Guideline for Veterinary Pharmacovigilance, 2019

National Veterinary Hospital
Department of Livestock
Ministry of Agriculture and Forests
Royal Government of Bhutan

Legal basis and purpose

The legal framework for pharmacovigilance of veterinary medicinal products (VMPs) is given in Bhutan Medicines Rules and Regulation 2012, Chapter IX, Section 155 a. *identifying National Veterinary Hospital, Thimphu as the Veterinary Pharmacovigilance Centre (VPC)* and section 156 directing *such centers established to develop its procedure and constitute an expert committee who will meet on quarterly basis to discuss and assess the reports and make recommendations to National Pharmacovigilance Centre.* This guideline should be read in conjunction with the other pharmacovigilance guidelines contained in Chapter IX of the BMRR 2012.

When Veterinary Medicinal Products are initially authorized, the safety and efficacy of these products may only have been established in a countable number of animals. Therefore, the true safety and efficacy of these products can be known only once they are commercialized and used in a large number of animals. This is achieved through pharmacovigilance. Pharmacovigilance is the science and activities relating to detection and investigation of the effects of the use of veterinary medicinal products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products (USDA).

Adverse events following use of VMPs are associated with serious effects sometimes even leading to death both in human and animals. Tackling the problem of ADRs in animals not only will help the livestock and pet owners but also humans in the context of "One Health". In Bhutan, adverse events following the use of veterinary medicinal products in animals are grossly under-reported and many times such events are misunderstood or believed as a progress of disease. The first guideline, "Pharmacovigilance for Adverse Veterinary Drug Reaction(s), Monitoring and Causality Assessment, 2016" didn't take into consideration the adverse events following vaccination (AEFV). This guideline shall supersede the "Pharmacovigilance for Adverse Veterinary Drug Reaction(s), Monitoring and Causality Assessment, 2016". With the guideline in place, it is expected that there will be uniform understanding among animal health workers regarding the detection of adverse events, prevention and response, and reporting mechanism. The guideline gives an overview of Veterinary Pharmacovigilance especially pertaining to - detection and classification of ADRs including AEFV, roles of Livestock health workers at different centers, reporting system from the field of occurrence to Veterinary Pharmacovigilance Center (National Veterinary Hospital) and further to National Pharmacovigilance Center (Drug Regulatory Authority). This guideline is intended to be used for:

i. Guiding officials in Veterinary Pharmacovigilance Center
ii. Training the field personnel and to raise awareness.
iii. Guiding the field personnel in detection and reporting Adverse Drug Reactions including AEFV
iv. Guiding in conducting the causality assessment.

It is not intended to cover therapeutic vaccines (e.g. viral-vector based gene therapy, tumor vaccines, anti-idiotypic vaccines such as monoclonal antibodies used as immunogens), as these will require different considerations.

Definition of the terminologies

i. **ABON system/scale:** A method of causality assessment

ii. **Adverse Drug Event:** Any untoward medical occurrence that may present during the treatment with a pharmaceutical product but does not necessarily have a causal relationship with this treatment.

iii. **Adverse Drug Reaction (ADR):** A response which is noxious and unintended, and which occurs at doses normally used in human/animal for prophylaxis, diagnosis or therapy of disease or modification of physiological function. (WHO, 1972)

iv. **Allopathy:** Non-traditional, western scientific therapy, usually using synthesized ingredients, but may also contain a purified active ingredient extracted from a plant or other natural source; usually in opposition to the disease

v. **Causality Assessment:** It is the method by which the extent of relationship between a veterinary medicinal products and suspected reaction is established i.e. to attribute clinical events to VMPs in individual patients or in case reports.

vi. **De-challenge:** The withdrawal of a drug from a patient; the point at which the continuity, reduction of disappearance of adverse effects may be observed.

vii. **Drug Alerts:** Refers to the action of notifying a wider audience than the initial information holder(s) of a suspected association between drug and an adverse reaction.

viii. **Efficacy:** The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions.

ix. **Farms:** Livestock farms under Department of Livestock, Ministry of Agriculture & Forests

x. **Homeopathy:** Homeopathy is a therapeutic system which works on the principle "Like treats like". An illness is treated with the medicine which could produce similar symptoms in healthy person. The active ingredients are given in highly diluted form to avoid toxicity.

xi. **Individual Case Safety Report (ICSR):** Refers to a document providing the most complete information related to an individual case (information provided by the primary source to describe suspected adverse reaction(s) related to the administration of one or more medical products to an individual patient at a particular point of time).

xii. **Intolerance:** A low threshold to the normal pharmacological action of a drug.

xiii. **Lack of expected efficacy (LEE):** Refers to an unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation.

xiv. **National Pharmacovigilance Center:** Refers to the Drug regulatory Authority.

xv. **Off-label use:** The use of Veterinary Medical products that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product.

xvi. **Pharmacovigilance:** The detection and investigation of the effects of the use of veterinary medicinal products, mainly aimed at safety and efficacy in animals and safety in people exposed to the products. (USDA)

xvii. **Predisposing factors:** Any aspect of the patient's history (other than the drug) which might explain reported adverse events (genetic factors, diet, disease history, polypharmacy or use of herbal medicines).

xviii. **Re-challenge:** The point at which a drug is again given to a patient after its previous withdrawal.

xix. **Serious Adverse Event or Reaction:** Any untoward medical occurrence that at any dose results in the death or life threatening or requires inpatient hospitalization or prolongation of hospitalization or persistent or significant disability/ incapacity or congenital anomaly or medically important event or reaction.

xx. **Side effect:** Refers to any unintended effect of a pharmaceutical product occurring at doses normally used in animals/ people, which is related to the pharmacological properties of the medicine.

xxi. **Signal:** Refers to the reported information on a possible casual relationship between an adverse reaction and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the reaction and the quality of the reaction and the quality of information.

xxii. **Summary of product characteristics:** A regulatory document attached to the marketing authorization which forms the basis of the product information made available to prescribers and patients.

xxiii. **Traditional medicine:** Traditional medicine is the total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

xxiv. **Vaccine** is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters. (WHO)

xxv. **Veterinary Pharmacovigilance Center:** Refers to National Veterinary Hospital.

List of abbreviations

Abbreviation	Expansion
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AEFV	Adverse Events Following Vaccination
BQ	Black quarter
CAV	Canine adenovirus
CDV	Canine distemper virus
CVMP	Committee veterinary medicinal products
DRA	Drug Regulatory Authority
DVH	Dzongkhag Veterinary Hospital
EMA	European Medicines Agency
HS	Hemorrhagic septicemia
IBD	Infectious bursal disease
ICSR	Individual case safety report
LAV	Live attenuated vaccine
LEC	Livestock Extension Centers
MD	Foot and mouth disease
MLV	Modified live virus vaccine
NCAH	National Centre for Animal Health
NCD	Newcastle disease
NPC	National Pharmacovigilance Committee
NSAID	Non-steroidal anti-inflammatory drugs
OTC	Over the counter drugs
PPR	Peste des petits ruminants
RNR_EC	Renewable Natural Resources Extension Centers
RUB	Royal University of Bhutan
SPC	Standard product characteristics
TVH	Thromde Veterinary Hospital
UGT	Uridine di-Phosphate glucuronosyltransferase
USDA	United States Department of Agriculture
VICH	Veterinary International Conference on Harmonization
VMP	Veterinary medicinal products
VPC	Veterinary Pharmacology Committee
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terminology
WHO-UMC:	WHO – Uppsala Monitoring Center

Table of contents

Pharmacovigilance

Pharmacovigilance of veterinary medicinal products (which includes immunobiologics) 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. (USDA)

Importance of Pharmacovigilance

When a medicine is released onto the market there is still a great deal that is unknown about the safety of the product. The information collected during the pre-marketing phase is incomplete with regard to adverse drug reactions and this is mainly because:

- ✓ Patients/animals used in clinical trials are limited in number and are not true representative of the population at large. In addition, the conditions of use of medicines differ from those in clinical practice and the duration is limited.
- ✓ Information about rare but serious adverse reactions, chronic toxicity and use in special groups (such as young /geriatric/ pregnant animals) or drug interactions is often incomplete.

Therefore, it is important to have record of less common but sometimes very serious ADRs

Scope of Pharmacovigilance

- ✓ To improve Animal health care and safety in relation to the use of VMPs, and all medical and paramedical interventions.
- ✓ To know the lack of expected drug efficacy/ quality defects of veterinary medicinal products.
- ✓ To detect problems related to the use of VMPs and communicate the findings in a timely manner.
- ✓ To contribute to the assessment of benefit, effectiveness and risk of VMPs, encouraging their safe, rational and more effective (including cost-effective) use.
- ✓ To promote understanding, education and clinical training in Pharmacovigilance and its effective communication to animal health professionals and the public.
- ✓ To avoid the environmental problems due to veterinary medicinal products.
- ✓ Aid in identifying therapeutic failure and adverse drug interactions.

Establishment of Pharmacovigilance Center in Bhutan

Prior to the establishment of DRA in 2003, Pharmacovigilance activities such as sensitization programs and workshops were introduced to the Pharmacy professionals by the Essential Drug Program under Ministry of Health**.** For the success of Pharmacovigilance system, the presence of an effective drug regulatory body in the country is essential to take appropriate regulatory measures as WHO states that “a Pharmacovigilance system must be backed up by the regulatory body”. As per Bhutan Medicines Rules & Regulations; DRA is identified as National Pharmacovigilance Center.

Roles of Veterinary Pharmacovigilance center

- ✓ Sensitize animal health professionals on Pharmacovigilance.
- ✓ Monitor Pharmacovigilance activities in veterinary sector
- ✓ Conduct causality assessment of the reported adverse reactions/events
- ✓ Encourage voluntary reporting of the ADR/AEFV by animal health professionals and market authorization holders
- ✓ Identify committee member for National Pharmacovigilance Committee.
- ✓ Act as a link between DRA and DOL regarding Pharmacovigilance.
- ✓ Notify the public and relevant stakeholders about the ADR/events through mass media such as news, bulletins, drug alerts and seminars when required
- ✓ Conduct regular public awareness programs
- ✓ Conduct workshops and trainings on various aspects of Veterinary Pharmacovigilance.

Veterinary Pharmacovigilance Committee

Veterinary Pharmacovigilance Committee will consist of:

- ✓ Head, NVH (Chairperson)
- ✓ NPC focal person from NVH (Member secretary)
- ✓ NPC co-focal person from NVH (member)
- ✓ One veterinarian and one para-veterinarian (member)

***Note**: Relevant specialist will be involved where required*

Adverse Drug Reactions

Adverse Drug reaction is any response to drug(s) that is noxious and unintended in doses normally used in animals or people for diagnosis, treatment or prevention of disease, or for the modification of physiological function.

Classification of ADR

1. **Type "A"**

- Augmented pharmacologic effects
- Dose dependent and predictable (medicine actions)
- Tend to be fairly common, dose related (i.e. more frequent or severe with higher doses) and may often be avoided by using doses which are appropriate to the individual patient.

2. **Type "B"**

- Bizarre effects (or idiosyncratic) –
- **dose independent and unpredictable (Patient reactions)**

- Characteristically occur in only a minority of patients and display little or no dose relationship. Type B is further classified:

a. Immunological

Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes.
E.g. Ampicillin rash, Penicillin hypersensitivity

b. Non- immunological

Unpredictable non- immunological drug reactions include:

i. **Pseudo allergic reaction:** a reaction with the same clinical manifestations as an allergic reaction but lacking immunological specificity.

ii. **Idiosyncratic reaction:** A genetically determined, qualitatively abnormal reaction to a drug related to a metabolic or enzyme deficiency. *E.g., Ivermectin toxicity of collie-related breeds due to deficiency of MDR1 gene type-P glycoproteins that prevents flushing from the brain and accumulation over the period of time.*
Acetaminophen toxicity in cats due to lack of UDP-glucuronosyltransferase (UGT) enzyme which is required for breakdown of acetaminophen by glucuronidation in the liver.

iii. **Intolerance** – A low threshold to the normal pharmacological action of a drug.
E.g., Paracetamol toxicity in dogs exposed to toxic dose of >100mg/kg body weight or at normal dose for prolonged use.

3. Type "C"

- Chronic/ continuous effects.
- These reactions are associated with long-term drug therapy *E.g., prolonged use of NSAIDs induced nephropathy.*

4. Type "D"

- Delayed appearance of effects,
- Difficult to diagnose.
- Carcinogenic and teratogenic effects. *E.g., use of Chlorphenaramine maleate in pregnant animals*

5. Type "E"

- End of treatment effect/ Withdrawal reactions
- Undesired effects of ceasing the drug. *E.g., withdrawal of opiate analgesics*

6. Type "F "

- Failure of therapy

- Undesirable reduction in drug efficacy. *E.g., decrease efficacy of antibiotics due to AMR*

Adverse Event Following Vaccination (AEFV)

Vaccination is one of the most effective and widely used interventions in preventing diseases both in humans and animals. The benefit of vaccination has been demonstrated for authorized vaccines, both at individual as well as community level. Prominent examples are the global eradication of Rinderpest virus in animals and smallpox virus in human. However, no vaccine is 100% safe or effective. As the incidence of vaccine-preventable diseases is reduced by increasing coverage with the efficacious vaccine, vaccine-related adverse events, whether causally related or perceived as such, become increasingly prominent.

Type of vaccines

***Live Attenuated Vaccine*:** A vaccine prepared from disease causing pathogens (virus or bacteria) that have been weakened under laboratory conditions. Live microorganisms provide continual antigenic stimulation giving sufficient time for memory cell production. *E.g., PPR, Marek's Disease, IBD, ND*

***Inactivated (Killed Antigen) Vaccine**:* Inactivated vaccines are made from microorganisms (viruses, bacteria and other) that have been killed through physical or chemical processes. *E.g., FMD, HS, BQ, Rabies, ND*

***Recombinant Vaccines*:** Recombinant vaccines, like inactivated whole-cell vaccines, do not contain live components of the pathogen. They differ from inactivated whole-cell vaccines, by containing only the antigenic parts of the pathogen. These parts are necessary to elicit a protective immune response. *E.g., Recombinant Canine Distemper Vaccine*

Toxoid Vaccines (Inactivated toxins): Toxoid vaccines are based on the toxin produced by certain bacteria. The toxin invades the bloodstream and is largely responsible for the symptoms of the disease. The protein-based toxin is rendered harmless (toxoid) and used as the antigen in the vaccine to elicit immunity. To increase the immune response, the toxoid is adsorbed to aluminium or calcium salts, which serve as adjuvant. *E.g., Tetanus, Diphtheria.*

Classification of AEFV (adopted from American Animal Hospital Association)

Event	Examples
Transient injection-site reactions	Visible or palpable lumps caused by an abscess, granuloma, or seroma; injection-site pain, pruritus, local swelling.
Sustained injection-site reactions	Permanent hair loss (generally associated with ischemic vasculitis), discoloration of skin, focal necrosis of skin (also called rabies vaccine ischemic vasculitis), granuloma (post-vaccination "lumps").

Transient non-specific systemic effects	Lethargy, anorexia, fever, regional lymphadenopathy, nonlocalizable soreness/discomfort, diarrhea, vomiting, encephalitis, polyneuritis, arthritis, seizures, behavioral changes.
Allergic (hypersensitivity) and immune-mediated reactions	**Type 1 (acute anaphylaxis):** Angioedema (acute-onset swelling affecting the head and ears especially), urticaria (hives), collapse, acute-onset diarrhea, vomiting, dyspnea, systemic anaphylaxis (shock), and death.
	Type 2 (cytotoxic): Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia.
	Type 3 (immune-complex): Cutaneous ischemic vasculopathy (often attributed to rabies vaccine) that can occur at the injection site or a distant location ("satellite lesions") (such as the ear tips, foot pads, tail, and scrotum, undefined immune-mediated diseases [polyarthritis, glomerulonephritis]) and "Blue-Eye".
	Type 4 (delayed-type hypersensitivity): Less clearly described; associated with diminished cellular immunity and the release of pro-inflammatory cytokines. May be associated with post-vaccinal granuloma formation.
Failure to Immunize	Interference from maternally derived antibody is considered the most common cause; administration of vaccine at a volume/dose less than that prescribed by the manufacturer; genetically predisposed "non-responder" or "low responder;" inactivation of vaccine antigen (e.g., allowing reconstituted CDV vaccine to stand at room temperature for more than 2 hrs.); mixing of incompatible vaccines in the same syringe
Tumorigenesis	Malignant transformation of mesenchymal cells in susceptible patients.
Multi-systemic infectious/inflammatory disorder	Described in young Weimaraner dogs. The syndrome is not well characterized. May be linked to a poorly characterized immune deficiency in the breed.
Transient Immune Suppression	When combination vaccines containing modified-live CDV and CAV-1 or CAV-2, along with other vaccines, are first administered to puppies, transient suppression of cell-mediated immunity (not known to be clinically significant) may occur as early as 3 days postvaccination and can persist for 7 or more days.
Reactions caused by the incorrect or inappropriate administration of vaccine	In addition to injection-site abscesses, fatalities have been reported (rare) following subcutaneous administration of avirulent-live *Bordetella bronchiseptica* bacterin (intended for intranasal administration).
Reactions associated with residual virulence of attenuated vaccine	Post-vaccinal cough and/or sneezing associated with intranasal administration of attenuated vaccine (e.g., *B. bronchiseptica* + parainfluenza virus or feline *B. bronchiseptica*, feline herpesvirus-1 + calicivirus).

	NOTE: This is not vaccine "reversion to virulence."
Vaccine-induced interference with diagnostic tests	Examples include: false-positive PCR test results for parvovirus antigen in feces in dogs recently vaccinated with MLV parvovirus vaccine; leptospirosis vaccination may cause false-positive test results with commercially available diagnostic tests that detect antibody.
Reversion of vaccine virus to a virulent pathogen	Although frequently discussed in the literature, true reversion to virulence (vaccine-induced clinical infection) is considered rare to non-existent following administration of currently licensed vaccines as long as the vaccines are used in the species for which they were licensed. The potential for reversion to virulence exists when using attenuated (MLV) canine/feline vaccine in a wild, hybrid, or exotic animal.

Reporting adverse reaction/event

How to Recognize ADR(s) and AEFV in Patients

ADRs are difficult and sometimes impossible to distinguish from the disease being treated since they may act through the same physiological and pathological pathways. However, the following approach is helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine administered/dispensed is medicine prescribed
2. Take proper detailed Anamnesis of the patient.
   - ✓ A full medicine and medical history should be taken
   - ✓ An ADR should always be your first differential diagnosis
   - ✓ Ask if this adverse reaction can be explained by any other cause E.g. patient's underlying disease, other medicines including over-the-counter medicines or traditional medicines, toxins or foods
   - ✓ A medicine-related cause must be considered, especially when other causes do not explain the patient's condition
3. Establish time relationships by answering the following question: Did the ADR occur immediately following the medicine administration? Some reactions occur immediately after the medicine has been given while others take time to develop. And in cases of mass ADRs, how many are affected within the same time frame?
4. Carry out a thorough physical examination with appropriate laboratory investigations if necessary:
   - ✓ Remember: only a few medicines produce distinctive physical signs
   - ✓ Exceptions include medicine eruptions, steroid-induced dermal atrophy, acute extra-pyramidal reactions
   - ✓ Laboratory tests are important if the medicine is considered essential in improving patient care Try to describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis
5. Effect of de-challenge and re-challenge should be determined

- ✓ De-challenge (withdrawal of the suspected medicine)
- ✓ Re-challenge (re-introducing the suspected medicine after a de-challenge). Re-challenge is only justifiable when the benefit of reintroducing the suspected medicine to the patient overweighs the risk of recurrence of the reaction, which is rare.

6. Check the known pharmacology of the medicine
   - ✓ Check if the reaction is known to occur with the particular suspected medicine as stated in the package insert or other reference.
   - ✓ Remember: if the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular suspected medicine.

Who should report ADR/AEFV?

Livestock health personnel

What to report?

- ✓ All untoward effect of veterinary medicinal products either included in the Essential Veterinary Drugs list or available in the market pharmacies.
- ✓ All serious reactions and interactions.
- ✓ Adverse reactions which are not clearly stated in the package insert.
- ✓ All adverse reactions or poisonings due to traditional or herbal remedies.
- ✓ Adverse reaction from off-label use of VMPs.
- ✓ Lack of expected efficacy

Off - label use of veterinary medicinal products (VMP)

VMPs should always be used according to the SPC of the product but situations occur where they are used 'on purpose or unintended' as not covered by SPC. However, under-reporting of adverse event following off-label use is more common globally due to fear of legal/financial consequences. Reports from Off-label use provide useful information on the safety of VMPs e.g., provides information on risk of incorrect administration. Off- label use of VMP occurs when:

- Target species are not indicated
- Age of the animal not indicated
- Contraindicated physiological status (Pregnancy/ lactation/ egg laying period etc)
- Breed not indicated
- Incorrect route of administration
- Wrong dosage or treatment regime
- Wrong reconstitution of medicine
- Concurrent use of products

Lack of Expected Efficacy (LEE)

Pre-requisite for the event to be qualified as LEE are:

- The use of product is in complete accordance to the SPC.
- The expected efficacy of the product is not observed even after administration at a higher dose than the recommended dose.

Where to report?

Report to TVH/DVH/NVH or through DRA's online reporting system (ADR form).

How to Report:

Individual case safety report (ICSR) is enclosed in this guideline. Request for the forms and adverse reaction/event information may also be obtained from your Center/head agencies/National Veterinary Hospital/DRA. The adverse reaction/events can be reported online (www.dra.gov.bt). The ICSR form should be completed in detail as far as possible before submitting. There are five sections to validate the ICSR (Refer annexure I).

The basic Principles for Efficient Reporting

For details, refer to Guidelines on reporting (Annexure 1)

- ✓ In-time reporting -Report the suspected adverse drug reaction as soon as it occurs- the report involves less work and is more accurate.
- ✓ If possible, take the decision to report whilst the patient is still with you, so that the details can be filled in at once on the reporting form.
- ✓ Take detail history of other factors (e.g., other medications) that may contribute to causing the event.
- ✓ Keep a vigilance for signs and symptoms that may enhance or exclude the possibility of a medicine induced reaction. All follow-up / supplementary information should be documented and submitted to NVH/DRA with "FOLLOW-UP REPORT" clearly indicated on the top right corner of the form.
- ✓ Accuracy and completeness- Ensure that each reported suspected ADR reporting form is filled in accurately and with all the necessary information, as much as is available to you. This is very important for assessing the causality of the medicine to have caused that reaction.
- ✓ Always write legibly.

What will happen to the Reports?

The causality assessment for reports received will be done using ABON system by NVH and submitted to DRA. These reports will be further submitted and analyzed by expert reviewers if required.
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. A well completed adverse drug reaction report submitted could result in any of the following:

a. Additional investigations into the use of the VMP.
b. Educational initiatives to improve the safe use of the VMP.
c. Appropriate package inserts change to include the potential for the reaction reported by you.
d. Changes in the scheduling or manufacture of the VMP to make the medicine safer.

Causality Assessment

Causality Assessment is the method by which the extent of relationship between a veterinary medicinal products and suspected reaction is established, that is to attribute clinical events to VMPs in individual patients or in case reports. Naranjo's scale and European ABON scale/system are the most commonly used from the several methods that are developed for causality assessment. This guideline adopts the European ABON scale/system of causality assessment.

Causality assessment system

- ✓ For serious adverse reaction/events, causality assessment will be performed collectively by Veterinary Pharmacovigilance Committee and DRA.
- ✓ In case of non-consensus concerning the outcome of the causality assessment, the detailed clarification/information may be sought from the primary reporter and causality assessment may be confirmed by the third party (e.g., NPC will be considered third party to VPC).
- ✓ In the assessment of case reports the following elements can be recognized:
    i. ***Quality of documentation*** (E.g. completeness and integrity of data, quality of diagnosis, follow-up).
    ii. ***Coding:*** VMPs should be registered in a systematic way, for example by using the WHO Drug Dictionary (which is based on the INN nomenclature (generic) and the ATC classification). For the coding of the adverse events the WHO Adverse Reaction Terminology (WHOART) or another internationally recognized terminology (e.g., MedDRA) should be used.
    iii. ***Relevance*** with regards to the detection of new reactions, drug regulation, or scientific/educational value. The following questions especially may be asked:
        - *New VMP? (*Products on the market less than five years are usually considered new drugs).

- *Unknown reaction?* (i.e., not included in the approved Summary of Product Characteristics or unlabelled). It is also important to know whether the reaction is described in the literature e.g., Side Effects of Drugs given in the National Veterinary Drug Formulary.
- *Serious reaction?*

✓ ***Identification of duplicate reports:*** Certain characteristics of a case (Animal ID, microchip number, sex, age, dates of VMP exposure, owner details, etc.) may be used to identify duplicate reporting.

ABON scale

According to ABON coding six main factors are taken in account:

1. Associative connection in time (including de-challenge and re-challenge) and with anatomical sites.
2. Pharmacological and immunological explanation (Known Pharmacology & toxicology of the product, VMP concentration in blood and dose effect relationship)
3. Presence of characteristic product or treatment related or Pathological phenomenon
4. Previous knowledge of reported cases (literature or adverse event reported before)
5. Exclusion of other causes
6. Completeness and reliability of the data in the case report

The **ABON** system consists of four categories:

Category A	Probable
Category B	Possible
Category O	Unclassified
Category N	Unlikely

The Categorization of the case report under ABON coding is done using a questionnaire developed by European Medicines Agency. The minimum Criteria:

For inclusion in Category 'A' (Probable):

- There is associative connection in time.
- Adverse event fits the pharmacological/ toxicological profile of the product.
- There is no other plausible explanation.
- There is no indication of insufficient/unreliable information.

For inclusion in Category B (Possible):

- There is associative connection in time.
- Adverse reaction/event fits the pharmacological/toxicological profile of the product.
- There is other equally plausible explanation possible.
- There is no indication of insufficient/unreliable information.
- There have been reports of adverse reaction/event before.

For Inclusion in Category O1 (Inconclusive):

- There is associative connection in time.
- Adverse event fits the pharmacological/toxicological profile of the product.
- There is no other plausible explanation possible.
- There is inconclusive/unreliable or insufficient information.

For Inclusion in Category O (Unclassifiable/ Un-assessable):

- There is inconclusive/unreliable or insufficient information where associative connection in time, pharmacological/toxicological profile of the product and other plausible explanation cannot be answered.

For Inclusion of Category N (Unlikely):

- Sufficient information exists to confirm that the product or treatment did not cause the adverse event
- There is no indication for unreliable or insufficient information

Relation of Veterinary Pharmacovigilance Center with other parties

- All the suspected adverse reactions/events and outcome of the causality assessments shall be reported to **DRA** without delay.
- **Pharmaceutical companies** need the same information as the regulatory authority. It will depend on the local situation whether companies are to be informed directly or via the regulatory authority.
- **A Pharmacovigilance Center** shall seek the support of professional veterinary/human medical and pharmaceutical associations. In the case of an emergency, these associations shall be informed in time.
- In addition, PVC shall explore opportunities to develop linkages with **Pharmacovigilance Center/related organization or institutions** in other countries.
- **Academia:** PVC shall collaborate with Royal University of Bhutan (RUB) in including Pharmacovigilance in the curriculum of diploma/degree programs at appropriate institutes like College of Natural Resource.

- **Media and consumer organizations:** Support from national associations of consumer and patients may add to the general acceptance of Pharmacovigilance.

Annexure

Annexure 1: Guide to reporting any adverse reaction/event following use of VMPs

A. PATIENT DETAILS

1. Patient Details

- ✓ *Patient name*
- ✓ *Age at time of event or date of birth:* A reporter must report either the date of birth or age of the patient at the time the event or reaction occurred.
- ✓ *Sex:* A reporter must mention the gender of the patient.
- ✓ *Weight:* The weight of the patient should be in kilograms (Kg).
- ✓ *Physiological sate of the animal:* Neutered, intact, pregnant etc.
- ✓ *Vaccination history:* name(s) and date(s) of the vaccination done.

2. Tentative/ confirmatory diagnosis: state the diagnosis of the animal for which the suspected drug had been given.

3. Relevant tests/ laboratory data

A reporter must mention any laboratory data (if available).

4. Other relevant history

A reporter must mention any relevant history pertaining to the patient including pre-existing medical conditions (E.g. allergies, pregnancy, alcohol use, hepatic/renal dysfunction).

B. OWNER'S DETAILS

- ✓ Name
- ✓ Address
- ✓ Contact number (mobile no/ land line)
- ✓ Email Address (If available)

C. SUSPECTED DRUG(S)

It maybe one more than one drug. The details of suspected medication(s) such as the *drug name (brand or generic name), manufacturer, batch no./lot no., expiry date, dose used, route used, dates of therapy started and stopped, and indication of use* must be provided by the reporter.

D. SUSPECTED ADVERSE DRUG REACTION (s)

1. Describe reaction and any treatment given:

- ✓ *A reporter must briefly describe the event in terms of nature, localization etc. For E.g.; patient developed rash over ventral aspect of the body.*
- ✓ *The reporter must also indicate if any treatment is given against the Suspected Adverse Drug Reaction.*
- ✓ *Reporter must also mention if the suspected drug was withdrawn or continued.*
- ✓ *Date of reaction started:* A reporter must report the date on which the reaction first occurred.
- ✓ *Date of reaction stopped:* If the reaction stopped, the date should be reported.

2. Outcomes of the reaction till date: The reporter must tick the outcome of the event as:

- **'Recovered'** - if the patient has recovered from the event
- **'Recovering'** - if the patient is recovering from the existing adverse event
- **'Continuing'** - if the patient is continuing to have the symptoms of the adverse event which occurred

3. Seriousness of the reaction:

If any event is serious in nature, a reporter must select the appropriate reason for seriousness.

- **'Death'**- if the patient died due to the adverse event
- **'Hospitalization/prolonged'**- if the adverse event led to hospitalization or increased the hospital stay of the patient
- **'Life-threatening'**- if patient was at substantial risk of dying because of the adverse event
- **'Significant Disability'**- if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions
- **'Congenital anomaly'**- if exposure of drug prior to conception or during pregnancy may have resulted in an adverse outcome in the foetus.
- **'Other Medically Significant' -**when the event does not fit the other outcomes, but the event may put the patient at risk and may require medical or surgical intervention to prevent one of the other outcomes

4. Previous exposure/ reaction(s) to the suspected drug (s)

State whether the animal was previously exposed to the suspected drug(s) and any ADR was evident.

E. OTHER MEDICATIONS:

A reporter should include all the details of concomitant drugs including self medication, Over the Counter medication, herbal remedies etc. with therapy dates (start and stop date.)

F. REPORTER

Name and Professional address: A reporter must mention his/her name and professional address on the form. The identity of the reporter will be maintained confidential if necessary.

Date of report: Mention the date on which he/she reported the adverse event.

NOTE: For quality reporting, all the above-mentioned fields are essential. In case of incomplete information, the reporter must take care that at least mandatory fields are present. Following are the mandatory fields for a valid case report.

Patient information: initials, age at onset of reaction, gender etc.

Suspected adverse reaction: A reaction term(s), date of onset of reaction

Suspected medication: Drug(s) name, dose, date of therapy started, indication of use, seriousness and outcome.

Reporter: Name and address, date of report

Annexure 2: Veterinary pharmacovigilance form

Reporting form for ADR and AEFV

Adverse Drug Reaction ☐

Adverse Events Following Vaccination ☐

Lack of expected drug/vaccine efficacy ☐

ANIMAL DETAILS

Name/ID no.: Species: Breed/Production type:
Sex (male/female): Age: Weight (Kg):

Physiological status: Pregnant ☐ Intact ☐ Neutered ☐ Lactating ☐ Others ☐

Health status of the animal: Good ☐ Fair ☐ Poor ☐ Critical ☐ Unknown ☐

Tentative diagnosis: Confirmatory Diagnosis:

Vaccination History:

Relevant Data/ Laboratory Report (If any):

OWNER DETAILS

Name:
Address:
Contact no:

Email Address (if any):

SUSPECTED DRUG/VACCINE(s)

Drug/ vaccine name (Trade and Generic Name)	Prescribed for/ Indication	Manufactured by	Batch No.	Expiry Date	Date of medication/ vaccination started	Date of medication/ vaccination stopped	Route of Administration	Dose & frequency administered	Date of reaction Started	Date of reaction stopped	Storage Details

Who administered the drug/vaccine (s)?

Veterinarian Para veterinarian Owner Other (s)

SUSPECTED DRUG/VACCINE REACTION (S)

Describe the Adverse Drug reaction(s) or AEFV in detail including Clinical signs, site of reaction, predisposing factors if any, details of treatment given to address the reaction (If required please use additional sheet).

Outcome of the reaction till date (Please tick the appropriate)

Recovered ☐

Recovering ☐

Continuing ☐

Other (s) (Please specify)

Do you consider the reaction to be serious? YES ☐ NO ☐

If yes, please indicate why the reaction is considered to be serious (Tick all that is appropriate)

Patient died due to reaction ☐
Prolonged hospitalization ☐
Life threatening ☐
Significant disability ☐
Medically significant (including congenital anomaly) (Give details)

Previous exposure/ reaction(s) to the suspected drug/vaccine.

Previous Exposure to the suspected drug/vaccine. Yes ☐ No ☐ Date (s):

Previous Reaction to the Suspected drug/vaccine. Yes ☐ No ☐ Describe:

OTHER MEDICATION/VACCINATION(S) (INCLUDING SELF MEDICATION TO THE PATIENT)

Please tick all that is appropriate:

Was other medicine/vaccine(s) used: Prior ☐ Concurrently with the drug suspected? ☐

Drug/Vaccine Name (Both Generic and brand name)	**Dosage**	**Route of administration**	**Date started**	**Date stopped**

Who administered the product?

Veterinarian ☐ Para veterinarian ☐ Owner ☐ Others ☐

REPORTER'S DETAIL

Name:
Designation:
Address:
Contact no:

Date: **Signature:**

Annexure 3: Clinical signs of anaphylaxis in different animal species

Species	Shock Organ(s)	Pathology	Clinical Signs
Dogs	Liver	Hepatic and intestinal engorgement, visceral haemorrhage.	Initially excitement, urticaria, angioedema and pruritus, then vomiting and defecation. Finally collapse, dyspnoea and convulsions.
Cats	Respiratory tract Gastrointestinal tract	Bronchoconstriction, pulmonary hemorrhage, edema and emphysema, edema of the glottis.	Initially angioedema and pruritus around the face, then salivation, dyspnea, vomiting, incoordination and collapse.
Horses	Respiratory tract Gastrointestinal tract	Pulmonary edema and emphysema, intestinal edema and hemorrhage.	Initially shivering, sweating and incoordination. Possibly coughing, dyspnea and diarrhea. Finally collapse.
Cattle & Sheep	Respiratory tract	Pulmonary hemorrhage, edema and emphysema.	Initially urticaria, angioedema, pruritus and restlessness. Coughing, severe dyspnoea and cyanosis. Also, defecation, urination and bloat.
Pigs	Respiratory tract Gastrointestinal tract	Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.	Dyspnoea, cyanosis, pruritus and collapse.

Annexure 4: Adverse reaction/event reporting system