



**GUIDELINE FOR ADVERSE VETERINARY DRUG
EVENTS MONITORING (PHARMACOVIGILANCE)**

FIRST EDITION

**THE VETERINARY DRUG AND ANIMAL FEED
ADMINISTRATION AND CONTROL AUTHORITY
(VDFACA)**

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Foreword

Medicines are one of the most essential components in the animal health care system. This indisputable fact makes rational selection, procurement, distribution, and use of medicines of paramount importance in animal health care. Worldwide, numerous numbers of veterinary drugs are being released into the market every day with incomplete knowledge as to their safety levels when used by wide variety of population category other than the one studied in the limited clinical trials making safety of medicines as one important concern.

Hence a complete pharmacovigilance system needs an up to date and practical guideline to provide information on the safety and efficacy of a veterinary drug once it is marketed is limited to premarketing evaluation, clinical trials and other factors in the product development process. Moreover pharmacovigilance can also provide guidance to the various partners of pharmacovigilance as to what their roles and responsibilities should be towards the maintenance of a national drug safety.

I would like to take this opportunity to thank all those who contributed in developing and printing this Adverse Drug Event monitoring/Pharmacovigilance Guideline. I also call upon interested parties to continue their support by forwarding their comments and suggestions to the Veterinary Drug and Feed Administration and Control Authority (VDFACA), P.o.box 31303 Addis Ababa, Ethiopia., Tel.251-115524045, e-mail: vdfaca@ethionet.et.

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Abbreviations

ADE Adverse Drug Event

AEs Adverse Events

ADR Adverse Drug reaction

MAH Market Authorization Holder

RAs Regulatory Authorities

SPC Summary of Product Characteristics

VDFACA Veterinary Drug and Feed Administration and Control Authority of Ethiopia



Definitions

1. "Veterinary drug" means any substance or mixture of substances used in the diagnosis, treatment or prevention of animal disease, and includes products used to treat against internal and external parasites and disease transmitting vectors, biological products, sanitary items and veterinary instruments.
 2. "Pharmacovigilance" means the science and activities relating to the detection, assessment, understanding and prevention of adverse affect or any other possible drug related problems.
 3. "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 Exposure to veterinary drugs. Included are events related to a suspected lack of expected efficacy according to approved labeling or noxious reactions in humans after being exposed to veterinary drug(s).
 4. "Serious adverse event" is any adverse event which results in death, is life-threatening, and results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect.
 5. "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 veterinary drug.
 6. "Adverse Event Report" is a direct communication from an identifiable first-hand reporter that includes at least an identifiable reporter, an identifiable animal(s) or human(s), an identifiable drug and one or more adverse events.
 7. "A spontaneous report" is a communication to a market authorization holder (MAH), regulatory authority or other organization that describes an adverse event involving one or more drugs.
 8. "Signal" is reported information (at least 3 spontaneous case reports) on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.
 9. "Product quality defect" is quality problems of products i.e.; suspected contamination, questionable stability, defective components, poor packaging or labeling, or unexpected therapeutic ineffectiveness.
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10. "Lack of efficacy" lack of expected efficacy of a veterinary drug according to the indications claimed for.
 11. "Off-label use" the use of a veterinary drug that is not in accordance with the summary of the product characteristics (SPC), including the misuse and serious abuse of the product.
 12. "Marketing authorization holder" is the company in whose name the marketing authorization has been granted or other legally delegated company.
 13. "Authority" means Veterinary Drug and Animal Feed Administration and Control Authority of Ethiopia.
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Introduction

Pharmacovigilance mainly aimed at safety and efficacy in animals and safety in people exposed to the veterinary medicinal products. It is important to monitor the continued safety and efficacy of veterinary drugs in use and thus helps to increase public and animal health. An adverse event (AE) reporting and monitoring system facilitates the collection of unbiased and timely safety data observed during veterinary clinical practice in 'real life' circumstances. It is also important in detection of lack of efficacy, detection and prevention of counterfeit and substandard products in veterinary practice.

This guideline only deals with the spontaneous reporting system for identification of possible adverse events (AEs) following the use of marketed veterinary drugs. All adverse events should be considered reportable according to the requirements outlined in this guidance and key players to this activity are all stakeholders, including market authorization holders (MAHs), animal health professionals and owners of animals. Early detection and reporting of safety and efficacy problems following veterinary drug use in animals is helpful to reduce the harmful effects resulting from use of these veterinary drugs, to assess the risk and benefit of the product, and improve the selection and rational use of drugs through provision of timely warning to animal healthcare professionals.

This guideline can assist MAHs, regulatory authorities (RAs), animal health professionals and owners to understand the importance of AEs monitoring, procedures of reporting AEs and the essential components of a AEs case report to improve drug safety. These essential components include information about the patient animal, and description of the adverse events, the suspected drug(s) and the reporting individual or body.

Principles of efficient reporting by reporters, data handling and analysis are also covered.

Proclamation no. **728/2011** gives Veterinary Drug and Feed Administration and Control Authority the mandate to carry out post-marketing surveillance in order to ensure the safety, efficacy and quality of medicines that are marketed in Ethiopia.

According to article 7 of the proclamation No **728/2011** the authority is responsible to:

- Carry out post marketing surveillance with a view to assessing the resulted benefit and damage of registered veterinary drugs.
- Undertake and coordinate post marketing surveillance of Veterinary Drug or Feed supplied for sale, and based on the results, take necessary measure against non-compliance with the relevant requirements.
- Ban the use of veterinary drugs and its registration shall be suspended or revoked where, the finding of a post marketing surveillance proves that: it lacks the expected safety, efficacy or quality for the intended use, its risk outweighs its benefit; or and its withdrawal period and residue in the treated animal does not comply with national or international requirements.

More over the holder of the certificate of registration shall supply to the Authority the pharmacovigilance information that he possesses relating to the veterinary drug during the post market surveillance

Scope

The scope of adverse event reporting and monitoring in this guideline is the detection and investigation of possible adverse events following the use of marketed veterinary drugs and is mainly concerned with the safety and efficacy in animals and the safety in people exposed to these products. AE reporting and monitoring covers all veterinary drugs including biologicals, herbal drugs, and veterinary medical devices circulating in the Ethiopian market.

Rationale for AEs Monitoring

Information on the safety and efficacy of a veterinary drug once it is marketed is limited to premarketing evaluation, clinical trials and other factors in the product development process. Therefore, premarketing safety evaluation of veterinary drugs at the time of registration is inherently limited due to the following three reasons:

- (i) The animal population in clinical trials is very selective and limited. Many types of animals with different characteristics are often excluded from studies, such as
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animals in certain age groups and sex, animals with diseases other than the one being treated and animals using other drugs concurrently. This often prevents the identification of side effects caused by interaction of more than one drug given at the same time.

- (ii) The duration of clinical trial is short. Such studies do not allow the detection of adverse effects that appear after long periods of use or exposure, especially with chronic medication.
- (iii) Differences between countries which lead to variation in patient factors, variation in drug utilization among animal health professionals, variation in drug manufacturing processes used which influence pharmaceutical quality and composition of locally produced products and those imported outside the country.

For these reasons, it is obvious that safety and efficacy monitoring of a drug is carried out through the life cycle of each veterinary drug. VDFACA, Marketing authorization holders and animal health professionals are responsible for monitoring these products.

Objectives of AE Monitoring

1. To monitor the nature and frequency of AEs including periodic re-evaluation of the benefit-risk ratio of drugs in order to assist the regulatory bodies, scientists and owners take appropriate action to minimize risks of AEs to animals by:
 - i. Providing updated veterinary drug safety information to animal health care professionals and other stakeholders.
 - ii. Upgrading package inserts, designing appropriate package insert information and dissemination of information regarding a recall or withdrawal of the product from the market or restrictions for marketing
 - iii. Raising awareness by designing proper education programmes for animal health professionals, animal owners and others
 - iv. Initiation of further studies for education value. For example benefit of the drug especially in the long term for prevention of relapse or study of new indication, overuse, misuse or possible mechanism underlying the adverse reaction observed.
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2. To identify risk factors that may predispose, induce or influence the development, severity and incidence of adverse events in animals.

Basic Principles of Efficient AE Reporting

- (i) Report the adverse event immediately after it occurs, as delay in reporting will make reporting inaccurate and unreliable.
- (ii) If possible, take the decision to report whilst the patient animal is still with you, which gives a chance for the reporter to clear any ambiguity by re-questioning the owner or examining the patient animal, so that the details can be filled in at once on the reporting form.
- (iii) Think about any other factors which may contribute in causing the event such as other prescribed drugs, self-medication, herbal products, feed, chemicals, ask the owners particularly about other drugs taken.
- (iv) If you get any supplementary data later, e.g. if the same patient animal develops the effect again or if something happens which increases your suspicion or seem to exclude the reaction, please send in a supplementary note immediately using the AEs reporting form with the patient animal identifiers.
- (v) All reports must have at least the following four data elements
 - a) An identifiable patient(human or animal(s))
 - b) A suspected adverse event
 - c) A named suspected drug (s)
 - d) An identifiable reporter
- (vi) Always write legibly.
- (vii) One animal or one human being, or a medically appropriate group (for example a herd) exhibiting similar clinical signs should be included in a single report.

Reporting of Adverse Drug Events (ADEs)

Collection of reports from several reporters in different parts of the country assists in making associations (strengthening of signal) between a particular drug and the

adverse event. Therefore, it is better to ensure that all necessary information for reporting of AE reports are obtained and reported through the reporting form.

1. Components of an ADE Report

An ADE report should include at least the following components;

- (i) Animal/human affected information
- (ii) Adverse event description (include laboratory results if available)
- (iii) Information related to the suspected drug(s)
- (iv) Information about the reporter

The reporter should fill these components in the report format (Annex 1) for proper assessment of the AE case reports:

I. Animal information

- (i) Number of animals treated
- (ii) Number of animals showing signs
- (iii) Number of animals dead (if available)
- (iv) Characteristics of animals showing reactions (Species/breed, sex, age and weight)
- (v) Physiological condition of the animal

II. Adverse Event(s)

- a) Brief description of the AE(s): describe briefly as clearly as possible the nature of the adverse event being reported including the signs and severity.
 - b) Time or date of onset of the adverse event: state the time of onset or the occurrence of the adverse event in relation to the administration of the drug. Indicate the date of onset in the following order; day, month and year. Describe also whether the adverse event appeared immediately following drug administration or not and the duration of symptoms.
 - c) Describe whether the AE disappeared or continued when there was complete withdrawal of the treatment or reduction of the dose of the drug.
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- d) Include other relevant information such as treatment history of the animal, laboratory tests done and postmortem findings to confirm the case.

III. Suspected drug(s)

1. Name of the suspected veterinary drug (s): trade name and generic name of the drug including its manufacturer, batch number and expiry date should preferably be reported.
2. Administered dose, frequency and route of administration should be clearly filled on the format.
3. The dates of beginning and termination of the administration of each drug should be stated, and preferably recorded as follows: date/month/year. If drug administration has not been terminated at the time of reporting, state 'Continuing'
4. Reason for use: state indication or condition for which the drug(s) was given for.
5. Particulars of other veterinary drug(s) administered to the animal concurrently with the suspected drug, including drug administration for at least one month previously with dosage, route of administration, duration of administration and indications.
6. Mention if any treatment given to the patient animal after experiencing the AE.
7. Provide relevant information on medical devices

IV. Reporter's Information

Writing the name and contact address of the reporter will help the regulatory body to get in touch if more information is needed. It will also help to send feedback to the report. Personal particulars such as name, address of the animal health facility (vet hospital, institution, vet clinic, animal health post or others), e-mail address (optional), signature, telephone number and date of reporting the reaction (indicating date/month/year) are required. The contact details will be kept confidential and will not be passed on to anyone outside without the reporters' permission. While the VDFACA publishes information derived from these reports, it never includes the personal details of the people who made the reports.

2. Who Should Report

The following concerned bodies should report any case of suspected AEs when encountered to the patient animal or human in contact as part of their responsibility.

- (i) All animal health professionals including specialists, veterinarians, veterinary science graduates, veterinary pharmacists, animal health assistants, traditional medicine practitioners and others
- (ii) Animal health institutions using veterinary drugs (government and private veterinary clinics, veterinary pharmacies, and research and education institutions)
- (iii) Marketing Authorization Holders (manufacturers and/or local agents) should have safety data reporting system to the regulatory authority, which are reported to them from users of their products. It is mandatory for veterinary drug MAHs to monitor their products in the market and report any suspected undesirable effects to the authority.
- (iv) Animal owners can report to nearby animal health professionals and/or animal health clinic to be reported through.

3. What to Report

Any undesirable adverse event suspected to be associated with use of veterinary drug, biological, herbal drugs, and medical devices should be reported. The following events should be reported.

- i. Serious adverse events
 - ii. Unexpected adverse events
 - iii. An observed increase in frequency of a known adverse event
 - iv. All suspected AEs associated with drug-drug, drug-feed or drug-feed supplements interactions
 - v. AEs in special field of interest such as drug abuse and drug use in pregnancy and during lactation
 - vi. AEs observed after off-label use of drugs
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- vii. An adverse event to veterinary drugs, which occurs in humans
- viii. Environmental problems

4. How to Report

The System of AEs notification in Ethiopia is a centralized reporting, whereby suspected case reports of AEs are reported by different bodies to Veterinary Drug and Animal Feed Administration and Control Authority (VDFACA). Reporters should send accurate information to achieve a better and efficient program on AEs monitoring in Ethiopia.

- a. Send your report in a standardized self adhesive postage paid “yellow form”, which you can find it from VDFACA offices and regional and/or woreda animal health coordination offices and veterinary clinics, you can also find it from VDFACA website (<http://www.vdfaca.gov.et>).
 - b. Dully fill the AEs reporting form
 - c. Use a separate form for each patient animal showing different AEs
 - d. A completed AEs case report form should immediately be sealed and mailed preferably directly to VDFACA within three days or through other reporting centers for onward transmission to the VDFACA
 - e. Reports can also be submitted online by going to the VDFACA website <http://www.vdfaca.gov.et> and clicking on “adverse drug event reporting”.
 - f. Reports may be sent by e-mail through vdfaca@ethionet.et
 - g. AE reports may be faxed in cases of perceived urgency
 - h. Any follow-up information for an AE case that has already been reported can be sent on another AE form, or communicated by telephone, fax or e-mail. To enable this information be matched with the original report it is very important that follow-up reports are identified and the following should be indicated in the report;
 - i. That it is a follow-up information,
 - ii. The date of the original report and
 - iii. The patient animal identities.
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Management of an adverse event report

Immediately after an individual adverse event report is received several activities should be initiated.

1. Coding of the report:

Firstly, a unique case-number should be given to each report. This is needed to identify an individual case for further communication and possible follow-up information. This number could consist of an initial for the Authority and reporter, a consecutive number and the reporting year (e.g. VD-AER/HZ/001/18).

2. Acknowledge the reporter (s):

Secondly, an acknowledgement letter or note will be sent to the reporter for every AE report received with an additional reporting form. If the information for a case is very limited and further information is expected (for example, to complete the necessary components), a request for more information should be made, especially if a significant or unexpected adverse event is reported.

3. Causality assessment:

Thirdly, for each case an attempt should be made to assess the causal relation of the adverse event to the product administration. This assessment can be quite complex and should preferably be done by a veterinarian. It should take into account the following factors:

- i. Associative connection with the treatment, in time or in anatomical sites
 - ii. Pharmacological and/or immunological explanation, blood levels, dose-effect relationship
 - iii. Presence of characteristic product related clinical or pathological phenomena.
 - iv. Previous knowledge of similar reports
 - v. Exclusion of other causes
 - vi. Completeness and reliability of the data in the case reports
 - vii. Dechallenge and rechallenge assessment if available
 - viii. If necessary, an active cohort study may be conducted by the authority for further investigation of signals
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4. Inform the MAH:

If the adverse event report was received directly by the VDFACA the MAH or importer should be informed on the case for further investigations.

5. Handling of the reports:

The AE reports shall be stored in a confidential database or any other secured system at VDFACA. The details of the reporter and the code given to it should be stored separately. Publications will not disclose trade name of products unless regulatory actions have been taken.

6. Communication of findings:

The outcome of the report, together with any important or relevant information relating to the reaction reported, will be communicated to the reporters and other parties as appropriate. After a significant AE is detected and a decision on the course of action determined, the information shall be communicated rapidly and systematically to animal health professionals, MAHs, livestock and fishery offices, other public and private animal health institutions, the media and the public.

Possible regulatory outcomes

If an adverse event is confirmed based on the causality assessment of the reports and/or active surveillance of the suspected products the following regulatory measures may be decided based on the severity of the AEs the veterinary medicine imposes.

- Suspension or revocation of market authorization;
 - Inclusion of additional label warning statements;
 - Product recalls;
 - Formulation or manufacturing process changes; or
 - Education of product users through the media or other appropriate forums.
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**Veterinary Drug and Animal Feed
Administration and Control Authority**

For Official Use Only

Adverse event no

Date received

Date acknowledged

Veterinary Drugs Adverse Event Reporting Form

1. Animal Information								
Species/Breed	Sex	age	weight	Physiological condition (eg. Pregnancy)	Number of animals treated on this	Number of animals reacted	Number of deaths	
2. The Adverse Drug Event								
Date of onset of an adverse event				Description of the adverse event:				
Duration of the event								
laboratory findings (if done)				Postmortem findings (if any)				
Lab test	Result		test date					
3. Drugs suspected to have caused the adverse event								
Trade and Generic Name:			Manufacturer:		Batch Number:	Expiry Date:		
Route of Administration	Dose and Frequency		Date Started/Given	Date Stopped	Reason for use			
Details of products given concurrently				Drugs given after onset of the adverse event				
4. Product Quality Problems (Color change, change of odor, caking, precipitation, incomplete packs, poor packaging/labeling, etc.)								
5. Lack of Expected Efficacy								
6. Reported by:								
Name				e-mail			Phone No.	
Profession/Qualification								
Working institution/office								
Date reported					Signature:			