

##### **B.1.9 Age**

*User guidance:*

*(Estimated) age of the animal(s) affected.*

NOTE CONCERNING TRANSMISSION:  
NUMBER (2 DECIMALS) AND UNITS (MINUTES, HOURS, DAYS, WEEKS, MONTHS, YEARS, UNKNOWN)

**B.1.10 State of health at time of exposure**

NOTE CONCERNING TRANSMISSION:  
LIST: GOOD, FAIR, POOR, UNKNOWN

**B.1.11 Illness/reason for use of VMP(s)**

*User guidance:*  
*The actual reason for use should be noted, not by default the registered indication(s). Mention symptoms if informative.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2 VMP(s) data and usage**

*User guidance:*  
*The information below should be given for all VMP(s) involved in the AE.*

**B.2.1 Brand name**

*User guidance:*  
*Brand name of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.2 Registration number**

*User guidance:*  
*Registration number of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.3 Active ingredient**

*User guidance:*  
*Active ingredient of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.4 Strength**

*User guidance:*  
*Concentration of the active ingredient of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.5 Dosage form**

*User guidance:*  
*Dosage form of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
LIST (TO BE DETERMINED)

**B.2.6 Company**

*User guidance:*

*Company involved with the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.7 Lot number**

*User guidance:*

*Lot number of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.8 Route of exposure**

*User guidance:*

*Route of exposure/administration of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
LIST (TO BE DETERMINED)

**B.2.9 Dose per administration**

*User guidance:*

*Real dose administered, not by default the dosage as registered.*

NOTE CONCERNING TRANSMISSION:  
TEXT

**B.2.10 Interval of administration**

*User guidance:*

*Interval of administration or frequency or administration of the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
LIST (TO BE DETERMINED)

**B.2.11 Date of first exposure**

*User guidance:*

*(Approximate) date of first exposure/treatment with VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
DATE FORMAT: DAY, MONTH, YEAR

**B.2.12 Date of last exposure**

*User guidance:*

*(Approximate) date of last exposure/treatment with VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
DATE FORMAT: DAY, MONTH, YEAR

**B.2.13 Who administered the VMP**

*User guidance:*

*Category of the person who administered the VMP involved in the AE.*

NOTE CONCERNING TRANSMISSION:  
LIST: VETERINARIAN, OWNER, MEDICAL STAFF, OTHER, UNKNOWN

**B.2.14 Use according to label**

*User guidance:*

*Information on whether the VMP was used according to its label recommendations.*

NOTE CONCERNING TRANSMISSION:

LIST: YES, NO, UNKNOWN

**B.2.15 Explanation for off-label use**

*User guidance:*

*Explanation on why the VMP was not used according to its label recommendations. To be filled only if 'no' was selected in B.2.14.*

NOTE CONCERNING TRANSMISSION:

TEXT

**B.3 Adverse event data**

**B.3.1 Date of onset of AE**

*User guidance:*

*(Approximate) date on onset of the AE.*

NOTE CONCERNING TRANSMISSION:

DATE FORMAT: DAY, MONTH, YEAR

**B.3.2 Length of time between exposure to primarily suspect VMP(s) and onset of AE**

*User guidance:*

*Primarily suspect VMP(s) are those VMP(s) for which the submitting MAH is responsible. Length of time refers to the difference between B.2.12 and B.3.1.*

NOTE CONCERNING TRANSMISSION:

LIST OF BIOLOGICALLY RELEVANT CATEGORIES (TO BE DETERMINED)

**B.3.3 Duration of AE**

*User guidance:*

*(Approximate) length of time the AE lasted.*

NOTE CONCERNING TRANSMISSION:

TEXT

**B.3.4 Narrative of AE**

*User guidance:*

*Describe the sequence of events including:*

*administration of VMP(s)*

*all clinical signs*

*sites of reaction*

*severity*

*pertinent laboratory test results*

*necropsy results*

*possible contributing factors*

*treatment of AE*

*relevant medical history*

NOTE CONCERNING TRANSMISSION:

TEXT

**B.3.5 Adverse clinical manifestations**

*User guidance:*

*Adverse clinical manifestations observed in the AE.*

NOTE CONCERNING TRANSMISSION:  
LIST (TO BE DETERMINED)

**B.3.6 Treatment of AE**

*User guidance:*

*If the AE was treated, description of the treatment should be done in the narrative B.3.4.*

NOTE CONCERNING TRANSMISSION:  
LIST: YES, NO, UNKNOWN

**B.3.7 Relevant medical history**

*User guidance:*

*If there is relevant medical history for the affected animal(s) which will help the assessment of the AE, include it in the narrative B.3.4.*

NOTE CONCERNING TRANSMISSION:  
LIST: YES, NO, UNKNOWN

**B.3.8 Outcome to date**

B.3.8.1 Ongoing

B.3.8.2 Recovered

B.3.8.3 Alive with sequelae

B.3.8.4 Died

B.3.8.5 Killed/euthanized

B.3.8.6 Unknown

*User guidance:*

*The number of animal(s) in each category should be given. Sequelae mean irreversible effects. The total number from B.3.8.1 to B.3.8.6 should be equal to B.1.2.*

NOTE CONCERNING TRANSMISSION:  
LIST: INTEGER

**B.4 Dechallenge-Rechallenge information**

*User guidance:*

*The information in that section relates to affected animal(s).*

**B.4.1 Previous exposure to the primarily suspect VMP(s)**

*User guidance:*

*Only exposures outside the dates mentioned in B.2.11 and B.2.12. If yes is selected, put the dates of previous exposure in the narrative B.3.4.*

NOTE CONCERNING TRANSMISSION:  
LIST: YES, NO, UNKNOWN

**B.4.2 Previous AE to the primarily suspect VMP(s)**

*User guidance:*

*Only clinical manifestations outside those mentioned in B.3.5. If yes is selected, put the clinical signs in the narrative B.3.4.*

NOTE CONCERNING TRANSMISSION:  
LIST: YES, NO, UNKNOWN

**B.4.3 Did AE abate after stopping the primarily suspect VMP(s)**

*User guidance:*

*'Not applicable' is used when there is no repeated dose or long-lasting signs.*

NOTE CONCERNING TRANSMISSION:

LIST: YES, NO, UNKNOWN, NOT APPLICABLE

**B.4.4 Did AE reappear after re-introduction of the primarily suspect VMP(s)**

*User guidance:*

*'Not applicable' is used when the primarily suspect VMP(s) is not stopped or not re-introduced.*

NOTE CONCERNING TRANSMISSION:

LIST: YES, NO, UNKNOWN, NOT APPLICABLE

**B.5 Assessment of AE**

**B.5.1 Attending veterinarian's assessment**

*User guidance:*

*Assessment of the attending veterinarian on the association between the VMP(s) and the AE.*

*Description of the categories in the list is provided in appendix 1.*

NOTE CONCERNING TRANSMISSION:

LIST: PROBABLE, POSSIBLE, UNKNOWN, UNLIKELY, NO ATTENDING VET

**B.5.2 MAH assessment**

*User guidance:*

*Assessment of the MAH on the association between the primarily suspect VMP(s) and the AE.*

*Description of the categories in the list is provided in appendix 1.*

NOTE CONCERNING TRANSMISSION:

LIST: PROBABLE, POSSIBLE, UNKNOWN, UNLIKELY, NO ASSESSMENT

## **Appendix 1**

Reporting veterinarians and the MAH may comment on whether they consider that there is an association between the primarily suspect VMP(s) and the AE reported.

Four categories indicating the assessment of the likelihood of this association can be made.

**PROBABLE:** for inclusion in the category 'probable', all of the following minimum criteria should be met:

- There should be a reasonable association in time between the administration of the VMP and onset and duration of the reported AE.
- The description of the clinical phenomena should be consistent with, or at least plausible, given the known pharmacology and toxicology of the VMP.
- There should be no other equally plausible explanations for the AE.

When any of the above criteria cannot be satisfied (due to lack of sufficient information or conflicting data) then the association should not be assessed as 'probable'.

**POSSIBLE:** for inclusion in the category 'possible', association of the AE with administration of the primarily suspect VMP(s) is one of other possible and equally plausible explanations for the described event.

**UNLIKELY:** where sufficient information exists to establish that the described event was not likely to have been associated with administration of the VMP(s), or other more plausible explanations exist, the assessment should be categorized as 'unlikely'.

**UNKNOWN:** all events where reliable data is either unavailable or is insufficient to make an assessment should be categorized as 'unknown'.

## **Appendix 2**

To fill an AER related to human exposure to VMP(s), the following user guidance should be considered:

- A.3.1: enter the information on the 'attending physician'
- A.3.2: if different from animal owner, enter the information on the person exposed to the VMP(s)
- B.1: relates to the person exposed to the VMP(s)
- B.1.3: select 'human'
- B.1.4: not applicable for humans
- B.1.5: not applicable for humans
- B.1.11: for most cases 'accidental exposure' will be entered
- B.2.8: indicate the route of exposure
- B.2.9: indicate the dose to which the person was exposed
- B.2.10: for most cases 'once' will be entered
- B.2.12: for most cases there will be no date entered
- B.2.13: not applicable
- B.2.14: not applicable
- B.3.5: not applicable to humans
- B.5.1: assessment of attending physician