PHARMACOVIGILANCE GUIDE FOR ADVERSE DRUG REACTION MONITORING AND CAUSALITY ASSESSMENT, 2015

Post marketing Control Division,

Drug Regulatory Authority

Introduction

These Guidelines has been developed by the Post Marketing Control Division of Drug Regulatory to complement and support the efforts of all healthcare professionals on the important concept of Pharmacovigilance. It gives an overview of what Pharmacovigilance is, how to detect and classify ADRs. It also describes the role of Regional Pharmacovigilance Centres and reporting system to the Drug Regulatory Authority (National Pharmacovigilance Centre). The concepts and reporting requirements stated in this guideline are based mainly on the international guidelines.

The Pharmacovigilance guidelines are intended to be used by the following category of healthcare professionals as:

i. Guidance for officials in National Pharmacovigilance Centre and Regional Pharmacovigilance centers for the conduct of Pharmacovigilance activities

ii. Training material for the workshop to the healthcare Professionals and to raise awareness of the magnitude of the drug safety problem and to convince healthcare professionals that reporting of adverse reactions is their moral and professional obligation

iii. Guidance for detecting and reporting Adverse Drug Reactions

iv. Guidance for conducting the Causality Assessment.

However, this document is not applicable for monitoring of Adverse Event Following Immunization (AEFI) and Hemovigilance. **Some sections such as "Reporting of ADR" , "Analysis and Causality Assessment of ADRs" methods maybe adopted for monitoring of veterinary adverse drug reactions and herbal medicines.** Therefore, it is hoped that all healthcare professionals actively participate in Pharmacovigilance and to report all suspected adverse drug reactions to safeguard the patients' health.

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1.0 Definition of the terminologies

i. **ADR:** refers to Adverse Drug Reaction

ii. **Pharmacovigilance centre:** refers to either National Pharmacovigilance centre (NPC) or any Regional Pharmacoviglance centre (RPC).

iii. **Regional Pharmacovigilance center**: refers to Pharmacy department of the hospitals identified in the region for coordinating Pharmacovigilance activities.

iv. **An adverse event:** refers to 'any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment'. The basic point here is the coincidence in time without any suspicion of a causal relationship.

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

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

vii. **Lack of Efficacy:** refers to an unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation.

viii. **National Pharmacovigilance Centre:** refers to the Drug Regulatory Authority.

ix. **Serious Adverse Event or Reaction:** refers to a serious adverse event or reaction is any untoward medical occurrence that at any dose results in death or is life-threatening or requires inpatient hospitalization or prolongation of existing hospitalization or persistent or significant disability/incapacity or Congenital Anomaly or medically important event or reaction.

x. **Side Effect:** refers to any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the medicine.

xi. **Signal:** refers to the reported information on a possible causal 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 the information.

xii. **Spontaneous Reporting:** refers to a system whereby case reports of adverse drug reactions are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

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

2.0 Pharmacovigilance

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

2.1 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 adverse drug reactions and this is mainly because:

- Patients used in clinical trials are limited in number and are not representative to the public 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, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete.

Therefore, it is important to permit detection of less common but sometimes very serious ADRs.

2.2 Scope of Pharmacovigilance

- To improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions.
- To improve public health and safety in relation to the use of medicines.
- 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 health professionals and the public.

Wider scope: Pharmacovigilance may also aid in identifying medication errors, counterfeiting of medicinal products, quality defects, therapeutic failure, and adverse drug interaction.

3.0 WHO Programme 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 adverse drug reactions. 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 safer and more effective medicines.

Through an advisory committee, WHO plays an important role in the provision of expert advice on all matters relating to the safety of medicines. The Committee also exists to facilitate consistent policies and action among member countries and to advise those who may be concerned about action taken in another country.

4.0 Types of Adverse Drug Reactions

Adverse Drug Reaction (ADR) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.

Type A effects:

Augmented pharmacologic effects - dose dependent and predictable (medicine actions) 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. Such effects can usually be reproduced and studied experimentally and are often already identified before marketing.

Type B effects:

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. They are generally rare and unpredictable, and may be serious and are notoriously difficult to study. Type B effects are either immunological or nonimmunological and occur only in patients, with - often unknown - predisposing conditions. Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury, to highly specific autoimmune syndromes. Also non-immunological Type B effects occur in a minority of predisposed, intolerant, patients, e.g. because of an inborn error of metabolism or acquired deficiency in a certain enzyme, resulting in an abnormal metabolic pathway or accumulation of a toxic metabolite. Examples are chloramphenicol caused aplastic anaemia and isoniazid caused hepatitis.

Type C effects:

Chronic effects refer to situations where the use of a medicine, often for unknown reasons, increases the frequency of a "spontaneous" disease. Type C effects may be both serious and common (and include malignant tumours) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long term effects; there is often no suggestive time relationship and the connection may be very difficult to prove.

Type D effects:

Delayed effects (dose independent)
Carcinogenicity (e.g., immunosuppressants)
Teratogenicity (e.g., fetal hydantoin syndrome)

Type E effects:

End-of-treatment effects

Type F effects

Failure of therapy

5.0 Establishment of Pharmacovigilance system 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 but in particular Post Marketing Control Division of DRA is engaged in planning and conducting Pharmacovigilance activities.

After Bhutan gained the membership to WHO international Drug Monitoring program, the ADR reports are collected either by Regional Pharmacovigilance centres or DRA and has been uploading on the VigiFlow (database) managed by WHO-UMC.

5.1 National and Regional Pharmacovigilance centres

A governmental department (health authority, drug regulatory agency) can be a good host for a pharmacovigilance centre and hence DRA is identified as the National PV centre and pharmacy departments in the referral hospitals are identified as "Regional PV centres".

The Regional Pharmacovigilance centres are;

i. Jigme Dorji Wangchuck National Referral Hospital, Thimphu

ii. Eastern Regional Referral Hospital, Mongar

iii. Central Regional Referral Hospital, Gelephu

5.2 Role of National Pharmacovigilance centre

i. DRA as a National Pharmacovigilance centre conducts National Pharmacovigilance workshop and encourages voluntary reporting of ADR by the all the categories of Healthcare Professionals and Market Authorization Holders.

ii. Conduct National Pharmacovigilance Committee meetings to discuss on the regulatory actions and other pharmacovigilance policy issues.

iii. It also intends to provide information to end-users through adverse drug reaction news bulletins, drug alerts and seminars. The National Centre will also be responsible to promote the importance of reporting adverse drug reactions through medical journals, other professional publications, and communications activities.

iv. In the case of an emergency, the center may notify Healthcare professionals in particular doctors and pharmacists in collaboration with pharmaceutical company's experts.

v. The National Centre has to maintain contacts with international institutions working in pharmacovigilance, e.g. the WHO Department of Essential Drugs and Medicines Policy (Geneva) and the Uppsala Monitoring Centre, Sweden

5.3 Roles of Regional Pharmacovigilance Centres

i. Liaise with respective hospital management , national PV center, other regional PV centers and other related Institutions and groups

ii. Collection of data or ADR reports from other departments of the hospital and nearby health centers.

iii. Assist in data collection and verification, example completeness of the report, interpreting and coding of drugs, case causality assessment, signal detection and risk management.

iv. Share the uploaded report to National Pharmacovigilance Centre periodically or send the filled ADR report immediately if not uploaded on VigiFlow or in case of serious events.

v. As far as possible the center shall participate in inpatient care with respect to pharmaceutical treatments to monitor Adverse Drug Reactions.

vi. Organize meetings in hospitals, academia and professional associations, explaining the principles and demands of Pharmacovigilance and the importance of reporting.

vii. In addition, a pharmacovigilance centre should inform the regulatory authority about any cluster of case reports that is of possible interest, or when an adverse reaction is reported in high or increasing frequency.

5.4 Pharmacovigilance centre Staff

The expertise desirable in the routines of a pharmacovigilance centre includes clinical medicine, pharmacology, toxicology, and epidemiology. However, a new pharmacovigilance centre often starts with only a part-time expert - usually a physician or a pharmacist - and some secretarial support. It may soon become necessary to have one expert who is responsible for pharmacovigilance for most of his/her time and for secretarial assistance to be expanded. Continuity in accessibility and service is a basic feature of a successful pharmacovigilance centre. The centre therefore needs a permanent secretariat, for phone calls, mail, maintenance of the database, literature documentation, co-ordination of activities, etc.

6.0 Reporting of ADRs

Spontaneous reporting of suspected adverse drug reactions, a regional or country-wide system for the reporting is currently the major source of information in pharmacovigilance.
We follow spontaneous reporting structure which is voluntary and yellow form is used to collect the information on ADR. Each yellow card concerns an Individual Case experienced ADRs, thus it is also called Individual Case Safety Report (ICSR).

6.1 Who should report Adverse Drug Reactions?

- **Healthcare Professionals** are the preferred source of information in pharmacovigilance, for example physicians, practitioners, medical specialists, and dentists.
- **Nurses** and other health workers may also administer medicines and should report relevant adverse drug reactions experienced by the patients.
- **Pharmacists** can play an important role in the stimulation of reporting and in the provision of additional information (for example, on co-medication and previous medicine use).
- **Marketing authorization holder (MAH)**, being primarily responsible for the safety of their products, they are obligated to report **serious** adverse drug reactions they receive about their products to DRA. While the Non-serious ADRs should be included in the periodic safety update report (PSURs).

6.2 What to Report

Report adverse drug reactions such as:

- all ADRs of medicinal products either included in the Essential Medicines List or available in the market in Pharmacies.
- all serious reactions and interactions
- ADRs which are not clearly stated in the package insert.
- unusual or interesting adverse drug reactions.
- all adverse reactions or poisonings due to traditional or herbal remedies.

6.3 How, what and where to Report?

An Adverse Drug Reaction Form is enclosed in these guidelines. Requests for ADR forms and ADR information may also be obtained from your institution or can be obtained by contacting the DRA or Pharmacovigilance Centres or visiting DRA webpage. The adverse drug event form should be completed in as much detail as possible and returned to DRA or any Pharmacovigilance Centres.

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

An identifiable patient

- Patient initials
- Sex
- Weight
- Age at time of reaction or date of birth

Suspected medicine

- 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

- Description of the 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 (if healthcare professional)

6.4 How to recognize ADRs 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 a proper history and do a proper examination of 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 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.

6.5 Will reporting have any negative consequences on the reporter?

- The outcome of the report, together with any important or relevant information relating to the reported reaction, will be communicated to the reporter as appropriate.
- The details of the report are stored in a database at DRA and the analyzed report will be sent to the Uppsala Monitoring Center (UMC).
- The names of the reporters or any other health professionals named on the report and the patient will be removed before any details about a specific adverse drug reaction is used or communicated to others.

6.6 How to report: the Basic principles of efficient reporting

For details, refer to Guidelines on Reporting (Annexure II)

- 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 Pharmacovigilance center 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 Pharmacovigillance 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.

6.7 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 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 reaction 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.

7.0 Analysis and Causality Assessment of ADRs

7.1 Causality assessment

It is the method by which the extent of relationship between a medicine and a suspected reaction is established i.e. to attribute clinical events to medicines in individual patients or in case reports. There are several method that can be use to make a causality assessment of ADRs reports.

- The literature (9 points of consideration – Morges, Switzerland , 1981)
- Probability calculation (Bayes' Theorem)
- Aetiological – Diagnostic Systems (Bénchiou's group method)
- French imputation systems
- The European ABO Systems
- The US Reasonable Possibility Systems
- The Naranjo ADR Probability Scale
- WHO Causality Categories.

The WHO scale of assessment and the Naranjo's scale are the most commonly used scales. (How close is the relation between drug and event?)

7.2 Why causality assessment?

An inherent problem in Pharmacovigilance is that most case reports concern suspected adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a re-challenge is rarely ethically justified. In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'. In an attempt to solve this problem many systems have been developed for a structured and harmonized assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of

relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance.

7.3 Uses and limitation of Causality Assessment

- What it can do?
  - Decrease disagreement between assessors
  - Classify uncertainty
  - Mark individual case reports
  - Improve the scientific basis of assessment.

- What it cannot do?
  - Give accurate quantitative measurement of the likelihood of a relationship
  - Distinguish valid form invalid cases
  - Quantify the contribution of a drug to the development of an adverse event
  - Change uncertainty to certainty.

7.4 Advisory Committees

A multi disciplinary advisory committee is desirable, to support the pharmacovigilance centre with regard to the quality of the procedures in: data collection and assessment, the interpretation of the data, the publication of information.

As an advisory committee member, during the national pharmacovigillance committee meeting, any member(s) from the following discipline: general medicine, pharmaceutics, clinical pharmacology, toxicology, epidemiology, pathology, drug regulation and quality assurance, drug information may be co-opted.

7.5 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.

7.6 Causality Assessment of ADRs

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 NPC committee and respective PV centre committee.

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. NPC causality committee will be considered third party to PVC committee and vice-versa).

For details refer Annexure 5: Naranjo's Algorithm and Annexure 6: WHO probability scale.

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

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

2. *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.

3. *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 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). Also important is whether the reaction is described in the literature (e.g. national drug formulary, Martindale, www.sideeffects.embl.de for side Effects of Drugs.

4. *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.

7.6.1 The WHO-UMC causality assessment system

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

To illustrate how the system works, a comparison of the following criteria and wording of 'Probable' and 'Certain' is shown in the table 1.

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 phenomenologically, (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) Using a satisfactory rechallenge procedure if necessary
Probable / Likely	A clinical reaction, including laboratory test abnormality, with A reasonable time sequence to administration of the medicine, Unlikely to be attributed to concurent 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.

Various causality terms are in use but the above are used most widely.

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 Probability Scale

The score:-

> 8 = highly probable

5-8 = probable

1-4 = possible

0 = doubtful

8.0 Relation of pharmacovigillance center 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 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 centres*** in nearby countries. When more experienced, such centres 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 pre-graduate training.

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

9.0 References

1. Safety Monitoring of Medicinal Products. Guidelines for setting up and running a Pharmacovigilance Centre. Uppsala Monitoring Centre - WHO Collaborating Centre for International Drug Monitoring, EQUUS, London, 2000.
2. Safety of Medicines, A guide to detecting and reporting adverse drug reactions, WHO/EDM/QSM/2002.2
3. Safety Monitoring of Medicinal Products; Guidelines for setting up and running a Pharmacovigilance Centre, the Uppsala Monitoring Centre.
4. Guidelines for Detecting & Reporting Adverse Drug Reactions Individual Case Safety, Reports For Healthcare Professionals, Rational Drug Use and Pharmacovigilance Department- JFDA (2014).
5. Bhutan Medicines Rules and Regulation 2012.

Annexure 1: ADR form (Yellow form)

SENDING BY DIFFERENT ATTACHMENT, PLEASE MAKE IT YELLOW COLOUR

Annexure 2: Guidelines on ADR reporting

A. PATIENT INFORMATION

1. Patient Details

- *Patient name or initials:* A reporter should mention the name of the patient or initials of a patient. For e.g.: Ngawang Dema or ND (whichever is convenient).
- *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 in kilograms (Kg).

2. Relevant tests/ laboratory data

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

3. 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. 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.

C. SUSPECTED ADVERSE DRUG REACTION

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 upper and lower limbs.*
- *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.
- *Outcomes:* 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

2. ***Seriousness of the reaction:***

- If any event is serious in nature, a reporter must select the appropriate reason for seriousness e.g.:
  - **'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.

D. 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.)

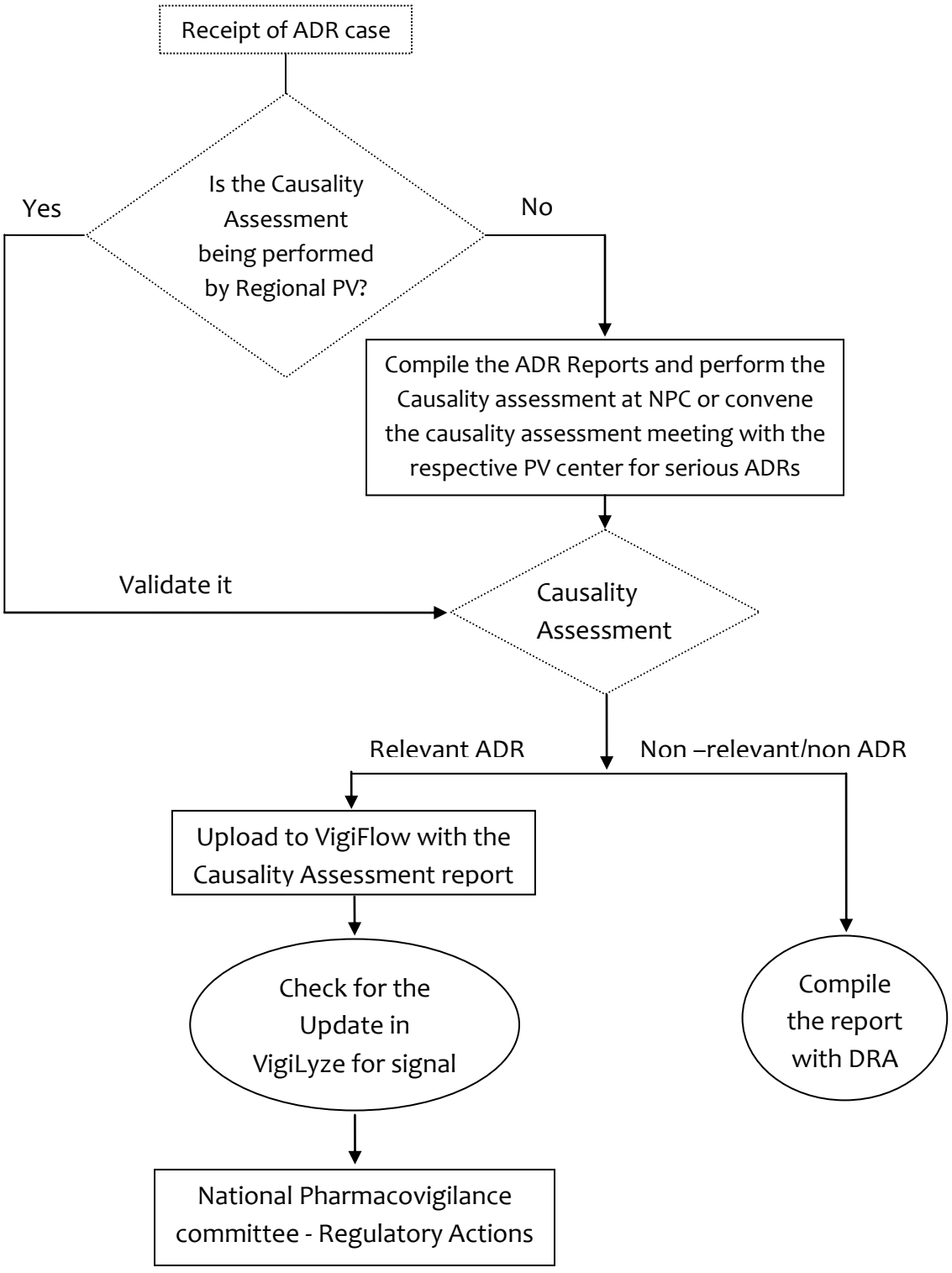
E. REPORTER

- *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.

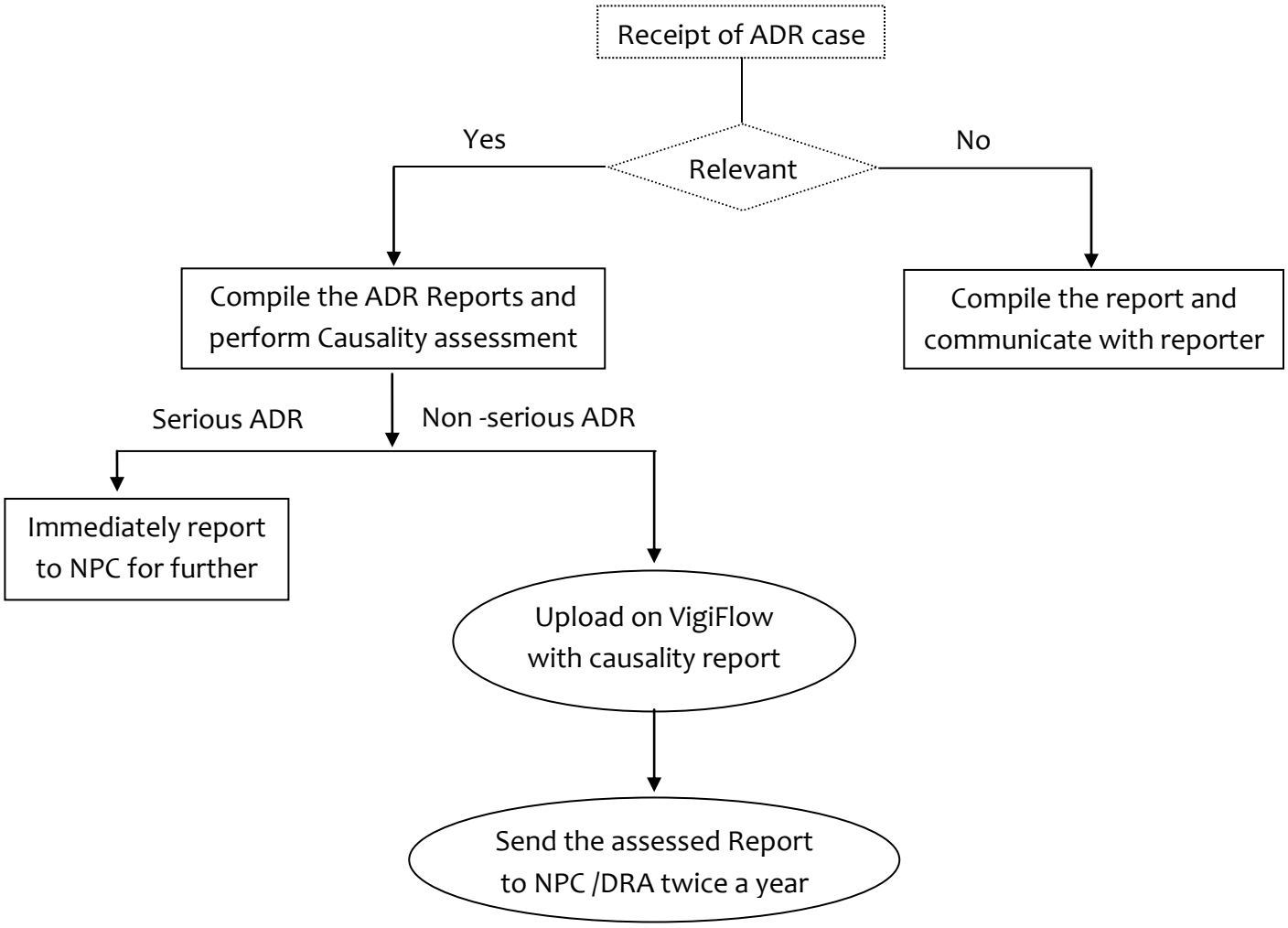
NOTE: For quality reporting, all the above mentioned fields are essential. In case of incomplete information, the reporter must take care that at least mandatory fields are present. Following are the mandatory fields for a valid case report and are **marked with asterisk** on the form:

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

Annexure 3: Process Flow of conducting Causality Assessment at the NPC



Annexure 4: Process Flow of conducting Causality Assessment at RPC



Annexure 5: Naranjo's Algorithm

ADR Report ID: ..... Date: .....

Circle the most appropriate answer in the columns below and provide justification for allocation of points in the remarks column.

Questions	Yes	No	Don't Know	Remarks
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	
Total Score				

Underline the appropriate range of Naranjo Probability Scale score below:

> 8 = Definite, 5-8 = probable, 1-4 = possible, 0 = doubtful

1. Assessor's Name: .....

Designation & Address: .....

.....

Signature:.....

2. Assessor's Name: .....

Designation & Address: .....

.....

Signature: .....

Annexure 6: WHO probability Scale

ADR Report ID: ..... Date: .....

Underline the most appropriate answer in the columns below and provide justification for allocation of points in the remarks column.

Score	Description	Remarks
C1 – Certain	Plausible time, not related to underlying condition, concurrent disease, other drugs or chemicals, related pharmacologically, +ve dechallenge, +ve rechallenge	
C2 – Probable	Reasonable time, unlikely to be related to concurrent disease, other drugs,+ve dechallenge, no rechallenge	
C3 – Possible	Reasonable time, may be due to concurrent disease, other drugs, no information on dechallenge	
C4 – Unlikely	Improbable temporal relationship, other confounding factors such as drugs, chemicals, underlying disease	
C5 – Unclassifiable	Insufficient information to analyse the report	

1. Assessor's Name: .....

Designation & Address: .....

.....

Signature: .....

2. Assessor's Name: .....

Designation & Address: .....

.....

Signature: .....

DRUG REGULATORY AUTHORITY

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For Feedback and queries, please contact:

Drug Regulatory Authority

Royal Government of Bhutan

P.O 1556

Phone: 337074.337075, Fax: 335803

Email: dra@dra.gov.bt Website: www.dra.gov.bt