

REPUBLIC OF ZAMBIA

**THE PHARMACEUTICAL REGULATORY AUTHORITY**

# **PHARMACOVIGILANCE REFERENCE MANUAL**



**First Edition**

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**REFERENCE MANUAL ON PHARMACOVIGILANCE  
FOR HEALTH WORKERS**

**Produced by the National Pharmacovigilance Unit**

**Pharmaceutical Regulatory Authority  
Ministry Of Health  
ZAMBIA**

## **FOREWORD**

All medicines have potential to cause harm during their usage. Adverse events associated with the use of medicines have considerable social and economic consequences. A system for continuous monitoring of the safety of medicines is therefore needed. In order for such a system to be successful, there is need to engage all health care professionals in a well-structured programme. The Government of the Republic of Zambia has since established the National Pharmacovigilance Unit under the Pharmaceutical Regulatory Authority to coordinate the drug safety monitoring programme in the country.

The science and activities relating to the detection, assessment, understanding and prevention of drug adverse effects or any other medicine related problem is referred to as “Pharmacovigilance”. The aim of a pharmacovigilance system is to ensure rational and safe use of effective medicines.

Success of any pharmacovigilance programme depends on well-motivated health workers who are conversant with the principles of drug safety monitoring. The National Pharmacovigilance Centre has developed this manual to serve as a reference document on the detection, management and reporting of adverse events to drugs, vaccines and herbal products. The manual also gives guidelines on the reporting of treatment failure cases and drug resistance surveillance to malaria, HIV and tuberculosis.

It is hoped that this manual will provide the necessary information on drug safety monitoring and will stimulate the active participation of health workers in pharmacovigilance.

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## **ACRONYMS**

ADE	–	Adverse drug event
ADR	–	Adverse drug reaction
AEFI	–	Adverse event following immunization
AIDS	–	Acquired Immunodeficiency syndrome
ART	–	Anti-retroviral therapy
ARV	–	Anti-retroviral
ATT	–	Anti-Tuberculosis Therapy
CIOMS	–	Council for International Organisations of Medical Sciences
HIV	–	Human Immunodeficiency Virus
IUATLD	–	International Union Against Tuberculosis And Lung Disease
MDR-TB	–	Multi-drug Resistance Tuberculosis
NPVU	–	National Pharmacovigilance Unit
TB	–	Tuberculosis
OTC	–	Over the counter
UMC	–	Uppsala Monitoring Centre
WHO	–	World Health Organisation

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## INTRODUCTION

Medicines are beneficial to mankind. They have helped to bring improved health and longer life to the human race. They affect the lives of hundreds of millions of people every day.

The use of medicines is, however, not without risks. Medicines have caused, do cause and will continue to cause lesser or greater harm to many people, alongside the many who benefit. There are also many people who do not derive any beneficial effect at all.

Furthermore, not all hazards of drugs can be known before a drug is marketed; neither tests in animals nor clinical trials will always reveal all the possible side effects of a drug. These may only be known when the drug has been administered to large numbers of people over considerable periods of time.

Adverse events associated with the use of medicines have considerable social and economic consequences. During the last decades it has been demonstrated by a number of studies that medicine mortality and morbidity is one of the major health problems which is beginning to be recognized by health professionals and the public.

The World Health Organisation has therefore recognized the need for developing effective systems for continuous monitoring of the effects of medicines, in all countries. More than 65 countries in the world have thus developed drug safety monitoring (pharmacovigilance) systems over the past thirty years.

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from health care providers and patients on the adverse effects of medicines, biological products, herbal and traditional medicines, with a view to identifying new information about hazards and preventing harm to patients. Pharmacovigilance is integral to effective clinical practice and its ultimate goal is to ensure rational and safe use of effective medicines.

The scope of pharmacovigilance systems is wide and includes the monitoring of all medicine related problems including adverse drug reactions, drug interactions, medication errors, drug abuse, drug overdose, treatment failures and drug resistance, product quality problems such as lack of efficacy, poor packaging and expired products, and counterfeit products.

This manual has been developed to introduce the concept of pharmacovigilance. It gives guidelines on the detection, management and reporting of medicine related problems and is intended for all health workers involved in the management of patients. Its purpose is to help health professionals participate effectively in the very important process of continuous surveillance of safety and efficacy of all products used in the prevention, treatment and diagnosis of disease.



# CHAPTER 1: INTRODUCTION TO DRUG SAFETY MONITORING

## A. DEFINITIONS

1. **Pharmacovigilance:** The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
2. **Drug or medicine:** A pharmaceutical product, used in or on the human body for the prevention, diagnosis or treatment of disease, or for the modification of physiological function.  
Definition may differ from legal definition e.g. National Drug Policy definition is slightly different  
“Drug” and “medicine” in this instance used interchangeably.
3. **Vaccine:** A suspension of attenuated live or killed micro-organisms or fractions thereof (i.e. purified protein subunits, polysaccharides, recombinant DNA or split virions) that are administered (IM, SC, PO, mucosal, or ID), to induce immunity and prevent infectious disease; a product of weakened or killed micro-organism (bacterium or virus) given for the prevention or treatment of infectious diseases.
4. **Adverse drug reaction:** A response to a medicine which is noxious (harmful) and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.  
In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).
5. **Unexpected adverse reaction:** An adverse reaction, nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug.  
May appear in the product data sheet but nature and severity of reaction may be different from what was previously known and documented.  
Here the predominant element is that the phenomenon is unknown.
6. **Side effect:** Any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug.  
Essential elements in this definition are the pharmacological nature of effect, that the phenomenon unintended, and there is no overt overdose.  
Examples: Drowsiness due to antihistamines; anaemia due to zidovudine, constipation due to opiates

7. **Adverse event or experience:** 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 causal relationship. Examples: Headache (due to e.g. previously undiagnosed malaria) presenting after taking anti-hypertensives; nausea (due to hypoglycaemia) after taking an anti-malarial drug.
8. **Adverse event following immunization:** A medical incident occurring after an immunization that is believed to be caused by the immunization
9. **Non-adherence:** May be defined as the failure of a patient to take medications as prescribed by the attending health worker. For instance where a medication has been recommended to be taken twice daily for seven days and the patient only takes the medicine for two days.
10. **Treatment failure:** Occurs when the expected treatment outcome is not achieved despite the patient taking the prescribed medications correctly. Drug resistance, product failure, bioequivalence problems and the use of substandard or counterfeit products may cause treatment failure.
11. **Drug resistance:** Is defined as decreased susceptibility of a pathogen to a drug
12. **Poor quality problems:** May include bioequivalence problems, expired products, poor storage or inadequate packaging information
13. **Counterfeit products:** Illegal copies of branded products and may contain little or none of the labelled active ingredients
14. A **Serious Adverse Event** is any event that:
  - Is fatal e.g. halofantrine induced cardio toxicity
  - Is life-threatening e.g. anaphylaxis from penicillin
  - Is permanently/significantly disabling e.g. discolouration of teeth from tetracycline
  - Requires or prolongs hospitalisation e.g. hypotension due to rapid injection of quinine
  - Causes a congenital anomaly e.g. phocomelia from thalidomide
  - Requires intervention to prevent permanent impairment or damage drug-induced renal failure

To avoid any confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided: The term 'severe' is not synonymous with serious. 'Severe' is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical

significance (such as severe headache). Seriousness (not severity), which is based on patient/event outcome or action criteria, serves as guide for defining regulatory reporting obligations.

15. **Signal:** Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.  
Usually more than one report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.  
Signals led to withdrawal of thalidomide (phocomelia) and reviewing of aspirin (gastro-intestinal effects) product information.
16. **Misuse:** use of a drug or substance, without or against health professional
17. **Abuse:** persistence or unjustified use of a drug or substance in a prolonged, unnecessary way or at excessive dosage
18. **Harmful use:** pattern of psycho-active drug or substance use that is causing damage to health (mental or physical)
19. **Dependence:** psychic craving for a substance (including drugs). This is an adverse drug reaction and has been reported for a number of drugs.  
Drug addiction is synonymous with drug dependence.  
Drug dependence is associated with tolerance and withdrawal reactions.
20. **Tolerance** is when increased doses of psychoactive substances are required to achieve effects originally produced by lower doses.
21. **Withdrawal state** (or syndrome) means symptoms of variable clustering and severity occurring on discontinuation of the drug or substance, or on dose reduction.

## B. THE DRUG SAFETY PROBLEM

### MAGNITUDE

Studies demonstrate medicine morbidity and mortality to be major health problem:

- In the USA: 39 prospective studies from US hospitals showed an overall incidence of serious ADRs of 6.7% and an overall incidence of fatal ADRs of 0.32% (106 000 individuals)  
*[Lazarou J, Pomeranz BH, Corey PN. JAMA 1998;279:1200-5]*
- ADRs are the 4<sup>th</sup>-6<sup>th</sup> largest cause of mortality in the USA.  
Europe: ADRs in some countries are responsible for more than 10% of hospital admissions (11.5% in Norway, 13% in France and 16% in UK).
- 25 studies (1970-95) showed that hospital admissions due to ADRs ranged from 4.2 - 6.0% with a median of 5.8%  
*[Pharmacoepidem. & Drug Safety 6; suppl 3: S71-S77 (1997)]*
- 16.2% of hospital admissions are drug-related

Therapeutic failure	54.8%
Adverse reactions	32.9%
Overdose	12.3%
Avoidable	49.3%

  
*[Nelson KM, Talbert RL. Pharmacotherapy 1996;16:701-7]*
- In addition to the sufferings of the patients, the treatment of adverse drug reactions imposes a high financial burden on healthcare. Some countries spend 15-20% of their hospital budget dealing with drug complications.  
Direct costs of ADRs as shown in 13 studies (1980-95)
  - Median length of stay in hospital = 8.7 days
  - Average cost per inpatient in Germany = 260 \$
  - Total estimated cost of ADRs in Germany = 588 million \$/year
  - 30.7% of admissions due to ADRs were estimated to be preventable*[Pharmacoepidemiol & Drug Safety 6; suppl 3: S79-S90 (1997)]*

Currently there are no estimates of the magnitude of the problem of ADEs in Zambia.

## MEDICINE RELATED PROBLEMS

### Adverse Drug Reactions

#### Categories of Frequency of ADRs (CIOMS)

Very common	$\geq 1/10$	$\geq 10\%$
Common (frequent)	$\geq 1/100$ and $< 1/10$	$\geq 1\%$ and $< 10\%$
Uncommon (infrequent)	$\geq 1/1,000$ and $< 1/100$	$\geq 0.1\%$ and $< 1\%$
Rare	$\geq 1/10,000$ and $< 1/1,000$	$\geq 0.01\%$ and $< 0.1\%$
Very rare	$< 1/10,000$	$< 0.01\%$

#### Why ADRs occur

The effects of any medical intervention cannot be predicted with absolute certainty. There is no drug or medical intervention that will not have some negative and undesirable effect on someone, somewhere at some time. Information about rare events may, by their very nature not be available until they happen.

Some causes of ADRs are preventable while others are inevitable and unavoidable.

#### Preventable reasons

1. An error in diagnosing the disease
2. Prescription of the wrong drug for the disease
3. Prescription of the wrong dose of the right drug
4. Choice of the right drug for the disease, but maybe the wrong drug for the patient because of genetic or ethnic predisposition, age co-morbid conditions, concurrent medication, allergy or intolerance
5. Choice of appropriate drug but without taking into account the potentially harmful interactive effects with other drugs or substances being taken by the patient
6. The full specification, indications, contraindications and risks of the drug may not have been read or fully understood
7. The patient may not comply with the doctor's advice or with the manufacturer's advice in the patient information leaflet
8. Self-medication
9. Polypharmacy (increased drug interactions)

## DRUG INTERACTIONS

A drug interaction is said to occur when the response of a patient to a drug is changed by the presence of another drug, food, drink or by some environmental chemical agent.

Drug interactions are an increasingly important cause of ADRs. Contributing factors include the introduction of new therapeutic agents with complex mechanisms of actions and the increasing prevalence of polypharmacy (e.g. drug treatment of HIV involves combination of several drugs with potential to cause significant drug interactions). About 4 – 5% of prescription drugs used in hospital have the potential for interaction. About 7% of ADR may be due to interaction, and up to 1% of hospital admissions are due to interactions [*Drug Benefits and risks, Chris J. van Boxtel, Budiono Santoso, Ralph Edwards*].

### To minimize the risk of harmful drug interactions:

Health workers

- Must have adequate knowledge of the pharmacological mechanisms involved in drug interactions
- Should be aware of the drugs associated with greatest risk and the most susceptible patient groups
- Must be alert to the possible involvement of non-prescribed medicines and other substances in drug interactions

### Patients at particular risk of significant drug interactions

1. Elderly patients
2. Seriously ill patients
3. Patients with hepatic or renal disease
4. Patients on long-term therapy for chronic disease (AIDS, epilepsy, diabetes)
5. Patients with more than one prescribing doctor

### Drugs associated with greatest risk

1. Drugs that induce (e.g. phenytoin, rifampicin, carbamazepine, phenobarbitone) or inhibit (ciprofloxacin, erythromycin, ketoconazole) hepatic cytochrome P450 enzymes
2. Drugs with narrow therapeutic window e.g. phenytoin, warfarin, digoxin, immunosuppressants

## DRUG-FOOD INTERACTIONS

Some foods interact with drugs (due to chemicals they contain) e.g. foods containing tyramine such as cheese will cause reactions in patients given monoamine oxidase inhibitors, grapefruit juice may interact with terfenadine and some other drugs

## **TREATMENT FAILURE**

There are a number of reasons why a patient may not respond well to medication given:

1. Incorrect diagnosis, hence incorrect drug
2. Incorrect dose, strength, formulation
3. Drug interactions causing reduced efficacy
4. Poor compliance
5. Pharmaceutical defects and counterfeit
6. Resistance
7. Tolerance
8. Metabolic insensitivity of the patient (e.g. in hereditary coumarin resistance, a rare autosomal dominant condition).

## **QUALITY PROBLEMS AND COUNTERFEITING**

There are large volumes of drugs on the world market, which are either counterfeit (illegal copies) or substandard. Counterfeit drugs may also be substandard.

Substandard drugs may contain little or none of the labeled active ingredient.

They may include other substances or include even contaminated or poisonous ingredients. Some drugs are sold and used after their expiry dates and some are stored in conditions that damage them.

## **DRUG MISUSE: HARMFUL USE, ABUSE AND DEPENDENCE**

- The terms misuse, abuse and harmful use are often used interchangeably but it is useful to distinguish between the occasional "misuse" of a drug from the more persistent and damaging 'abuse' of a drug.
- Almost all drugs that are psychoactive have a misuse or abuse potential.
- Commonly abused substances include opiates, barbiturates, hallucinogens, alcohol and nicotine.
- Other drugs that can cause dependence are nasal decongestants, laxatives and analgesics

## **OVERDOSE (POISONING)**

Overdose or poisoning constitutes excessive pharmacological effects

Overdose may be:

- Relative or absolute
- Recreational
- Iatrogenic
- Intentional or accidental
- Acute or chronic

## CHAPTER 2: DIAGNOSIS AND MANAGEMENT OF ADRS

### TYPES OF ADVERSE DRUG REACTIONS

	<b>TYPE A</b>	<b>TYPE B</b>	<b>TYPE C</b>
<b>Definition</b>	Reactions due to (exaggerated) pharmacological effects	Patient reactions (allergic reactions, pseudo-allergy, metabolic intolerance, idiosyncrasy)	Reactions associated with increased frequency of a spontaneous disease 'statistical effects'
<b>Characteristics</b>	Fairly common (> 1 %)	Rare (< 1 %) & unpredictable	
	Expected	Unexpected	
	Dose related (i.e. more frequent or severe with higher doses)	No dose relationship	
	Suggestive time relationship	Suggestive time relationship	No suggestive time relationship Often long latency
	Reproducible and can be studied experimentally	Not reproducible experimentally	Not reproducible experimentally
		Low background frequency	High background frequency
		Causality uncertain	Connection between drug and effect may be very difficult to prove
		Less typical for a drug reaction	
<b>Examples</b>	Mechanism is known	Mechanism uncertain	Mechanism unknown
	Constipation (opiates)	Anaphylaxis	Congenital malformations
	Sedation (barbiturates)	Stevens-Johnson syndrome	Cancer
	Hypokalaemia (diuretics)	Blood dyscrasias (e.g. chloramphenicol induced aplastic anaemia)	Genetic defects
	Hypoglycaemia (antidiabetics)	Hepatitis (isoniazid induced hepatitis)	Second generation effects
	Urinary retention (antimuscarinic drugs)	Systemic lupus erythematosus (hydralazine)	



## **Type A**

Reactions caused by known drugs toxicities plus those related to the drug's pharmacology and/or dose are defined as Type A ADEs. They are often already identified before marketing. Type A reactions typically produce 70% to 80% of all ADRs.

Most such events should be preventable. They may often be avoided by using doses which are appropriate to the individual patient. Early detection systems may allow interventions that prevent the more severe toxicity manifestations.

Interactions between drugs, especially pharmacokinetic interactions, may often be classified as Type A effects although they are restricted to a defined sub-population of patients (i.e. users of the interacting drugs).

Factors that increase the incidence of type A reactions include extremes of age, hepatic and renal disease.

## **Type B**

Type B adverse effects: these are *patient reactions* and characteristically occur in only a minority of patients (with predisposing conditions)

Type B ADEs are either immunological or non-immunological.

- Immunological reactions may range from rashes, anaphylaxis, vasculitis, inflammatory organ injury to highly specific auto-immune syndromes
- 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

Type B ADEs that are the result of first-time drug use are thought to be unpreventable. However, with the continued development of new knowledge and new technologies in pharmacogenomics, novel strategies are anticipated that may actually prevent many Type B ADEs.

## **Type C**

Type C adverse effects ('statistical effects') refer to situations where the use of a drug, 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.

## DIAGNOSIS OF ADRS

- A. Ensure medicine ordered is medicine received and actually taken by patient at dose advised. Consider all drugs / medicines possibly taken by the patient:
- OTC
  - Contraceptives
  - Herbal / traditional
  - Abused drugs / alcohol
  - Long term treatment
- B. Verify that the onset of suspected ADR was after drug was taken, not before. Discuss carefully observation made by patient. Determine the time interval between beginning of drug treatment and onset of event.
- Was the event present before the patient began the medicine?
  - Did the event occur within a plausible time period of starting the medicine?
    - Headache a few hours after - Yes
    - Liver failure on the first day - No
- C. Consider whether the event pharmacologically plausible?
- Is it a side effect (class A reaction) of:
    - the drug(s) in question
    - the class?
  - Is it a known allergic (class B) reaction
    - the drug(s)
    - the class?
- D. Evaluate suspected ADR after discontinuing drugs or reducing dose and monitor patient's status (dechallenge)
- Trial withdrawal
    - Is the time to recovery consistent with the action of the drug?
  - Rechallenge
    - Same pattern?
    - No effect?

**Dechallenge:** withdrawal of a product from the patient's therapeutic regimen

- Positive dechallenge: improvement of reaction when dechallenge occurs. Resolution of suspected ADR when the drug is withdrawn is a strong, although not conclusive indication of drug-induced reaction
- Negative dechallenge: continued presence of an adverse experience after withdrawal of the drug.

**Rechallenge:** reintroduction of a product suspected of having caused an adverse event following a positive dechallenge.

- Negative rechallenge: failure of the product, when reintroduced, to produce signs or symptoms similar to those observed when the product was previously introduced.
- Positive rechallenge: reoccurrence of similar signs and symptoms upon reintroduction of product.

Rechallenge is only justifiable when the benefit of re-introducing the drug to the patient outweighs the risk of recurrence of the reaction. This is rare. In some cases the reaction may be more severe on repeated exposure. Rechallenge therefore requires serious ethical considerations.

E. Consider the possibility of a drug interaction

- Remember
  - OTCs
  - Contraceptives
  - Herbals / traditional
  - Drugs of abuse / alcohol
  - Long term medicines
- No problems observed with the first drug but problems occur when a second drug is commenced  
Is it the 2<sup>nd</sup> drug or is it an interaction?
  - has the patient taken the 2<sup>nd</sup> drug before?
  - OK when 1<sup>st</sup> drug is withdrawn?
  - knowledge of metabolism of the two drugs

F. Analyse alternative causes (other than the drug) that could on their own have caused reaction

G. Use relevant up-to-date literature and personal experience on drugs and their ADRs. Verify if there are previous conclusive reports on this reaction. The National Pharmacovigilance Centre is one resource for obtaining information on ADRs. The manufacturer of the drug can also be a source of information (caution: information may be biased!)

## MANAGEMENT OF ADRS

### Decisions are made by considering:

- Seriousness / severity of ADR
- Seriousness of disease
- Benefit / harm assessment

#### 1. If the reaction is serious

- Withdraw suspected (all?) drugs
- Treat urgently

#### 2. If the disease is serious

- Consider the effect of not having treatment
- Continue treatment and treat symptoms of reaction if necessary
- Consider an alternative drug
- Stop unnecessary drugs

#### 3. If the reaction is mild

- Continue treatment if necessary
- Stop unnecessary drugs
- Consider dose reduction
- Reassure and do nothing
- Symptomatic treatment if warranted

## BENEFIT/RISK ASSESSMENT

Whenever a drug is given to a patient, the prescriber should have a clear idea of what is to be achieved, the likelihood of success, and the chance of doing harm and try to balance these factors.

Although general knowledge about a drug may not be sufficient to cover a particular patient's situation, the benefits and risks of the drugs would be determined from available literature including the enclosure with the drug produced by the manufacturer.

For each drug prescribed the prescriber should ask the following questions:

### ***For benefit:***

1. What is the seriousness of the disease and how much will the drug do in reducing the seriousness?
2. How long will the disease last, and how much reduction can be expected from the drug?
3. In the case of prophylaxis, how prevalent is the disease and what reduction can be expected?

***For risk:***

1. How serious are the adverse reaction(s)?
2. How long will they last?
3. How frequent are they?

**PREVENTION OF ADES**

The following measures would help to reduce the incidence of ADEs:

1. All health workers should receive adequate training in the recognition and reporting of adverse effects. All health workers should be given sufficient basic education in pharmacotherapy.
2. Refer to textbooks and other reference materials providing information on drug reactions and interactions
3. Use drugs that you know very well so that you know which risks to anticipate. Then use the drugs in a way that minimizes the risks.
4. Do not change therapy from known drugs to unfamiliar ones without good reasons
5. Always consider the risks and benefits of any drug that you plan to use. Make comparisons among drugs for the same indication before deciding what is best to use for a particular patient.
6. Be aware of the general predisposing factors to ADEs. These include extremes of age, liver and kidney disease, previous history of allergy or reaction to drugs. Co-morbid conditions such as AIDS increase the incidence of ADEs (e.g. AIDS patients have a propensity to have allergic adverse reactions). Drug therapy should be adjusted to the individual. Be particularly careful when prescribing for children, the elderly, the pregnant and lactating, the seriously ill and patients with hepatic and renal diseases. Careful ongoing monitoring is essential in these patients.
7. Take extra care when you prescribe drugs known to exhibit a large variety of interactions and adverse reactions (e.g. anti-coagulants, anti-epileptics, hypoglycaemic drugs) with careful monitoring of patients with such reactions.
8. Beware of the interaction of drugs with certain foods, alcohol and household chemicals
9. Drugs should always be of the best possible quality
10. Avoid polypharmacy. Use few drugs whenever possible. The incidence of adverse reactions increases with the number of drugs.

11. Review the entire drugs used by patients regularly, taking special notice of those bought without a prescription (OTC, herbal preparations).
12. If patients show signs or symptoms not clearly explained by the course of their illness, think of adverse drug reaction
13. If you suspect an ADR, consider stopping the drug or reduce dosage as soon as possible and notify the ADR to NPVU

## CHAPTER 3: ADVERSE DRUG EVENT REPORTING

### POST MARKETING SURVEILLANCE

Post marketing surveillance involves the collection of clinical data, primarily on drug safety, on marketed medicines used in everyday practice.

#### **Why post marketing surveillance and reporting ADRs is important**

The purpose of postmarketing surveillance is to detect information about the drugs that could not be identified during clinical trials.

Information from pre-marketing phase of drug development incomplete due to:

1. Animal tests are insufficient to predict human safety
2. Clinical trials have limitations: patients used in clinical trials limited in number, clinical trial conditions differ from clinical practice and duration of trials limited

#### Limited number of patients

By market authorization < 5000 individuals are exposed to the drug. Only more common ADRs are detected. At least 30,000 exposures are needed so as not to miss at least one patient with an ADR of incidence of 1 in 10,000.

Furthermore the events detected in clinical trials will be incompletely detected and understood since they are few.

#### Limited population

Clinical trials usually include a small number of healthy, male volunteers and highly selected patients. In general they tell us how well a drug works for a defined disease and what potential harm it may cause. However, they provide only limited information for larger populations with different characteristics from the trial group (age, gender, state of health, ethnic origin etc).

Especially susceptible patients are usually not included in clinical trials and the effects of intercurrent disease or medication are little assessed.

Information on rare but serious ADEs, chronic toxicity, use in special groups (children, elderly, pregnant women) is therefore not available or incomplete from pre-marketing trials.

#### Limited duration

With most drugs some hazards may only be known when the drug has been administered to large numbers of patients over considerable periods of time.

Effects of aspirin (on the GIT), prolonged use of phenacetin (renal papillary necrosis) and thalidomide (phocomelia) were only realised after long periods.

#### **Post marketing surveillance serves the following purposes:**

1. Detection of unexpected adverse effects and interactions
2. Identification of risk factors
3. Quantitative measurement of the lack of safety
4. Determination of long term safety/toxicity

### Major aims of pharmacovigilance

1. Early detection of unknown safety problems
2. Detection of increases in frequency of adverse drug reactions
3. Refine and add information on suspected or known reactions e.g. identification of risk factors
4. Quantifying risks of drugs
5. Rational and safe use of medicines
6. Communication of information on safety of drugs

### SURVEILLANCE METHODS FOR ADVERSE DRUG REACTIONS

Method	Advantages	Disadvantages
Anecdotal reporting (e.g. in journals)	Simple; cheap	Relies on individual vigilance and astuteness; may only detect relatively common effects.
Voluntary organized reporting (doctors, pharmacists, pharmaceutical companies) or spontaneous reporting	Simple	Under-reporting; reporting bias by "bandwagon" effect
Intensive event monitoring; prescription event monitoring	Easily organized	Selected population studied for a short time
Cohort studies	Can be prospective; good at detecting effects	Very large numbers required; very expensive
Case-control studies	Excellent for validation and assessment	Will not detect new effects; expensive
Case-cohort studies	Good for studying rare effects with high power	As for cohort and case-control studies; complex calculations
Population statistics	Large numbers can be studied	Difficult to coordinate; quality of information may be poor; too coarse
Record linkage	Excellent if comprehensive	Time-consuming; expensive; retrospective; relies on accurate records
Meta-analysis	Uses data that have already been obtained	Need to obtain unpublished data; heterogeneity of different studies.



## **SPONTANEOUS REPORTING**

This is a system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

Principle: A health worker observes an undesirable medical event and connects it with drug exposure (SUSPICION). He then reports his suspicion to an information collection centre.

The aim of spontaneous reporting is to identify possible adverse drug effects and the subsets of population affected by the effects (e.g. age, sex, pregnancy etc)

### ***Advantages of spontaneous reporting schemes for ADEs***

- Inexpensive
- Covers all drugs
- Identifies immediate effects
- Identifies continuing effects

### ***Disadvantages***

- Requires suspicion
- Not all health workers will report
- Does not give estimates of rates

## **Drug safety monitoring systems**

Drug safety monitoring gained world-wide attention following the thalidomide incident in the 1960s. Thalidomide was a drug given to pregnant women to prevent “morning sickness”. The babies born to some of these women were badly deformed and it took a while before the link between the deformed babies and the drug was made. Once this link was established the drug was banned and regulatory authorities all over the world became aware of the fact that seemingly safe drugs could have potentially serious adverse effects. The WHO therefore called for closer monitoring of the adverse effects of all drugs.

“Thalidomide” disaster resulted in many countries establishing drug safety monitoring systems.

Systematic spontaneous reporting of possible drug adverse effects began with the ‘Yellow card system’ in the UK in 1964. Currently 54 countries around the world have similar systems.

## **Benefits of reporting ADEs**

1. Helps to identify rare ADEs
2. Prevents medicine tragedies
3. Exposure of counterfeit and substandard medicines when healthcare personnel are alert to unexpected and apparently inexplicable adverse reactions, or to lack of effect.
4. Leads to improvement of information in labeling
5. Contributes to the development of a database on ADEs that would serve as a useful and relevant educational source

### How voluntary reporting can prevent medicine tragedies

The following are examples of drugs that have been withdrawn as direct result of ADR reporting. This shows how spontaneous reporting has helped prevent development of drug morbidity and mortality:

Drug	Year of marketing	Year withdrawn	Reason for withdrawal
Bromfenac	1997	1998	Hepatotoxicity
Benoxaprofen	1982	1982	Liver necrosis
Encainide	1987	1991	Excessive mortality
Mibefradil	1997	1998	Multiple drug interaction
Terfenadine	1985	1998	Fatal cardiac arrhythmias
Cerivastatin	1997	2001	Rhabdomyolysis

These drugs were withdrawn in fairly short period following introduction to the market. This was due to existence of drug safety monitoring systems. Compare with drugs such as phenacetin which were only withdrawn after many years of use due lack of an effective drug safety monitoring system.

The success of spontaneous reporting in preventing medicine tragedies is dependent on cooperation of health workers

### How voluntary reporting on ADEs can influence labeling

1. Cyclophosphamide has been on the market for several years in many countries. In January 2001 there were some new reactions included in the labels: Stevens Johnson Syndrome and toxic epidermal necrolysis.
2. Losartan was marketed in the USA since 1995. Some of the new reactions that have been discovered after launch and included in the Physician Desk reference are: vasculitis, allergic purpura (including Henoch-Schoenlein purpura), anaphylactic shock and anaphylactoid reaction.
3. Levofloxacin was launched in the USA in 1997. In February 2000 the label torsade de pointes was included.

### WHY PHARMACOVIGILANCE IN ZAMBIA

1. There are differences among countries in ADE occurrence and other drug-related problems as result of differences in:
  - Disease pattern and prescribing practices
  - Treatment seeking behaviour
  - Genetics, diet, local customs etc.
  - Traditional medicines used

2. There is limited information on ADEs in Zambia
3. The National Drug Policy acknowledges irrational use as problem e.g. preference for injections, unsupervised use of medicines, unjustified use of antibiotics etc.
4. There is need to have a reporting facility in Zambia for counterfeits, substandard drugs, ADRs etc
5. Currently there is no source of independent Information for public or health workers
6. Local data more would be more relevant for evidence-based decisions by regulatory authorities
7. Drug safety monitoring is an important tool for detecting ADRs, substandard drugs etc.
8. Will help ensure patients obtain safe and efficacious products
9. Results of ADE monitoring have important educational value

## **REPORTING ADEs**

A **case report** in pharmacovigilance can be defined as: a notification relating to a patient with an adverse medical event (or laboratory test abnormality) suspected to be induced by a medicine

### **What events should be reported?**

- For “new” drugs - report all suspected reactions, including minor ones (products on the market less than five years are usually considered “new”)

drugs)

- For established or well-known drugs - report all serious or unexpected (unusual) suspected ADEs;
- Report if an increased frequency of a given reaction is observed;
- Report all suspected ADEs associated with drug-drug, drug-food or drug-food supplement interactions;
- Report ADEs in special fields of interest such as drug abuse and drug use in pregnancy and during lactation;
- Report when suspected ADEs are associated with drug withdrawals;
- Report ADEs occurring from overdose or medication error;
- Report when there is a lack of efficacy or when suspected product quality problems are observed.
- Report Any concerns about product presentation e.g. confusing labeling, packing
- Report counterfeit products
- Report reactions suspected of causing death, danger to life, admission to hospital, prolongation of hospitalization, birth defects.

#### **What product quality problems should be reported?**

- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labelling
- Expired batches

#### **Which medicines should be reported?**

- Allopathic medicines including over the counter drugs
- Diagnostic products and radio-contrast media
- Traditional/herbal medicines
- Biological products like vaccines and blood products

#### **When should an ADR be reported?**

Report as soon as possible

Reactions should be reported even if:

- You are not certain the product caused the adverse event
- You do not have all the details

#### **Who will report?**

- Health institutions- all levels
- All health professionals

- Members of the public
- Business houses – pharmacies
- Associations and interest groups (e.g. Diabetic Association of Zambia)

### **Why health workers are the best people to report**

- They have the right training to identify and correctly report adverse events
- Health professionals are in the best position to report suspected ADRs observed in their every day patient care, because they are the people who diagnose, prescribe, dispense and monitor the patients' response to the medicines
- Patients with ADEs are most likely see health workers for intervention
- Effectiveness of post-marketing surveillance programme depends on health workers' active participation.
- All healthcare providers should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication.
- You can reduce suffering and save thousands of patients' lives by doing just one thing: REPORT SUSPECTED ADVERSE DRUG REACTIONS including lack of effect.

### **Where to report**

- Direct to NPVU
- Through DHMT, Health facility or health professions (doctors, pharmacists etc)

### **How to report**

- Using the ADE report form, which could be forwarded to nearest health center
- By telephone or fax or e-mail. All verbal (including telephone) should be transcribed immediately onto ADE report form

### **The ADE report form**

Refer to the form in the Appendix

The main features on the ADE report form are:

1. Date of reporting
2. Patient characteristics: initials, sex, ID, NRC, date of birth, weight (in kilograms), height (in centimeters), pregnancy status and HIV status
3. Description of the problem
4. Outcome
5. Products given to the patient in the past 28 days (including drugs, vaccines and herbal treatments)

6. Reporter's details (Name, designation, contact address and telephone number). The reporter's details are considered confidential and are to be used only for data verification, completion of case report and case follow-up.

### **Characteristics of a Good Case Report**

- Adverse event(s) details
- Baseline patient characteristics
- Therapy details
- Time to onset of symptoms and signs
- Diagnosis of the event
- Clinical course of the event and outcomes
- Laboratory data
- Any other relevant information

### **Reporting Of Drug Dependence**

The cardinal features that indicate dependence and should be reported are:

1. Unexpected neuropsychiatric symptoms which are regarded as pleasurable by the patient, and particularly if their use is associated with objective changes in mood or behaviour.
2. The development of tolerance indicated either by reducing drug efficacy or tendency to increase dose
3. Withdrawal symptoms, even those that may appear only to be related to the presenting illness, particularly when apparently satisfactory clinical management has been utilized.

Strong suspicions of dependence should always be reported.

## **WHAT HAPPENS TO THE REPORT**

### **Verbal report (including telephone)**

- Verbal reports will immediately be transcribed onto the ADE Report Form.
- If at health centre, the report is forwarded to the District Pharmacovigilance Coordinator
- If from a private health practitioner (e.g. private clinic or pharmacy) the report can be forwarded to the District Pharmacovigilance Coordinator or sent directly to the National Pharmacovigilance Unit as convenient or preferable

**Health centre**

The health centre will ensure report has as much detail as is available

If some details unclear, seek and record clarification

Forward report to District Coordinator

**Provincial or District Coordinator:**

Ensure report has as much detail as is available

May carry out further investigations and record findings

May assist reporters to correctly complete ADE Report Forms

Forwards ADE Report Forms to Pharmacovigilance Centre

**National Pharmacovigilance Unit:**

1. Receives all reports
  2. Acknowledges receipt of all reports
  3. Carries out case causality assessment
  4. Decides on further investigations
  5. May refer report to Expert Review Panel
  6. May recommend regulatory action
  7. Advises reporter of action taken
  8. Adds report onto national database
- Liases with other pharmacovigilance systems

**CAUSALITY ASSESSMENT**

Causality assessment is the systematic review of data about an ADE to determine the likelihood of a causal association between the event and the medicine received:

- How close is the relationship between drug and event?
- Did the drug cause the event?

**From the report we derive:**

- Duration to onset of the event

- Reaction terms
- Severity and seriousness
- Results of dechallenge & rechallenge
- Outcome information

### **Requirements for causality assessment**

- Information available on the report
- Pharmacological knowledge
- Knowledge of previous reports received
- WHO database
- Knowledge of any literature reports

### **To assess causality**

- Causality assessment is assessment of the strength of the relationship between the drug and the event
- We can seldom say without any doubt that a specific drug caused a specific reaction
- We work with imperfect data and our conclusions are those of probability
- Many case reports are needed at national and international level to provide the means for determining real cause and effect
- Sometimes epidemiological studies are needed to confirm causality

### **Importance of case causality assessment**

Case causality assessment is an essential discipline. It ensures:

- Careful review of report details
- Standardised assessment
- An in-depth understanding of the data
- Standardised data for later evaluation
- The ability to sort reports by quality

### **Definitions**

Dechallenge: withdrawing the drug(s) and recording the outcome – improved or not improved

Rechallenge: giving one drug again under the same conditions as before and recording the outcome – recurrence or no recurrence

### **WHO causality categories**

#### **Certain**

A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

- Event with plausible time relationship



- No other explanation – disease or drugs
- Response to withdrawal plausible
- Event definitive – specific problem
- Rechallenge required

### **Probable/likely**

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

- Event with reasonable time relationship to drug intake
- No other explanation
- Response to withdrawal clinically reasonable
- No rechallenge

### **Possible**

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- Event with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal lacking or unclear

### **Unlikely**

A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanations.

- Event with duration to onset that makes a relationship improbable (but not impossible)
- Diseases or other drugs provide plausible explanations

### **Conditional/unclassified**

A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

- An adverse event has occurred, but there is insufficient data for adequate assessment, or
- Additional data is awaited or under examination

### **Unassessable/unclassified**

A report suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

## **The process of causality assessment**

### **Objective evaluation**

- Dates of use of drug(s)
- Date of onset of event
- Nature of event – (apply ADR term)
- Response to dechallenge
- Response to rechallenge
- Outcome

### **Subjective assessment**

Is a reaction plausible?

Consider:

- Indication for use
- Background or past disease
- Pharmacology
- Prior knowledge of similar reports with the suspect drug or related drugs

Discuss and consult

Make a decision on causality

Be prepared to revise your decision

## **CHAPTER 4: MALARIA**

### **MALARIA SITUATION ANALYSIS IN ZAMBIA**

The malaria situation analysis in Zambia acknowledges that malaria is the leading cause of mortality and morbidity, and the disease burden is worse in the biologically vulnerable: children under five years of age and pregnant women. In order to achieve this, a strategic framework was designed to highlight the activities that are to be implemented by the National Malaria Control Program (NMCP) in order to reach the global and regional roll back malaria goals:

The development of drug resistance in Zambia however, has had a major impact on the success of malaria control. The country has experienced treatment failures to chloroquine, which was once a first line drug, and now sulphadoxine/pyrimethamine (SP) had recorded treatment failures as high as 32.6% in certain parts of the country

by early 2003. After the documentation of Chloroquine resistance in 1983, OPD cases increased from 167 cases per thousand population to 428 cases per thousand population in 2003. The public health impact of drug resistance is an increase in the disease prevalence rates, under five mortality rates and a corresponding increase in case fatality rates. This was evidenced by an upward surge in all epidemiological indicators of the malaria disease.

Artemisinin Combination Therapy (ACT) has now been adopted as the first line treatment for malaria in Zambia. It is extremely important to ensure that what happened when Chloroquine was in use does not happen to ACTs, which are more expensive and currently the best treatment for malaria.

The use of combination therapy is expected to have a positive impact on malaria transmission by lowering the rates of gametocytaemia after treatment. Artemisinin derivatives are advocated for in antimalarial combination therapy because they quickly reduce the level of parasitaemia and hence the parasite pool from which resistant *P. falciparum* strains may arise.

## **RATIONALE FOR PHARMACOVIGILANCE OF ANTI-MALARIA DRUGS IN ZAMBIA**

- Malaria transmission in Zambia is high. Therefore there is high frequency of anti-malarial treatments with many people being exposed to anti-malaria drugs
- Zambia has adopted ACT. Since there are many patients who receive malaria treatment an opportunity is provided to assess the safety of ACTs when used on a wide scale.
- There is little experience with ACTs in Zambia outside clinical trials
- Presumptive treatment of fever as malaria in the informal sector is widespread in Zambia. Many cases of incorrect dosing, inappropriate treatment and drug interactions are therefore expected.
- Administration of anti-malarial drugs in patients with c-morbid illness such as HIV is a concern
- There is need for surveillance of drug resistance to anti-malaria drugs

## **TREATMENT FAILURE**

### **Classification of Therapeutic Response**

Three categories of therapeutic response, namely Early Treatment Failure (ETF), Late Treatment Failure (LTF) and Adequate Clinical and Parasitological Response (ACPR) can be used.

#### **1. Early Treatment Failure**

The response can be classified as Early Treatment Failure (ETF) if the patient develops any one of the following conditions during the first three days of follow-up:

- Development of danger signs or severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitaemia;

- Parasitaemia on Day 2 higher than Day 0 count irrespective of the axillary temperature
- Parasitaemia on Day 3 with axillary temperature  $\geq 37.5^{\circ}\text{C}$ .
- Parasitaemia on Day 3  $\geq 25\%$  of count on Day 0.

## **2. Late Treatment Failure**

The therapeutic response can be classified as Late Treatment Failure (LTF) if the patient develops one of the following conditions during the follow-up period from Day 4 to Day 28:

### Late Clinical Failure

- Development of danger signs or severe malaria after Day 3 in the presence of parasitaemia without previously meeting any of the criteria of Early Treatment Failure;
- Presence of parasitaemia and axillary temperature  $\geq 37.5^{\circ}\text{C}$  on any day from Day 4 to Day 28, without previously meeting any of the criteria of Early Treatment Failure.

### Late Parasitological Failure

- Presence of parasitaemia on Day 28 and axillary temperature  $< 37.5^{\circ}\text{C}$  without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure.

## **3. Adequate Clinical and Parasitological Response (ACPR)**

The response to treatment can be classified as Adequate Clinical and Parasitological Response (ACPR) if the patient showed:

Absence of parasitaemia on Day 28 irrespective of axillary temperature, without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure or Late Parasitological Failure.

## **Causes of malaria treatment failure**

Factors that contribute to malaria treatment failure include:

- Incorrect dosing
- Poor compliance
- Poor drug quality
- Drug interactions
- Poor or erratic absorption
- Misdiagnosis

These factors may contribute to the development and intensification of drug resistance through increasing the likelihood of exposure of parasites to suboptimal drug levels

## **Anti-Malarial Drug Resistance**

Anti-malarial drug resistance has been defined as the ability of a parasite strain to survive and/or multiply despite administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject. The drug in question must gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action.

The definition of resistance requires demonstration of malaria parasitaemia in a patient who has received an observed treatment dose of an anti-malarial drug and simultaneous demonstration of adequate blood and metabolite concentrations using established laboratory methods.

In general, resistance occurs through spontaneous mutations that confer reduced sensitivity to a given drug or class of drugs.

### **Reporting Malaria Treatment Failure**

- All suspected malaria treatment failure cases in people should be reported to the National Pharmacovigilance Unit (NPVU) of the Pharmaceutical Regulatory Authority (PRA) through a completed Adverse Drug Event (ADE) form discussed earlier.
- Following this form will be the anti-malarial drug resistance request form (refer to appendix) that must be completed by the requesting health facility. This form will have to be submitted together with the specimen to the reference laboratory for drug resistance testing.

## **CHAPTER 5: HUMAN IMMUNO-DEFICIENCY VIRUS**

### **RATIONALE FOR PHARMACOVIGILANCE FOR ARVs**

- ADRs to ARVs are common and troublesome. Patients need to continue the drugs despite the ADRs.
- HIV complications and ADRs affect multiple overlapping body systems
- There is need to treat the ADRs
- Treatment of HIV involves polypharmacy with drugs that have potential for drug interactions
- Patients with HIV often have co-morbid illnesses and are taking many other drugs besides ARVs, factors that increase susceptibility to ADRs.
- Rapid emergence of drug resistance especially with poor compliance

## ARV DRUG RESISTANCE

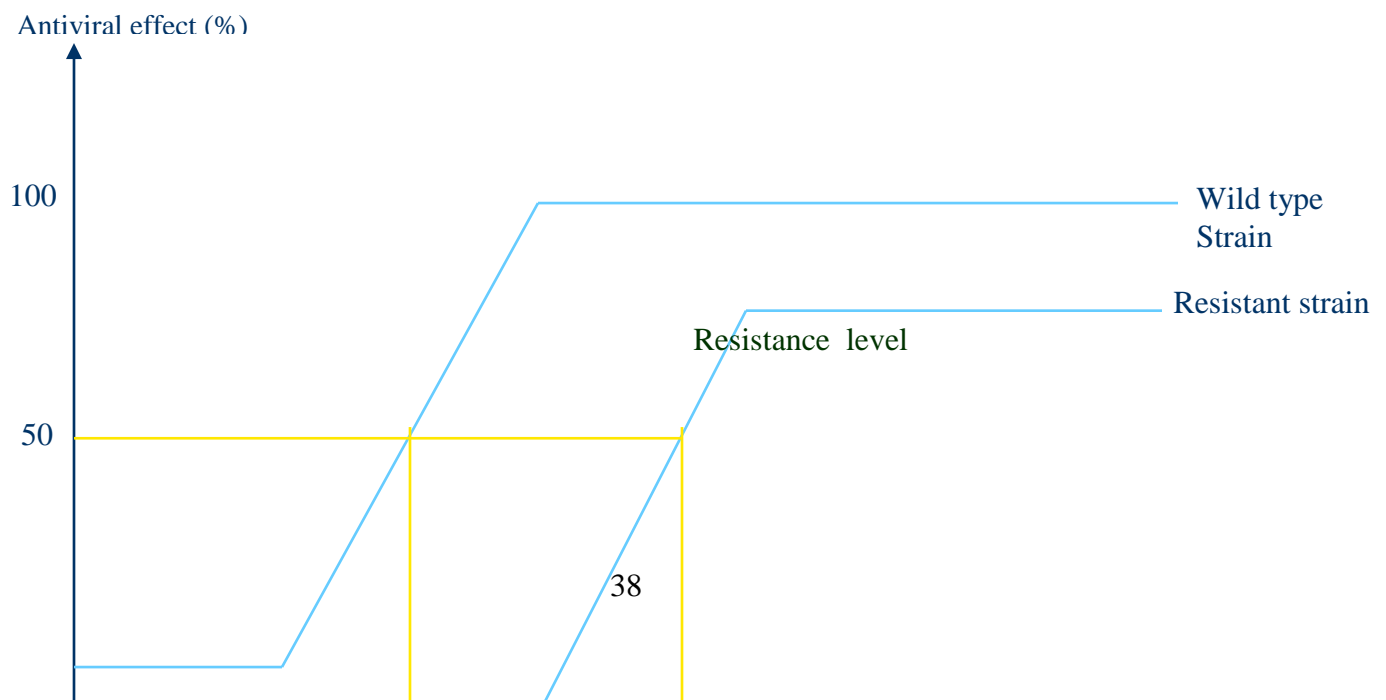
The life-cycle of HIV offers several targets for intervention using anti-retroviral drugs (ARVs). Anti-HIV agents in current use for the treatment of HIV-1 infected patients attack three distinct stages of HIV replication:

- **Reverse transcription:** which can be inhibited using nucleoside analogues or non-nucleoside compounds. These compounds are commonly known as reverse transcriptase inhibitors (RTIs)
- **Viral protein processing (part of the viral maturation process):** which can be inhibited using protease inhibitors (PIs)
- **Entry of virus into host cells:** which can be inhibited by fusion inhibitors (FIs)

Other drugs acting on alternative targets, such as integrase inhibitors, are being developed.

Therapy involving combinations of these different classes of anti-retrovirals (ARVs) greatly inhibit replication of the HIV-1, thus slowing disease progression. However, HIV-1 has a remarkable ability to mutate and thus evolve resistance to specific ARV agents. HIV drug resistance is defined as “**Decreased susceptibility of HIV-1 to a drug**” (Fig. 1). When resistance emerges, an anti-HIV drug that was once effective becomes less able to fight the virus. That drug will need to be switched to a more expensive and possibly more difficult to administer second-line alternative. The consequences of HIV drug resistance are many and include:

- Treatment failure
- Poor patient compliance due to new complicated regimens
- Increased direct and indirect health costs
- Transmission of resistant HIV strains to treatment-naive subjects
- The need to develop new anti-HIV drugs



0

Drug concentration

$IC_{50}$

$IC_{50}$

Resistant strain

*Figure 1. Phenotyping assay used to determine the susceptibility of a virus to drug(s) in a virus culture assay.  $IC_{50}$  means the concentration of the drug needed to inhibit virus growth in vitro by 50%. X-fold rise or fold changes of drug is calculated by dividing the  $IC_{50}$  from the patient virus isolate by the  $IC_{50}$  from a sensitive laboratory virus strain.*

## **TREATMENT FAILURE**

This is a situation where the current antiretrovirals used by a patient are no longer effective. Effectiveness is described in three ways as defined by the Department of Health and Human Services (U.S) guidelines, namely, Virologic, Immunologic or Clinical.

### **Virologic failure**

- Viral Load of more than 400 copies per milliter at 24 weeks of ART.
- Viral Load of more than 50 copies per milliter at 48 weeks of ART.
- Viral Load rebound to more than 400 copies per milliter after viral suppression.

### **Immunologic failure**

Failure of CD4 count to increase by more than 25 to 50 per cubic millimeter at 4 months after initial of HAART regimen or failure of an additional increase of 50 to 100 cells per cubic millimeter per year in chronic therapy.

### **Clinical Failure**

Occurrence or recurrence of an HIV-related event at or after three months of therapy.

### **Causes of treatment failure include:**

- Infected with a resistant virus.
- Failure by the drugs to reach the virus due to inadequate adherence, altered metabolism or rapid clearance, poor absorption, drug interaction, noncompliance with food requirements, limited potency of drug(s), etc.

## **Diagnosis of Treatment Failure**

This is achieved through

1. Monitoring of CD4 counts (Immunological) and viral load (virological) in the laboratory
2. Clinical appearance of the patient, i.e. Appearance of HIV stage III disease symptoms.

## **Management of Treatment Failure**

ART is for life once commenced. It is important that laboratory markers and the clinical picture of a patient on ART are monitored. Evolution of resistant HIV in the body leads to treatment failure. Continuing to take ARVs in the presence of resistant viruses is not beneficial because the patient will be exposed to toxic drugs and spend money on ineffective drug(s).

Surveillance and monitoring of drug resistance is an important part of expanded access to HIV treatment, by contributing to the evaluation of the efficacy of regimens and programmes, and providing important public health information. Zambia needs to establish systems, which will provide HIV drug resistance information:

- To support better patient management
- To assist public health bodies in targeting education and prevention programmes to address increasing rates or high prevalence of drug resistance
- To support rational use of antiretroviral drugs by treatment programme planners and individual clinicians
- To support the development and revision of treatment guidelines
- To provide a resource for addressing important questions on HIV drug resistance patterns and spread related to HIV genetic diversity.

Health workers are expected to participate effectively in implementing and sustaining this programme.

## **Reporting Treatment Failure Cases**

All suspected treatment failure cases in people on ART should be reported to the National Pharmacovigilance Unit (NPVU) of the Pharmaceutical Regulatory Authority (PRA) through a completed Adverse Drug Event (ADE) form discussed earlier. Following this form will be the HIV drug resistance request form (refer to appendix) that must be completed by the requesting ART center. This form will have to be submitted together with the specimen to the reference laboratory for drug resistance testing.



## **CHAPTER 6: TUBERCULOSIS**

### **ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE**

#### **DEFINITIONS**

**Natural resistance:** Resistance found in wild strains as a result of continuous multiplication, which does not constitute a significant population.

**Acquired resistance:** Resistance that occurs as a result of deficient therapy, i.e. genuine or masked monotherapy. Exposure to single drug suppresses the growth of bacilli susceptible to that drug but permits the multiplication of pre-existing drug-resistant organisms.

**Primary resistance:** When the drug-resistant tubercle bacilli are transmitted to other persons may lead to disease that is drug resistance from the onset.

**Multi-drug resistance:** This is resistance to both isoniazid and rifampicin, with or without resistance to other agents.

**Treatment failure:** Patients who begin treatment for smear-positive pulmonary TB and who remain smear positive, or become smear positive again, at 5 months or later during the course of treatment are considered to have treatment failure.

## **CAUSES OF TREATMENT FAILURE TO ATT/ANTI-TUBERCULOSIS DRUG RESISTANCE**

Drug Resistance Tuberculosis (DR-TB) has microbial, clinical and programmatic causes, but essentially it is a man-made phenomenon. Microbiologically, resistance is caused by a genetic mutation that causes a drug to be ineffective the mutant bacilli. The emergence of drug-resistant M.Tuberculosis has been associated with the following factors:

### **A. Health Care Providers: Inadequate regimens**

- Inadequate guidelines
- Non compliance with guidelines
- Absence of guidelines
- Poor training
- No monitoring of treatment
- Poorly organized or funded TB Control Programs

### **B. Drug: Inadequate supply/quality**

- Poor quality
- Stock-outs or delivery disruptions
- Poor storage conditions
- Wrong dose or combination

### **C. Patients: Inadequate drug intake**

- Poor adherence or poor DOT
- Lack of information
- Lack of transportation
- Side effects
- Social barriers
- Malabsorption
- Substance abuse disorders

## **DIAGNOSIS OF ATT TREATMENT FAILURE**

### **Microscopy**

Use in drug resistance is limited:

- Cannot distinguish viable from non-viable bacilli. Even with adequate treatment, specimens from MDR-TB patients may remain smear positive after they become culture-negative, suggesting that bacilli are non-viable.
- Cannot distinguish between drug-susceptible and drug-resistant.

### **Culture**

Quality of laboratory processing is of vital importance. Culture yields can be adversely affected by harsh or insufficient decontamination, poor quality culture media and incorrect incubation temperature. Laboratory errors such as mislabeling as well as cross-contamination during aerosol-producing procedures may lead to false-negative or false-positive results.

### **Identification**

Preliminary identification of the strains is based on acid-fastness and cord formation. Definitive identification will be based on at least the niacin production test, the nitrate reduction test, and thiophene carboxylic acid hydrazine (TCH) resistance test. Only cultures identified as *M. tuberculosis* are tested for susceptibility. MOTT or NTM are not tested for susceptibility. Para-nitro benzoic acid (PNBA) is also used for identification of *Mycobacterium tuberculosis*. *M. tuberculosis* does not grow on PNBA.

### **Susceptibility Testing**

Drug susceptibility testing (DST) plays a key role in assessing drug resistance. Resistance to isoniazid and rifampicin is referred to as multi-drug resistance. There are a number of different techniques for DST, all essentially comparing growth of the mycobacterium to a control. The following are some of the common DST techniques:

- Proportion method
- Absolute concentration
- Resistance ratio
- Broth or liquid methods
- Detection of metabolic changes
- Mycobacteriophage-based
- Molecular

### **MAGNITUDE OF THE PROBLEM OF ATT DRUG RESISTANCE**

Surveys by WHO/IUATLD Global Project on Anti-tuberculosis Drug resistance Surveillance have shown that drug resistant TB, including MDR-TB is found in all regions of the world and is increasing.

The WHO/IUATLD 2002 report showed a median prevalence to at least one ATT drug among new cases to be 10.2%. The median prevalence of MDR was 1.1%. The median prevalences of resistance to specific drugs were as follows: streptomycin – 6.3%, isoniazid – 5.9%, rifampicin – 1.4% and ethambutol – 0.8%. The prevalence of MDR-TB was highest in the former Soviet Union countries. High prevalences were also found in China, Ecuador and Israel. Europe and Africa reported the lowest median levels of drug resistance.

Among previously treated cases, the median prevalence to at least one drug was 18.4% and 7.0% for MDR. Median prevalences to specific drugs were as follows: isoniazid – 14.4%, streptomycin – 11.4%, rifampicin – 8.7% and ethambutol – 3.5%.

A nationwide survey conducted in South Africa in 2001 and 2002 indicated moderate levels of MDR-TB ranging from 0.9% to 2.6% among new cases. The prevalence of MDR in Mozambique in its 1998 – 1998 survey was 3.5%.

## **DRUG RESISTANCE SURVEILLANCE**

One of the aims of ensuring effective management of TB is to minimize the development of drug resistance. To avoid emergence of ATT drug resistance, there is need for a properly organized system that ensures prompt diagnosis and effective treatment within a well implemented TB control strategy.

The use of drug sensitivity tests for monitoring and guiding TB treatment programmes has been recommended. Continuous drug resistance surveillance, culture and drug susceptibility testing are important for a successful TB control programme. It is fundamental to have laboratory services that would offer high quality sputum smear microscopy, culture and drug susceptibility testing.

Surveillance of ATT drug resistance serves as an important tool for monitoring the effectiveness of TB control programs and improving national and global TB control efforts.

A successful drug resistance surveillance programme depends on the cooperation of health workers. All cases of suspected treatment failure should be reported and investigated thoroughly.

## **REPORTING ATT TREATMENT FAILURE CASES**

All cases of suspected treatment failure should be reported to the National Pharmacovigilance Unit using the ADE reporting form as discussed earlier. Sputum samples should be submitted to a TB reference laboratory for culture and drug sensitivity testing. Submission of sputum samples should be accompanied by the ATT drug resistance request form (refer to appendix).

### **ATT Drug Resistance Request Form**

The main object of the request form is to identify the patient as a new case or previously treated for TB. The form should have the following information:

- Patient identification; name and TB or hospital number
- Requesting unit

- Age and sex
- Type of specimen
- Date collected
- Patient history
- Documented data on previous treatment episodes
- Final decision on history of previous treatment.

### **SPECIMEN COLLECTION AND TRANSPORTATION**

A good sample is a prerequisite for TB diagnosis. Reliable accurate laboratory results require good sample collection & transportation

This requires team work: Laboratory staff, Clinicians, Nursing staff and Patients

- Patients should be given clear instructions to produce good sputum specimen and not saliva.
- An essential pre requisite for safe collection of satisfactory specimens is a robust leak proof and clean container.
- Containers must be rigid to avoid crushing in transit and must have a water-tight, wide-mouthed, screw top to prevent leakage and contamination. The containers should be packed in material that will absorb any leakage caused by accidents.
- Before transportation, specimens should be kept in the fridge at 4<sup>0</sup> C.
- Containers should be free from paraffin and other waxes or oils. These may appear as acid-fast artifacts or may react with other bacteria and cause them to appear to be acid fast.
- For homogenisation of the mucus and organic debris and for decontamination on transit, an amount of 0.6% cetylpyridinium bromide (CPB) or 1% cetylpyridinium chloride (CPC), equal to the volume of sputum, is added if it is likely that the samples may be exposed to room temperature for more than 48hrs between collection and processing in culture laboratory.

## **CHAPTER 7: VACCINES**

### **ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)**

The goal of immunization is to protect the individual and the public from vaccine-preventable diseases. Although modern vaccines are safe, no vaccine is entirely without risks. Most vaccine-induced reactions are mild and temporary. In rare instances, reactions following immunizations can result in serious illnesses.

The association of an adverse event with specific vaccine is suggested if there is an unusual clustering of medical incidents in vaccines in a limited time interval following immunization, or if vaccines experience the event at a rate significantly higher than that in a similar age group who were not recently immunized.

Most AEFIs are mild and transient; the most frequent being fever and local inflammation following DPT. "Serious AEFIs" are extremely rare and are defined as those events that result in death or hospitalization. A "mild AEFI" is defined simply as one that is not serious. Serious AEFIs occur at rates that are a small fraction of the rate of complications caused by the diseases themselves.

Adverse reactions following immunization can undermine an immunization programme by causing parent and the community to lose confidence in the benefits of immunization. Therefore, it is important that immunization programmes monitor serious adverse events following immunization and that appropriate actions are taken to correct any programmatic errors.

## Known Adverse Events Associated with EPI Vaccines

Vaccine	Contraindication	Complication	Rate of Complication
BCG	Symptomatic HIV infection	Disseminated BCG infection BCG osteitis  Suppurative adenitis	< 0.1/100,000 vaccines < 0.1 - 30/100,000 vaccines 100 - 4300/100,000 vaccines
DPT (with whole cell pertussis components)	Evolving neurologic disease or history of serious reaction following previous dose of DPT is a contraindication for pertussis immunization. The pertussis component should be omitted and diphtheria and tetanus immunization completed.	Chronic neurologic damage  Death  Acute encephalopathy  Convulsions  Shock/Anaphylaxis	0.2 - 0.6/100,000 doses administered 0.2 - 0.3/100,000 doses administered 0.1 - 3.0/100,000 doses administered 0.3 - 90.0/100,000 doses administered 0.5 - 3.0/100,000 doses administered
Hepatitis B Recombinant Plasma derived		Anaphylaxis  Guillain-Barre syndrome	1/900000 vaccine doses  0.5/100000 vaccinees
Measles		Encephalopathy (including subacute sclerosing panencephalitis)  Anaphylaxis	0.5-1.0/1,000,000 vaccines  No reliable data
Oral polio Vaccine (OPV)		Vaccine associated paralytic poliomyelitis	1 case/3.3 million doses distributed or administered. 1 case/700,000 first doses distributed 1 case/6.9 million subsequent doses distributed.
Tetanus toxoid		Brachial neuritis	0.5-1 case/100,000 vaccinees.

### CAUSES OF AEFI

1. **Programmatic errors** (i.e. errors in handling and reconstitution of vaccines) are the most frequent causes of AEFI. They include
  - Too much vaccine given in a dose
  - Improper immunization site or route
  - Syringes and needles improperly sterilized
  - Vaccine reconstituted with incorrect diluent

- Wrong amount of diluent used
- Drug inadvertently substituted for vaccine or diluent
- Vaccine prepared incorrectly for the use, e.g. an adsorbed vaccine not been shaken properly before use
- Vaccine stored incorrectly
- Contraindications ignored, e.g. a child who experienced a severe reaction after a previous dose of DPT is immunized with the same vaccine.
- Reconstituted vaccine not thrown out at the end of an immunization session and used at a subsequent one.

## **2. Nature of the vaccine or individual response to the vaccine**

- Lymphadenitis following BCG administration, fever or febrile convulsions following measles or whole cell Pertussis immunization, and paralysis following administration of oral polio vaccine

## **3. Coincidence**

- Medical incidences that occur after immunization can be purely coincidental. There is no association between the immunization and the medical incident following the immunization.
- Sometimes illness appears to be more frequent following immunization, due to parental concern or more intense observation for illness following immunization.

## **4. Unknown cause**

- With continued research, unknown causes will hopefully be classified in one of the above three categories.

## **RESPONDING TO AEFI DURING ROUTINE IMMUNIZATION**

All providers of immunization services should monitor adverse events following immunization. Each adverse event should be investigated and efforts made to determine its cause. The detection of adverse events should be followed by appropriate treatment and communication with caretakers and health workers, and, if several people were affected, with the community. If the adverse event was determined to be caused by programmatic errors, operational problems must be solved through appropriate logistical support, training and supervision.

The detection of AEFI is the responsibility of the following:

- Health workers providing clinical treatment and / or immunization in both public private sectors
- Parents and caretakers who report AEFIs affecting their children
- Surveillance officers and researchers

There should be an index of suspicion when a child who received immunizations recently becomes ill and presents for treatment at the health facility.



**To detect AEFIs the following steps should be taken:**

1. Check the child health card to determine the immunization status of the child and whether the child received immunization recently.
2. Take the history of the illness from the time of onset to determine whether immunization could be linked to the illness.
3. Refer to the list of “trigger events” to determine if the illness falls within the list.

**WHO has identified five “trigger events”**

- BCG Lymphadenitis
- Any injection abscess following immunization
- Any death as a result of immunization
- Any hospitalization as a result of immunization
- Any untoward reaction believed to have been caused by immunization

4. Assess the situation to decide if the child is presenting with the “normal” mild side- effects of immunization or with a suspected AEFI.
5. If the illness is NOT an AEFI but the normal side-effects of immunization, proceed with treatment and explain to the caretaker what has happened and that the benefits of the immunization far outweigh the risks. Ensure that the child is up to date with all immunizations.

If the illness IS a suspected AEFI, report the case as described below.  
If you are unsure, consult your supervisor.

**Reporting AEFI**

- All suspected AEFI should be reported by the health worker to the district within 24 hours.
- The health worker who detected the case should gather all the relevant information that is available at this point, by completing the AEFI Case Investigation Form. This form can only be completed in full after the completion of the AEFI case investigation. A copy of the report should be sent to NVPU.
- Hospitalizations and deaths should be considered as “serious” and should be reported immediately.
- All the listed “trigger events” should be reported for any vaccine administered.

**Role of the laboratory in the analysis**

The most important role of laboratories is to diagnose or to confirm a diagnosis of a medical event. Laboratory testing of vaccine is of limited value. The vaccine used on the day of immunization should not be available for testing, as good practice requires that all measles vaccine be thrown out at the end of the

session. Testing of vaccine from the same lot may be used, but the value of the findings will be weakened. Testing of vaccine is done for the following reasons:

- In the case of an injection site abscess, vaccine must be tested to determine the sterility of the vaccine.
- In the case of a long-lasting local reaction, a test must be performed to measure the amount of aluminum in the vaccine.
- In the case of a suspected cluster of AEFI to measles vaccine, a test must be performed to identify the diluent.

Vaccines sent to the laboratory for testing must be accompanied by a copy of the case investigation report and clear instructions what the vaccine should be tested for. No vaccine should be sent before the case investigation has been carried out.

### **Actions to take once a conclusion has been reached**

Feedback must be provided to all those involved in the investigation, but especially to the caretaker or other family members of the patient. If the AEFI was causing serious concern in the community or generating media interest, the outcome of the investigation should be communicated, as well as the actions taken.

### **AEFI CAUSALITY ASSESSMENT**

- Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the event & the vaccine(s) received
- It is a critical part of AEFI monitoring
- Whether an AEFI is or is not attributable to the vaccine or the vaccination program determines steps needed to be taken to address the event

### **Importance of AEFI Causality Assessment**

- Identification of urgent problems for investigation/action
- Identification of programmatic & batch problems
- Detection of signals for potential follow-up & research
- Basis for estimation of rates of serious AEFIs
- Comparison of AEFIs between vaccine products
- Validation of pre-licensure AEFI data

### **Quality of AEFI Causality Assessment**

Depends on:

- Quality of AEFI case report
- Quality of the causality review process

## **CHAPTER 8: HERBAL AND TRADITIONAL MEDICINES**

### **HERBAL AND TRADITIONAL MEDICINES**

The World Health Organization estimates that 65%-80% of the world's population use traditional medicine as their primary form of health care. Herbal medicine, in which plants (dried or in extract form) are used as therapeutic substances, is one of a number of practices encompassed by the term "complementary and alternative medicine" The use of herbal medicine is the dominant form of medical treatment in developing countries. However, the use of herbal medicine is expanding rapidly across the world and has been increasing in developed countries in recent years. Assessment of the safety and efficacy of these medicines is therefore an important issue for the health professions.

### **CLASSIFICATION OF ADRs ASSOCIATED WITH HERBAL PRODUCTS**

Adverse effects of herbal medications may be intrinsic or extrinsic (Box 1). The patient's age, genetic constitution, nutritional state, concomitant diseases and concurrent medication may affect the risk and severity of adverse events, as can consumption of large amounts or a wide variety of herbal preparations, or long-term use

#### **Intrinsic**

Intrinsic effects are those of the herb itself and are characterised, as for pharmaceuticals:

- Type A reactions: predictable reactions, overdose, interactions with pharmaceutical products
- Type B reactions: idiosyncratic reactions (allergy, anaphylaxis)

#### **Extrinsic**

Extrinsic effects are not related to the herb itself, but to a problem in commercial manufacture or extemporaneous compounding. They are due to failure of good manufacturing practice:

- Misidentification
- Lack of standardization
- Contamination
- Substitution
- Adulteration
- Incorrect preparation
- Inappropriate labeling and/or advertising

### **REPORTING OF ADRs ASSOCIATED WITH HERBAL PRODUCTS**

ADR reporting is as essential for herbal products as it is for pharmaceuticals in providing post marketing surveillance.

Reporting of ADEs associated with herbal products should be undertaken in the same way as for pharmaceuticals.

The reports should be made on the same ADE reporting forms that are used for all the other products.

**Practice points**

- Routinely include questions on use of herbal medication when taking a patient's drug history
- Keep in mind that patients may not consider "natural substances" in the same way as pharmaceuticals
- Question possible use of herbal medications with suspected adverse drug reactions, and include information on herbal medicines in ADE reports
- Always consider the possibility of long term use of herbal products as a cause of ADRs

## **CHAPTER 9: PHARMACOVIGILANCE SYSTEM IN ZAMBIA**

### **ORGANISATIONAL AND OPERATIONAL STRUCTURE**

[Refer to the appendix]

### **FUNCTIONS OF THE NATIONAL PHARMACOVIGILANCE UNIT**

The National Pharmacovigilance Unit based at Pharmaceutical Regulatory Authority shall:

1. Collection, collation, review and evaluation of all ADE reports received. NPVU shall maintain a database of ADEs.
2. Provision of feedback to reporters
3. Transmission of the assessed reports to the WHO international drug monitoring programme (UMC)
4. Identification and investigation of signals
5. Communication of relevant safety information to the national authorities, health professionals, pharmaceutical companies and other relevant stakeholders
6. Advice to healthcare professionals and consumers on drug safety issues
7. Education and training
8. Information sharing at regional and global levels. NPVU shall maintain contacts with international regulatory bodies working in pharmacovigilance and exchange information on drug safety.
9. Assess the regulatory information relating to safety in order to determine what action, if necessary, needs to be taken to improve safe use. Based on the available data, the advisory committee shall make recommendations on product label amendments, product withdrawals and suspension.

### **CONTACT PERSONS AND INSTITUTIONS**

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## **APPENDIX**

**Appendix 1: Organisational and Operational Structure of the Zambia  
Pharmacovigilance System**

**Appendix 2: The Adverse Drug or Vaccine Reaction/Event Report Form**