



Pharmacovigilance for Adverse Veterinary Drug Reaction(s), Monitoring and Causality Assessment, 2017.

GUIDELINES

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

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1. Introduction

Adverse Drug Reactions (ADRs) in animals in Bhutan is presumed to be under reported and many times misunderstood or believed as progress of disease. Guidelines in identifying and reporting mechanism are nonexistent in animal sector in Bhutan. ADRs are associated with serious effects, sometimes even leading to death, both in human and animals. In Western world ADR is ranked as the fifth major cause of mortality in human population. This fact indicates the possibilities of ADRs in animals, since the physiological metabolism pathway for the drugs are similar in animals and humans. Tackling the problem of ADRs in animals will not only help the livestock and pet owners but also humans in the context of “One Health”.

With this guideline in place, it is expected that there will be uniformity in understanding the reporting mechanism, identifying and assessing ADRs and follow up actions among animal health workers in the sector.

The guideline give an overview of what Pharmacovigilance is, how to detect and classify ADRs, describes the roles of livestock health workers at different centers and reporting system from the field to Veterinary Pharmacovigilance Center (National Animal Hospital) and further to National Pharmacovigilance center (Drug Regulatory Authority).

This guideline is intended to be used for the purpose of:

- i. Guiding officials in Veterinary Pharmacovigilance Center and Regional Veterinary Pharmacovigilance Centers (Regional Livestock Development Centres) on their roles in monitoring and assessing ADRs.
- ii. Training the field personals and to raise awareness of the magnitude of the safety problems.
- iii. Guiding the detection and reporting ADRs.
- iv. Guiding in conducting causality assessment.

2. Definition of terminologies

- i. **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.
- ii. **Adverse Drug Reaction:** 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)
- iii. **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.
- iv. **Causality Assessment:** The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according to established algorithms.
- v. **Dechallenge:** The withdrawal of a drug from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.
- vi. **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.
- vii. **Efficacy:** The ability of a drug to produce the intended effect as determined by scientific methods, for example in pre-clinical research conditions.
- viii. **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.
- ix. **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).

- x. ***Lack of efficacy:*** Refers to an unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation.
- xi. ***National Pharmacovigilance Center:*** Refers to the Drug Regulatory Authority, Bhutan.
- xii. ***Placebo:*** An inactive substance (often called a sugar pill) given to a group being studied to compare results with the effects of the active drug.
- xiii. ***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)
- xiv. ***Rechallenge:*** The point at which a drug is again given to a patient after its previous withdrawal.
- xv. ***Regional Veterinary Pharmacovigilance Center:*** Refers to four Regional Livestock Development Centers (RLDCs) i.e. RLDC Tshimasam, RLDC khangma, RLDC Wangdue and RLDC Zhemgang as focal agencies for all matters related to veterinary ADRs within their Dzongkhags of jurisdiction.
- xvi. ***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.
- xvii. ***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.
- xviii. ***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.

- xix. ***Spontaneous Reporting***: Refers to a system whereby case reports of ADRs are voluntarily submitted from the health/ veterinary professionals and pharmaceutical manufacturers to the national regulatory authority.

- xx. ***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.

- xxi. ***Traditional medicine***: Traditional medicine is the sum 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.

- xxii. ***Veterinary Pharmacovigilance Center***: Refers to National Animal Hospital, Bhutan, as the apex institute in Bhutan for all matters related to veterinary ADRs.

- xxiii. ***Vigibase***: The name of the WHO Global ICSR Database.

- xxiv. ***WHO-UMC***: refers to WHO collaborating centre- Uppsala Monitoring centre located at Sweden.

3. Pharmacovigilance

Pharmacovigilance is the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (WHO).

3.1 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 ADRs 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.

3.2 Scope of Veterinary Pharmacovigilance

- ✓ To improve animal health care and safety in relation to the use of medicines, and all veterinary and para-veterinary interventions.
- ✓ To know the lack of expected drug efficacy/ quality defects of veterinary medicinal products.
- ✓ To detect problems related to the use of medicines and communicate the findings in a timely manner.
- ✓ To contribute to the assessment of benefit, effectiveness and risk of medicines, 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 veterinary professionals and the public.
- ✓ To avoid the environmental problems due to veterinary medicinal products.
- ✓ Aid in identifying therapeutic failure and adverse drug interactions.

4. WHO Program for International Drug Monitoring

As a means of pooling existing data on ADRs, WHO's Programme for International Drug

Monitoring was started in 1968, after the 20th world health assembly adopted the resolution to start a project on the feasibility of international system of monitoring ADRs. As per WHO, there is agreement between WHO and the Government of Sweden. The WHO Headquarters is responsible for policy issues, while the operational responsibility rests with the Uppsala Monitoring Centre (UMC).

Currently, as of September 2015, 122 countries have joined the WHO Programme for International Drug Monitoring. Bhutan gained the 119th membership to this program in December 2014. The collaborating centre in Uppsala, Sweden (UMC) is responsible for maintaining the global ADR database, VigiBase. The WHO collaborating Centre analyses the reports in the database to:

- ✓ Identify early warning signals of serious adverse reactions to medicines.
- ✓ Evaluate the hazard.
- ✓ Undertake research into the mechanisms of action to aid the development of safe and more effective mechanisms.
- ✓ Through an advisory committee, WHO plays an important role in the provision of expert advice on all the matters relating to the safety of medicines. The committee also exists to facilitate consistent policies and action among member countries and to advice those who may be concerned about action taken in another country.

5. Establishment of Pharmacovigilance Centers in Bhutan

Prior to 2003, or the establishment of DRA, 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 Centre. In particular Post Marketing Control Division of DRA is engaged in planning and conducting Pharmacovigilance activities.

5.1 National Pharmacovigilance Center, Veterinary Pharmacovigilance Center and Regional Veterinary Pharmacovigilance Centers

Drug regulatory Authority (DRA) is the National Pharmacovigilance center. According to Bhutan medicine Rules and regulation, Chapter IX, 155 b, National Animal Hospital (NAH) is the Veterinary Pharmacovigilance Center and four Regional Livestock Development Centers as Regional Veterinary Pharmacovigilance Centers.

The four Regional Veterinary Pharmacovigilance Centers are:

- i. RLDC Tshimasam
- ii. RLDC Wangdue
- iii. RLDC khangma
- iv. RLDC Zhemgang.

5.2 Roles of Veterinary Pharmacovigilance Center.

- ✓ Veterinary Pharmacovigilance Center is responsible to conduct workshops and trainings on various aspects of veterinary Pharmacovigilance activities.
- ✓ Encourage voluntary reporting of the ADR by all categories of livestock health professionals and market authorization holders
- ✓ Identify committee member for National Pharmacovigilance Committee.
- ✓ Act as bridge between Drug Regulatory Authority and Department of Livestock.
- ✓ Provide information to end users through adverse drug reaction news, bulletins, drug alerts and seminars.
- ✓ Promote reporting adverse veterinary drug reactions through journals, other professional publications and communication activities.
- ✓ In case of emergency, the center may notify veterinary professionals and relevant stake holders including pharmaceutical company's expert.

5.3 Roles of Regional Veterinary Pharmacovigilance Centers

- ✓ Sensitize the veterinary professionals in their respective regions.
- ✓ Collection of data or ADR reports from all centers providing veterinary services in the country.
- ✓ Assist in verification of the ADR reports (completeness of the report, interpreting and coding of the drugs, case causality assessment, signal detection and risk management).
- ✓ Organize workshops/ meetings/ trainings in their respective regions.

6. ADRs and its classifications

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)** and are those which are due to (exaggerated) pharmacological effects. Type A effects 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. Amphotericin rash, penicillin hypersensitivity.

b. Non- immunological

Unpredictable non- immunological drug reactions include:

- i. **Pseudo allergy:** It is mainly induced by direct activation of mast cell and their degranulations by the drugs like vancomycin and radio contrast media. The clinical symptoms are like that of Type-I hypersensitivity except that it does not involve drug specific IgE.
- ii. **Idiosyncratic:** It is due to in born error of metabolism or acquired deficiency of enzyme(s) resulting in an abnormal metabolic pathway or accumulation of toxic metabolite. e.g. Drug induced haemolysis due to deficiency of Glucose-6-phosphate dehydrogenase.

iii. **Intolerance**

3. Type “C”

Letter “C” refers to Chronic/ continuous. These reactions are associated with long-term drug therapy e.g. Benzodiazepine dependence and Analgesic nephropathy.

4. Type “D”

Letter “D” refers to Delayed in appearance, making it difficult to diagnose. These reactions refer to carcinogenic and teratogenic effects.

5. Type “E”

End-of-treatment effects.

6. Type “F “

Failure of therapy.

7. Reporting Adverse Drug Reaction(s)

7.1 Who should report ADR?

- i. Veterinarians
- ii. Para veterinarians
- iii. Market authorization holders.

7.2 What, how and where to report?

What to report?

- ✓ All ADRs of medicinal products either included in the Essential Veterinary Drugs list or available in the market pharmacies.
- ✓ All serious reactions and interactions.
- ✓ ADRs which are not clearly stated in the package insert.
- ✓ All adverse reactions or poisonings due to traditional or herbal remedies.
- ✓ An Adverse Drug Reaction Form (Individual case safety report) is enclosed in these guidelines. Requests for ADR forms and ADR information may also be obtained from your center/ head agencies/ NAH/ DRA. The ADR form should be completed in as much detail as possible and returned to NAH or Regional Veterinary Pharmacovigilance Centers.

The Five components to validate sections in the individual case report (ICSR) are as follow:
(Refer ADR form annexure I)

- An Identifiable patient
 - ✓ Species of the animal
 - ✓ Breed of the animal
 - ✓ Age of the animal at the time of the Adverse Drug Reaction/ Adverse Drug Event
 - ✓ Weight of the animal (Kilograms)
 - ✓ Sex of the animal
 - ✓ Name of the animal
 - ✓ Predisposing factors (if any)
 - ✓ Physiological status of the animal.

- An identifiable owner
 - ✓ Name of the owner
 - ✓ Address of the owner
 - ✓ Contact number (mobile no/ land line no), E-mail address.

- Suspected drug
 - ✓ Name (Generic and brand name)
 - ✓ Strength (concentration)
 - ✓ Dose, frequency
 - ✓ Dosage form
 - ✓ Route of administration
 - ✓ Indication for use
 - ✓ Duration of use, date started, date stopped
 - ✓ Batch number.

- Suspected adverse reaction.
 - ✓ Seriousness of the reaction
 - ✓ Date the reaction started, stopped
 - ✓ Date the drug withdrawn or continued after ADR
 - ✓ Treatment provided for the reaction
 - ✓ Relevant tests/laboratory data (if available).

- An identifiable reporter
 - ✓ Name, initials
 - ✓ Address
 - ✓ Contact details

- ✓ Qualification.

8. How to Report: 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.
- ✓ Send the report quickly to any nearest Regional Pharmacovigilance Center or NAH or DRA.
- ✓ Strong suspicion and follow-up: Continue your strong suspicion of the medicine-induced illness in the same patient and in other patients.
- ✓ 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 NAH/ Regional Veterinary Pharmacovigilance Center, “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.

9. How to recognize ADR(s) 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 ordered is the medicine received and actually taken by the patient at the dose advised.
2. Take proper detailed anamnesis of the patient.
 - ✓ A full medicine and medical history should be taken.
 - ✓ An ADR should be your first differential diagnosis at all times.
 - ✓ 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.
 - ✓ It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is.

- ✓ 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.
 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 or if the laboratory tests results will improve management of the patient.
 - ✓ Try to describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis.
 5. Effect of Dechallenge and Rechallenge should be determined
 - ✓ Dechallenge (withdrawal of the suspected medicine)
 - ✓ Rechallenge (re-introducing the suspected medicine after a dechallenge).

Rechallenge is only justifiable when the benefit of reintroducing the suspected medicine to the patient outweighs 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.

10. What will happen to my Adverse Drug Reaction Report?

The report will be uploaded on the data base after performing the causality assessment using the standard operating procedure (SOP No. DRA/PMCD/ADR/15-01) of DRA.

The Information obtained from your reported reactions promotes the safe use of medicines on a local and international level. Your reported case will be entered into the national adverse drug reaction database and analyzed by expert reviewers. A well completed adverse drug report submitted by you could result in any of the following:

- ✓ Additional investigations into the use of the medication.
- ✓ Educational initiatives to improve the safe use of the medication.
- ✓ Appropriate package insert changes to include the potential for the reaction reported by you.
- ✓ Changes in the scheduling or manufacture of the medicine to make the medicine safer.

Therefore, the purpose of ADR reporting is to reduce the risks associated with drug prescribing and administration and to ultimately improve patient care and safety.

11. Analysis and Causality Assessment of ADR (s)

Causality Assessment: It is the method by which the extent of relationship between a medicine and suspected reaction is established i.e. to attribute clinical events to medicines in individual patients or in case reports.

Though there are several methods of causality assessment WHO scale, Naranjo's scale and European ABON scale is most widely used.

11.1. Advisory Committee

- ✓ Director General/Director, Department of Livestock (DoL), MoAF, Bhutan
- ✓ Drug Controller, Drug Regulatory Authority, Bhutan.
- ✓ Head, Animal Health Division, DoL, MoAF, Bhutan.
- ✓ Head, National Animal Hospital, DoL, MoAF, Bhutan.
- ✓ Head, National Centre for Animal Health DoL, MoAF, Bhutan.
- ✓ Heads, Regional Livestock Development Centers (Tshimasham, Wangdue, Khangma and Zhemgang) DoL, MoAF, Bhutan.

11.2. Causality Assessment Committee

- ✓ The Causality Assessment Committee will comprise a minimum of two experts (either two pharmacists or one pharmacist and one general practitioner) and relevant specialist will be involved where required.

11.3. Causality Assessment of ADRs

- ✓ Either Naranjo's Algorithm or WHO Probability Scale will be adopted based on the consensus of the causality assessment committee involved. However, in case of analysis of serious ADRs, both the methods should be used to assist in confirming the case. For serious ADRs, causality assessment will be performed collectively by National Pharmacovigilance Committee and respective Pharmacovigilance Committees.

- ✓ 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 (eg. National Pharmacovigilance causality committee will be considered third party to PVC committee and vice-versa).

For details refer Annexure 3: WHO probability scale table 1 and Naranjo's Algorithm table 2.

In the assessment of case reports the following elements can be recognized:

- ✓ **Quality of documentation** (e.g. completeness and integrity of data, quality of diagnosis, follow-up).

- ✓ **Coding:** Drug names 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.

- ✓ **Relevance** with regard to the detection of new reactions, drug regulation, or scientific or educational value. The following questions especially may be asked:
 - *New drug?* (Products in the market less than five years old are usually considered new drugs).
 - *Unknown reaction?* (i.e. not included in the approved Summary of Product Characteristics or unlabelled). Also important is, whether the reaction is described in the literature. e.g. National drug formulary etc, side effects of drugs.
 - *Is it a serious reaction?*

- ✓ **Identification of duplicate reports:** Certain characteristics of a case (sex, age or date of birth, dates of drug exposure, etc.) may be used to identify duplicate reporting.

12. Relation of Veterinary Pharmacovigilance Centers with other parties

1) **The Drug Regulatory Authority** in the country needs to be informed about suspected adverse reactions without delay, especially when unusual (e.g. reactions not included in the approved Summary of Product Characteristics) or serious.

2) **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.

3) **A Pharmacovigilance Centre** should seek the support of **professional veterinary/human medical and pharmaceutical associations**. In the case of an emergency, these associations should be informed in good time.

4) In addition it may be helpful to make contacts with **National Pharmacovigilance center** in nearby countries. When more experienced, such centers may be helpful with staff training.

5) **Academia:** The need for Pharmacovigilance and the nature of its procedures are a natural part of the curriculum of diploma/ degree training e.g. college of Natural Resource.

6) **Media and consumer organizations:** Support from national associations of consumer and patients may add to the general acceptance of Pharmacovigilance. Good relations with leading journalists may be helpful.

13. Annexure

Annexure 1: Guidelines on ADR reporting

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:* If known, the weight of the patient should be recorded in kilograms (Kg).
- ✓ *Physiological state 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 drug or 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 eg; 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 was first occurred.*
- ✓ *Date of reaction stopped: If the reaction recovered, the date on which the reaction recovered 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 child.
- **‘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 being exposed to the suspected drug (s) and any ADR was being evident.

E. OTHER MEDICATIONS:

A reporter should include all the details of concomitant drugs including self medication, Over the Counter medication, herbal remedies 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, and date of therapy started, indication of use, seriousness, and outcome.

Reporter: Name and address, date of report.

*Reporters name and address will be kept confidential.

Annexure 2: Veterinary Pharmacovigilance Form

Adverse Drug Reaction

Lack of Expected Drug Efficacy

A. ANIMAL DETAILS

Species: Breed/Production type: Sex (male/female):

Age: Weight(Kg):

Physiological status: Pregnant Intact Neutered Lactating Others

State of health at the time of treatment: Good Fair Poor Critical Unknown

Tentative diagnosis: Confirmatory Diagnosis:

Vaccination History:

Relevant Data/ Laboratory Report(If any):

B. OWNER DETAILS

Name:

Address:

Contact no:

Email Address(if any):

C. SUSPECTED DRUG (S)

Drug Name (Trade and generic name)	Prescri-bed for/ Indicati- on	Manufac- turer	Batch no	Expiry Date	Route of Admin- istration	Date Started	Date stopped	Storage Details

Who administered the drug (s)?

Veterinarian

Para veterinarian

Owner

Other (s)

D. SUSPECTED DRUG REACTION (S)

1. Describe the Adverse Drug reaction(s) or event (s) 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).

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

Recovered

Recovering

Continuing

Other (s) (Please specify)

3. 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)

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

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

Previous Reaction to the Suspected drug. Yes No Describe:

E. OTHER MEDICATION (S) (INCLUDING SELF MEDICATION TO THE PATIENT)

Please tick all that is appropriate:

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

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

Who administered the product?

Veterinarian Para veterinarian Owner Others

F. REPORTERS DETAIL

Name:

Designation:

Address:

Contact no:

Date:

Signature:

Annexure 3: Causality Assessment

Table 1: WHO probability scale

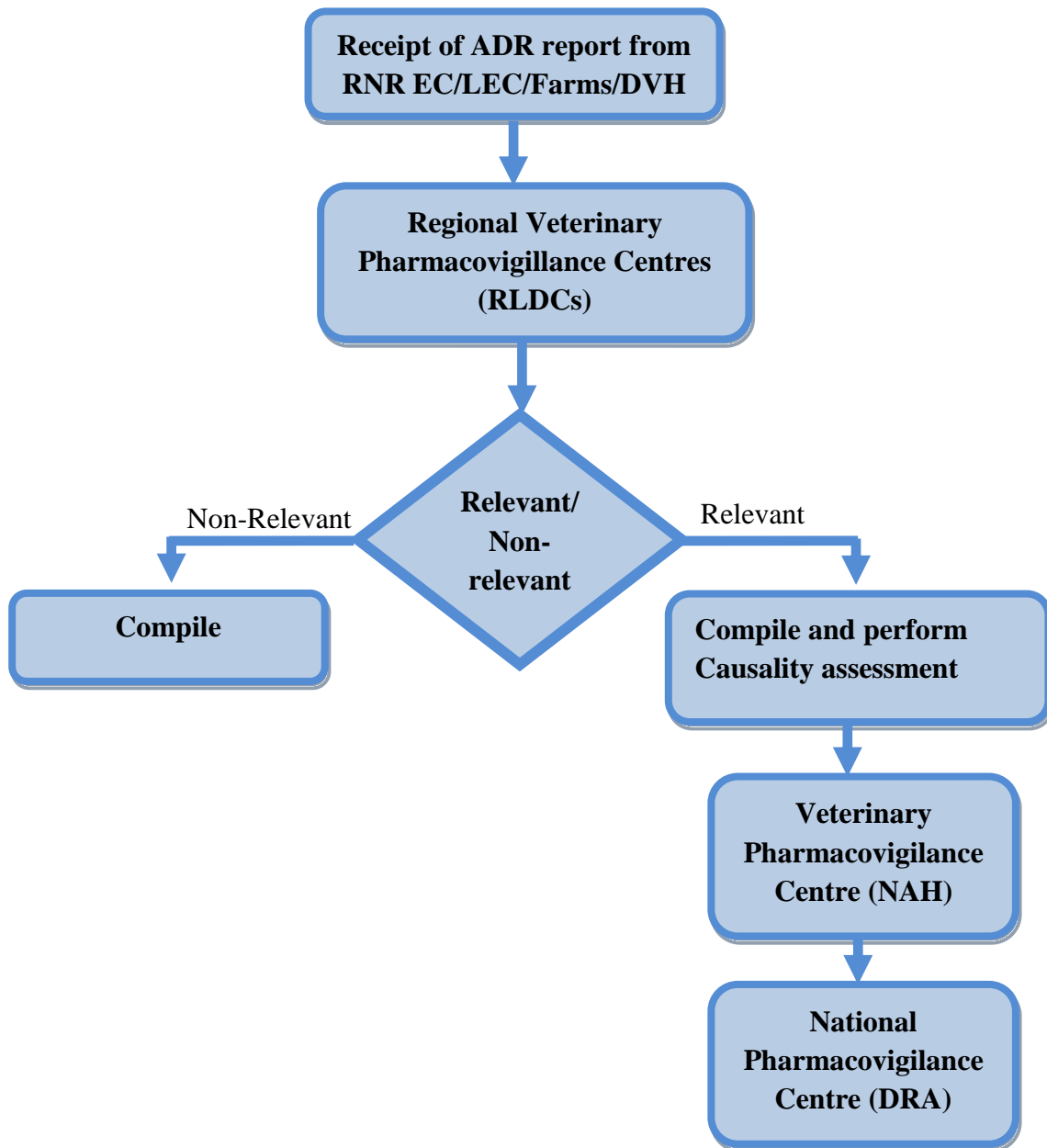
Term	Description
Certain	A clinical reaction, including laboratory test abnormality, occurring in a plausible time relationship to medicine administration, and which cannot be explained by concurrent disease or other medicines or chemicals. The response to withdrawal of the medicine (dechallenge) should be clinically plausible. The reaction must be definitive pharmacologically or phenomenological, (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) Using a satisfactory rechallenge procedure if necessary
Probably/ likely	A clinical reaction, including laboratory test abnormality, with A reasonable time sequence to administration of the medicine, Unlikely to be attributed to concurrent disease or other medicines or chemicals, and which Follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possible	A clinical reaction, including laboratory test abnormality, with A reasonable time sequence to administration of the medicine, but which could also be explained by concurrent disease or other medicines or chemicals. Information on medicine withdrawal may be lacking or unclear.
Unlikely	A clinical reaction, including laboratory test abnormality, with a temporal relationship to medicine administration which makes a causal relationship improbable, and Other medicines, chemicals or underlying disease provide plausible explanations.
Conditional/ Unclassified.	A clinical reaction, including laboratory test abnormality,
Unassessable/ Unclassified	More data is essential for a proper assessment or the additional data are under examination.

Table 2: Naranjo's Algorithm

Questions	Yes	No	Don't Know
1) Are there previous conclusive reports on this reaction?	+1	0	0
2) Did the ADR appear after the suspected drug was administered?	+2	-1	0
3) Did the ADR improve when the drug was discontinued?	+1	0	0
4) Did the ADR appear with re-challenge?	+2	-1	0
5) Are there alternative causes for the ADR?	-1	+2	0
6) Did the reaction appear when placebo was given?	-1	+1	0
7) Was the drug detected in blood at toxic levels?	+1	0	0
8) Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9) Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10) Was the ADR confirmed by any objective evidence?	+1	0	0

The Naranjo's Probability Scale The score:- > 8 = highly probable 5-8 = probable 1-4 = possible 0 = doubtful

Annexure 4: Process Flow of conducting Causality Assessment



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