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VETERINARY MEDICINES DIRECTORATE

GUIDELINES FOR PHARMACOVIGILANCE

Document No.	Effective Date:	Review Due Date:
Revision No.	Revision Date:	

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Prepared by			
Reviewed by			
Approved by			

Approval

Document Revision History

Version	**Effective Date**	**Description of changes**	**Reason for changes**	**Approved by**

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Abbreviations

ADR - Adverse Drug Reactions

MAH - Market Authorization Holder

SF - Substandard and Falsified

VMD - Veterinary Medicines Directorate

VMP - Veterinary Medicinal Product

Definitions

For the purpose of this document, the following definitions (adapted from the World Health Organization) are used.

Falsified- Medical products that deliberately/fraudulently misrepresent their identity, composition, or source.

Post-marketing surveillance - Surveillance activities that occur following market approval of a medicine, including maintenance of product authorization and/or registration of variations or renewals; regular inspections of manufacturers, wholesalers, distributors, and retailers; quality control testing; pharmacovigilance; promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products.

Quality assurance - An integrated system of activities involving planning, quality control, quality assessment, reporting, and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence.

Screening tests - The qualitative and/or quantitative tests that could rapidly acquire preliminary analytical information or data on the quality of medical products in the field.

Simple random sampling - Random sampling is a probability-based sampling technique whereby a group of subjects is selected (a sample) for study from a larger group (a population). Each subject is chosen entirely by chance, and each has an equal (or non-zero in the case of complex random sampling) chance of being included in the sample.

Substandard - Also called "out of specification," refers to authorized medical products that fail to meet either their quality standards or specifications, or both.

Introduction

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects (events) or any other drug-related problem (WHO definition). Adverse effect is any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any use of a VMP. It's the detection and investigation of the effects of the use these products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products. The aim of a pharmacovigilance system is to monitor medicine safety and efficacy on an on-going basis and to identify any changes in the risks and benefits (including efficacy) arising from the use of a Veterinary Medicinal product (VMP). It monitors the safety of veterinary medicines, including vaccines, used for the prophylaxis, diagnosis or treatment of disease in animals once they reach the market after authorisation.

The task of veterinary pharmacovigilance is to ensure;

i Safe use of veterinary medicines in animals
ii Safety of animal-derived food
iii Safety for people who get into contact with veterinary medicines
iv Safety for the environment

Before granting market authorization for a VMP, aspects of quality, efficacy and safety of the new drug are studied by experts of the regulatory authority with the aim to guarantee a

maximum of drug safety. The aim cannot be achieved by a scientific evaluation before granting market authorization. It is necessary to undertake continuous Surveillance of the VMP under field conditions. Many adverse effects can be seen only after the use of the drug in clinical practice in a large population of animals. Sensitive subpopulations such as young or specific sensitivities of the animal species and breed can only be discovered by use of the drug in large scale. Pharmacovigilance of marketed drugs is a shared responsibility of the regulatory authority and the Market Authorization Holder (MAH).

Objectives of Pharmacovigilance

i Preventing harm from adverse reactions in animals arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and
ii Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to farmers, animal health professionals and the public.
iii To monitor safety, quality and efficacy of veterinary products available in the market in different areas/region at various levels of distribution/supply chain with the aim to assess the exposure of animals to poor-quality medicines and propose appropriate actions;
iv To identify possible causes of inferior quality of specific products to which animals are exposed.
v To test quality of veterinary products in order to support VMD in identification of manufacturers non-compliant with quality standards and in adoption of regulatory measures;
vi To detect and report any spurious/falsely labelled/falsified/ counterfeit products penetrate to the market and what may be the health impact for animals and humans;
vii To identify SF medical products that have reached consumers and to evaluate pharmacovigilance reporting by animal health professionals and farmers.
viii For raising awareness concerning the importance of reporting an unusual lack of efficacy of veterinary products.
ix To improve and enhance safety measures, which involve statistical analysis of adverse drug reactions (ADRs) as reported by Animal Health professionals and farmers, thereby detecting signals of ADRs that may warrant further investigation.

Importance of Pharmacovigilance

It is important to continually monitor the safety of a VMP after it moves from development into the wider population. During product development, pre-authorization studies (for example target animal safety studies, field studies) may identify common Adverse effects. However, the size and scope of the safety evaluation under field conditions is typically limited. Brief product exposure durations and exclusion off sub-groups, such as pregnant, old/young, those with co-morbid conditions or those receiving concomitant products create the product's initial profile, but do not indicate how the product will perform under field conditions in the wider population.

Therefore, it is important to put in place systems and procedures to collect and analyse reports from the field, to confirm or further improve knowledge about the product safety profile in the market place.

An effective pharmacovigilance system;

i Is a key component of drug regulation systems,
ii Promotes public health through early identification, assessment and risk mitigation of drug safety issues not identified pre-approval
iii Informs communications (labels, product information sheets, safety alerts) that help ensure approved products remain safe and effective
iv Promotes public trust/confidence

Benefits of an effective pharmacovigilance system.

i To ensure the health and welfare of animals and humans by;
ii Continued monitoring of the benefit/risk balance of VMPs,
iii Providing assurances on the continued safety of VMPs,
iv Increased knowledge of the safety profile, leading to better advice for the users,
v Updated and improved label warnings leading to safer use of medicines,
vi Removal from the market place of VMPs (or batches of VMPs) where a change in safety (or efficacy) profile, resulting in a negative benefit risk balance, has been identified.

Role of Marketing Authorization Holder

The MAH must ensure they have appropriate systems of pharmacovigilance and risk management in place to ensure responsibility and liability of their products on the market. They should;

i Establish and maintain a system of reporting ADR
ii Prepare and submit the following to the VMD;
iii Serious adverse reaction reports in animals
iv Reports of adverse reaction in human
v Periodic safety updates
vi Any information on;
    - Lack of efficacy
    - Adverse reactions related to off-label use
    - Potential environmental problems
    - Validity of withdrawal periods

Why is it important to report suspected adverse reactions?

As a practising veterinarian or veterinary health care professional you are in a unique position to observe adverse reactions when they occur, and your key role in reporting them will directly contribute to the safety of these medicines. Your observations are the basis on which the Competent Authority can give appropriate advice on safe and efficacious use of authorised veterinary medicines to you and your colleagues. A well-defined benefit to risk profile of authorised veterinary products is essential for selecting the right treatment in veterinary practice. To ensure that veterinary medicines are safe and effective, their authorisation is preceded by thorough pharmacological and toxicological investigations. However, only limited

numbers of animals can be treated in the studies that lead to the approval. Adverse reactions, which occur rarely or are specific for certain breeds or groups of animals, may come to light only when the medicines are widely used in clinical veterinary therapy. It therefore is essential that all suspected adverse reactions are brought to the attention of the VMD to enable it to continuously assess the benefits of a product in view of its risks.

What should be reported?

It is important that adverse reactions are reported even if a relation to the product(s) used is only suspected, especially the following types of reaction:

i an adverse reaction, which results in death
ii an adverse reaction, which results in significant, prolonged or permanent signs
iii an unexpected adverse reaction, which is not mentioned on the label or package insert
iv an adverse reaction to veterinary medicines, which occurs in man
v an adverse reaction, which is observed after off-label use of medicines
vi lack of expected efficacy (possibly indicating development of resistance)
vii a problem related to withdrawal periods, possibly resulting in unsafe residues
viii possible environmental problems
ix a known adverse reaction (mentioned on the package insert), which is serious or which seems to increase in frequency and/or seriousness.

If the suspected adverse reaction is serious, particularly if an animal has died, the incident should be reported immediately. It is important that as much detail as possible is reported. If available, laboratory data, post-mortem reports, photographs or other relevant information should be included, and likely differential diagnoses should be considered.

Legislative framework

There is a legal obligation for the VMD and for the Marketing Authorisation Holders (the pharmaceutical companies) to collect and evaluate the reports of suspected adverse reactions. It is required that the obtained information is shared between the Competent Authority and the concerned Marketing Authorisation Holder.

How are suspected adverse reactions reported?

The reporting should be done on the VMD Pharmacovigilance reporting form (**Annex 1**). It is important that the form is completed with as much detail as possible. Available laboratory data, post-mortem reports, photographs and other relevant information should be attached to the form.

What happens after a suspected adverse reaction has been reported?

Based on the available information an assessment of the causal relationship between the administration of the medicine and the reported reaction is made by the Competent Authority. Should a pattern of adverse reactions for a specific product emerge, regulatory actions to enhance the safety will be initiated depending on the conditions under which the adverse reactions have appeared and on their seriousness. Examples are:

i inclusion of warnings on the product label
ii changes in the authorised use of the product
iii suspension of the product from the market until the safety issues are solved.

A good pharmacovigilance system provides for the detection of adverse reactions and increased knowledge of known adverse effects in animals. The reporting of adverse reactions provides for continuous monitoring of the benefits and risks of veterinary medicines once they are marketed and thus contributes to their safe use.

Minimum requirements for adverse reaction reports

i A case report should provide at least the following data;
ii An identifiable source eg the name and address (Farmer, Veterinarian)
iii Animal details; species, sex, breed, age
iv Veterinary medicinal product concerned eg the name

The adverse reaction reports details

i Contents/ required information for serious adverse reaction reports
ii Marketing Authorization holder (MAH)
iii Name
iv Address
v MAH case reference number
vi Date of receipt of the report by the MAH
vii Source of report; spontaneous, clinical trial, post –authorization study
viii Details of the original reporter.
ix Animal details
x Number treated

Characteristics of the animals showing signs

i Species
ii Breed
iii Sex
iv Age
v Weight

Suspected Veterinary Medicinal Product

i Product name
ii Approved scientific names
iii MAH number
iv The Anatomical Therapeutic Chemical Classification System for veterinary medicinal products (ATCvet)
v Pharmaceutical form
vi Batch Number
vii Expiry date of the batch if relevant
viii Storage details if relevant
ix Other products used concurrently

All medicinal treatment over the last one-week period preceding the adverse reaction.

i Product name
ii Approved scientific names
iii MAH number

iv The Anatomical Therapeutic Chemical Classification System for veterinary medicinal products (ATCvet)
v Pharmaceutical form
vi Batch Number
vii Expiry date of the batch if relevant
viii Storage details if relevant

Details of the animal adverse reactions

i Description of adverse reaction including site and severity
ii Start date or onset of reaction
iii Stop date or duration of the reaction
iv Specific treatment adopted against the observed adverse reaction
v Number of animals showing signs
vi Number of dead animals
vii De-challenge information (any obvious effect of removal of treatment
viii Number of treated animals alive with sequalae
ix Number of treated animals recovered

Reporting form

The report of the adverse reaction by MAH or by Veterinarian to VMD or any other information should be reported using the Pharmacovigilance reporting form in annex 1

Post Marketing Surveillance

Post market surveillance studies should complement spontaneous adverse drug reaction reporting systems, which may indicate a problem, though it does not provide quantitative risk assessment. The Veterinary Pharmacovigilance covers not only safety aspects in animals and humans related to veterinary medicinal products, but also aspects of post authorization surveillance such as,

i Lack of expected efficacy of the VMP,
ii Adverse reactions reported related to off-label use,
iii Reported violation of approved residue limits possibly leading to investigation of the withdrawal period,
iv Potential environmental problems,

Strong national post-marketing surveillance programs is focused in quality, safety and efficacy of veterinary products and responding to public health risks which helps to protect citizens from the threats posed by substandard and falsified (SF) medicines. The majority of post - marketing surveillance concerns adverse drug reactions (ADRs) monitoring and evaluation and other quality complaints.

This guideline defines the regular sampling and surveying of both the regulated and unregulated supply chains to identify SF medical products and adverse events monitoring. Different methodologies are used to sample the market and range from random sampling through targeted sampling of particular products and outlets. Risk-based approaches are used to determine the types of medicines that will be sampled, the sampling locations, the sample size, and the appropriate analytical tests to perform.

This guideline will assist VMD Pharmacovigilance Division as well as Authorized Officers in Enforcement division including those working in the periphery to effectively carry out relevant duties.

Procedure for Post-Marketing Surveillance

1. Sampling plan is prepared according to the requirements of VMD.
2. Initial planning under the VMD is coordinated with other stakeholders.
3. VMD Officers/Authorized Officers carry out sampling according to an established and approved plan.
4. Recognised laboratories carry out tests according to regulations and guidelines (pharmacopeia methods or official verified/validated test methods in product dossiers).
5. Data are analysed by the laboratories and report developed by VMD which is responsible for sharing with all relevant stakeholders.
6. VMD carry out follow-up actions as appropriate.
7. Reporting of suspected ADRs to Audit and Risk Management Committee and evaluation and monitoring safety of reported suspected ADRs.
8. VMD conduct workshops relevant to post market surveillance activities to sensitize stakeholders.

Sampling and Testing Priorities

The Laboratory is involved in the planning stage of any sampling and testing activity. The role of laboratory is to provide all technical information about the tests to be used, the specifications of the products, the number of units per sample to collect for each medicine and key information related to the stability and proper handling of medicines during sampling. The laboratory should contribute and review the sampling form and ensure that all technical information to be collected per each sample is complete and accurate.

The type of testing and the specifications for each veterinary products are used to develop risk based sampling and testing steps as given below.

Monitoring veterinary medicines that are new to the market.

Monitoring veterinary medicines based on the risks associated with manufacturing complexity, dosage form, stability (e.g., temperature sensitivity), safety/efficacy (e.g., narrow therapeutic window), demand (e.g., high-burden diseases), therapeutic indication (e.g., infectious diseases), or other factors.

Monitoring the quality of veterinary medicines at key ports of entry. This type of monitoring serves as a first-line intervention, has been shown to deter the trading of poor-quality medicines, and requires close collaboration among the regulatory, customs, and law enforcement authorities.

Coordinating with ongoing sampling and testing initiatives.

Sampling plan

The quantity of the sample required for testing is prepared by recognised laboratory. The sample size may be a case-by-case decision depending on the number of pharmaceutical dosage units needed per test procedure, the number of presentations of the dosage forms to be tested, the availability of the product, the size of the market, the clinical use of the product, etc.

The laboratory prepares a sampling plan which contains detailed identification of sites where samples will be collected, medicines to be sampled, minimum number of dosage units to be collected per sample, number of samples to be collected per medicine, and total number of samples to be collected in the area for which the sampling plan is prepared. It contains also detailed instructions for sample collectors.

Information needed for risk based sampling and testing

1. Selection of area to Sample-Administrative and animal health structure, updated demographic information, disease prevalence, medicines supply chain, pharmaceutical sector information (number of outlets for each sector).
2. Selection of veterinary medicines- Most-used medicines according to the essential medicines list, complaint investigations, quality failures, most-sold medicines, higher risk medicines (stability, storage), medicines imported from countries with stringent regulations, supply system of targeted medicine, known points of distribution
3. Selection of collection sites- Complete and up-to date information about the Veterinary pharmaceutical sector in the area (number of outlets, levels of distribution, type of outlets, type of available sectors for supplies, geographical and administrative structure.
4. No. of dosage units/sample, No. of samples/ medicine, Total number of samples/area based on the objectives and testing methodology of the activity, data on the specifications for the medicine and its dosage form are required and should be available at VMD. The number of samples is determined based on the objectives and availability at the collection site.
5. Sample testing- Test to be applied or selected must be determined by VMD based on objectives of the sampling and testing activity according to the pharmacopoeial specifications or manufacturers' specifications.
6. Manufacturer's/Market authorization holders should provide necessary information related to the quality of their products.

Handling, storage, and transportation of samples

VMD officers, other relevant authorized officers and animal health institutions who involve in sending samples to laboratory should observe the following best practices throughout the chain of custody of the products:

i Avoid excessive mechanical vibration during transportation.
ii Store in original container, where available, and label accordingly.
iii Store away from sunlight and excessive humidity.

Collect all the information required for each sample with the location of collection, number of samples collected, name of the sample and any observation at the time of collection.

Samples that are light or heat sensitive may require special handling, transportation, and storage conditions. If cold storage is indicated, store in an appropriate container and monitor the temperature during transportation.

In the case that collectors are not transporting samples directly to the laboratory, samples with the accompanying documents should be sent by a courier service with required storage conditions. For each shipment it should be clearly indicated that samples are sent for laboratory

testing purposes only, will not be used on animals, have no commercial value and will not be placed on the market.

Testing

Laboratory will perform veterinary medicines quality testing to comply with international standards to ensuring the reliability and accuracy of test results and carry out the tests according to the pharmacopoeia/validated tests submitted in market authorization document.

Officers authorized by Ministry of Agriculture, Livestock and Fisheries and Cooperatives also be trained appropriately by the VMD and/or recognized laboratory to perform field-level visual inspection and appearance.

Following tests are, in principle, included: appearance, visual inspection; identity; assay for APIs declared on the label; test for related substances, microbial quality testing; for solid dosage forms – dissolution or disintegration, uniformity of dosage units (by mass or content), for liquid dosage forms – pH value and volume in containers/extractable volume; for parenteral products – sterility and bacterial endotoxins tests. Table 1 provides a summary of these tests and the potential product quality issues that can be detected by each test.

Inclusion of uniformity of content for single-dose dosage forms, or sterility and bacterial endotoxins tests, which are costly, time demanding and need more dosage units to be collected, should be considered in relation to target medicines and available resources. It is impossible to achieve 100% certainty about sterility of the product through testing only and inspections and enforcement of compliance with GMP principles may be more efficient tools for verification in some cases.

Table 1. Select tests to detect product quality issues

	Test	Possible product quality issue	Comments
1	Visual inspection	Falsely or incorrectly labelled, poor appearance, unregistered	Comparison with innovator or registered products in the country. VMD register of Medicines Registration Database is a good source of information.
2	Identification	Incorrect or absent active ingredient	Techniques vary depending on capacity and technology.
3	Assay Uniformity of dosage unit	Quantity of active ingredient inconsistent with claim on label	See Pharmacopeia sections on uniformity of dosage units,
4	Disintegration Dissolution	Dosage form performance	Harmonized across pharmacopeias – USP, EU, etc
5	Related substances/ Impurities	Degradation or impurities	Product specific Refer to pharmacopeial or other standards

6	Endotoxin Sterility Foreign particulate matter Viscosity pH	Toxicity or contamination of liquid and sterile formulation	Microbial testing may be necessary when available or outsourced

Data analysis and reporting

Depending on the data presented to VMD and the potential public health importance of the findings, the authority may take a variety of actions, including further testing of samples and requesting additional information or clarification from market authorization holders, or other appropriate regulatory action such as recall published in VMD website.

The results will first be shared with the respective stakeholders whose products are in the report before releasing the reports with other stakeholders, both those involved in the sampling and testing activities, and other relevant groups, and the general public. The trade names will not be included in the reports, only the active ingredients.

Results from post-marketing surveillance program can be available in the VMD web site. Sharing this information publicly can have a direct impact on the health and wellbeing of Animal health service providers and farmers.

Annex 1 VETERINARY PHARMACOVIGILANCE REPORTING FORM

REPORT FOR SUSPECTED ADVERSE REACTIONS IN ANIMALS OR IN HUMANS AFTER THE USE OF A VETERINARY MEDICINE

	Sender report identification-case ref. No:	Page
Safety issues in animals ☐ in humans ☐ Lack of expected efficacy ☐ Withdrawal period issues ☐ Environmental problem issues ☐	Reporting county: Purchase county: Report source:	
Address of competent authority	Name and address of sender	
Date complaint received by sender: (dd-Mon-yyyy) Type of report initial ☐ follow up ☐ (date, case number) Person who reported the reaction: Veterinarian ☐ Owner ☐ Physician ☐ Pharmacist ☐ Other ☐		
VETERINARIAN/PHARMACIST/PHYSICIAN Name: Address: Telephone no:	ANIMAL OWNER/HUMAN PATIENT Name: Address: Telephone no:	
ANIMAL DATA No. of animals treated: No. of animals showing signs: No. of animals died: Animal characteristics (animal(s) showing signs) Species: Breed/production type: Sex/physiological status: Female ☐ Male ☐ Pregnant ☐ Neutered ☐ Lactating ☐ Other: ☐ Weight (kilos): Age: State of health at the time of treatment: Good ☐ Fair ☐ Poor ☐ Critical ☐ Unknown ☐		

Reasons for treatment (prevention against what disease(s) or initial diagnosis:

PRODUCT DATA

Trade name (include dosage form and strength) M.A Number:

Active substance (INN): ATC vet code:

Batch no: Expiry dates: Storage details:

Treatment details:

Dose frequency: Route/site of administration:

Start date of treatment: Stop date or Duration:

Who administered the product: Veterinarian ☐ Owner ☐

Unknown ☐ Other(specify)

Use according to label: Yes ☐ No ☐ Unknown ☐ Explain:

Action taken after reaction: Drug withdrawn ☐ Dose reduced ☐ Other:

Did reaction abate after stopping drug? Yes ☐ No ☐ N/A ☐

Did reaction reappear after reintroduction? Yes ☐ No ☐ N/A ☐

List all other relevant medications given to animal(s):

Product name	company	Batch no	Route & site of admin	Dose, frequency, indication, duration of treatment (dates of beginning and end)

REACTION DATA

Date of onset unexpected signs:

Duration of reaction:

Describe the sequence of events including administration of product(s), all clinical signs, site of reaction, severity, pertinent lab test, necropsy results, possible contributing factors (if necessary use extra sheet):

Were the unexpected signs treated? If yes, give details of treatment including product(s) used:

Reaction data continued;
Outcome of reaction to date:

	Killed/ euthanised	Died	Under treatment	Alive with sequelae	Recovered	Unknown
No. of animals:						
Date when:						

ATTENDING VETERINARIAN'S LEVEL OF SUSPICION THAT DRUG CAUSED

Possible ☐ Unlikely ☐ No attending vet ☐

PREVIOUS EXPOSURE AND REACTION(S) TO PRODUCTS
Previous exposure to the suspect product? No Y☐ Date☐
Previous reaction to the suspect product? No Yes☐ Describe:☐
De-challenge information:

DETAILS OF SUSPECTED ADVERSE REACTION(S) IN HUMANS
Patient details: Sex: Pregnant Age/date of birth:
Occupation (if relevant):
Date of exposure:
Nature and duration of exposure, reaction details (including symptoms) and outcome:

CASUALTY ASSESSMENT

Classification: A(probable) ☐ B(possible) ☐ O(unclassified) ☐

O1(inconclusive) ☐ N(unlikely) ☐

Reasons for classification:

FOR COMPETENT AUTHORITY USE ONLY

Name and title of person responsible for the accuracy of the information | Signature | Date

Attachments included:	☐
Reports to follow:	☐