GOVERNMENT OF MALAWI
MINISTRY OF HEALTH

# GUIDELINES FOR NATIONAL PHARMACOVIGILANCE SYSTEM

DRAFT 2

SEPTEMBER 2009

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## INTRODUCTION

### Background Information

Malawi is a landlocked country in East Central Africa. It is bordered by Mozambique, Tanzania and Zambia. Health services in the country are provided by three main agencies: Ministry of Health 60%, Christian Health Association of Malawi 37%, Local Government 1% and other providers (private hospitals and clinics, commercial companies, the Army and the Police) account for the remaining 2%.

Apart from the above providers, there is also a large and active traditional health sector practicing traditional medication utilizing herbal medicines. The Herbalist Association of Malawi has a membership of approximately 75,000. Private shops also sell basic drugs such as the first line antimalarial drugs. The Pharmacy, Medicines and Poisons Board (PMPB) is charged with the responsibility of registration and quality control of all drugs. Using a 5 km radius as a yardstick, accessibility to health services by the populace is estimated at 54%.

Despite having good accessibility, there is lack of information on utilization of these services, thus low utilization a factor leading to self-medication. Some pharmaceuticals that used to be prescription only are now available over the counter, thus more accessible to the public. Though PMPB is vigilant especially at border posts on drug importation, with wide porous borders, counterfeit and sub-standard drugs find their way in the market. Public Health Programmes (Malaria, Tuberculosis, HIV/AIDS and EPI) administer registered medicines and vaccines. Some of the new medicines such as Artemisinin-based Combination Therapies (ACTs) and antiretroviral therapies (ARTs) do not have adequate safety data even at registration state. The extent of drug-to-drug interactions compounded with multiple disease patterns have not been well documented, thus the need to set up pharmacovigilance system in the country, to provide evidence on the safety of the medicines.

### Pharmacy Act

The Medicines Committee is mandated by the Pharmacy Act Section 56 (2007 Amendment) to: institutes drug registration with particular reference to the

evaluation of application dossiers and quality control assessment by looking at safety, quality and efficacy of drug samples; assess good manufacturing practice (GMP) reports from Inspectors after inspection of manufacturing plants; develop and review Drug Registration Guidelines for complimentary medicines such as herbal medicines; develop and review adverse drug reaction (ADR) reporting forms for pharmacovigilance program; develop concepts and strategies for the Drug and Poisons Information Centre; institute drug post marketing surveillance (PSM) systems; and develop, adopt and institute guidelines for product recall of medicinal products which are not safe, of low quality, not efficacious and a system for disposal of such products as well as expired drugs from various institutions.

Under the Pharmacy Act, the PMPB through the Medicines Committee shall take lead on setting up and managing the pharmacovigilance system in Malawi.

**Purpose of the Pharmacovigilance Guidelines**

These guidelines are intended for utilization by all health workers at both public and private health facilities. The guidelines shall be utilized for training health workers and as reference material for health workers from the health centre to the national level.

**Definition of Pharmacovigilance**

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

**The Goal of the National Pharmacovigilance System**

Pharmacovigilance system aims to assure the safety of medicines by ensuring reliable and timely exchange of information on drug safety issues. Pharmacovigilance is an arm of patient care which aims at making the best use of medicines for the treatment or prevention of disease. The ultimate goal of pharmacovigilance is the rational and safe use of medical drugs; assessment and communication of the risks and benefits of drugs on the market; and educating and informing of patients on safety of medicines.

**The Objectives of Pharmacovigilance**

The objectives of pharmacovigilance are to:

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;
- Improve public health and safety in relation to the use of medicines;
- Detect problems related to the use of medicines and communicate the findings in a timely manner;
- Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit;
- Encourage the safe, rational and more effective (including cost-effective) use of medicines;
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

**Pharmacovigilance Process**

The pharmacovigilance process comprises:

i. Monitoring medicines as used in everyday clinical practice and home settings to identify previously unrecognized adverse effects or indeed any changes in the patterns of their adverse effects,
ii. Assessing the risks and benefits of medicines in order to determine what action if any (such as product recall) is necessary to improve their safe use,
iii. Monitor the impact of any action taken.

**ESTABLISHMENT OF PHARMACOVIGILANCE SYSTEM**

The National Pharmacovigilance System shall comprise mainly of a National Pharmacovigilance Centre and Coordinator; Medicines Committee; District Investigation Team and Coordinator; Public Health Programmes; and Pharmacy, Medicines and Poisons Board. Other key stakeholders shall be Ministry of Health, relevant line ministries, manufacturers/suppliers and the media.

**National Pharmacovigilance Centre**

The National Pharmacovigilance Centre shall be based at the Pharmacy, Medicines and Poisons Board.

**Medicines Committee**

The Medicines Committee, one of the four committees mandated by the PMPB, shall act as the Expert Safety and Review Panel (ESRP). The committee shall provide expert review of pharmacovigilance system and make recommendations to the PMPB. The terms of reference for the committee are in annex 6.

**Public Health Programmes**

The Public Health Programmes, the consumers of the pharmacovigilance system reports shall support and strengthen the system. Malaria shall act as the precursor to start-off the setting up of the pharmacovigilance system. It is envisioned that the other programmes shall join soon. The Public Health Programmes shall follow up pharmacovigilance activities at the district level and report to the National Pharmacovigilance Coordinator. The roles and responsibilities of PHP are in annex 8.

**Pharmacy, Medicines and Poisons Board**

The Pharmacy, Medicines and Poisons Board shall host the National Pharmacovigilance Centre and the Coordinator; and provide the required logistics to set up office facilities. The PMPB shall review recommendations of the MC and advice on the action to be taken.

**Who Should Report Adverse Drug Reactions**

All health care professionals/workers, including doctors, dentists, pharmacists, nurses, and other health professionals are encouraged to report all suspected adverse drug reactions to medicines including vaccines, X-ray contrast media, medical devices, cosmetics, traditional and herbal remedies as applicable. The public shall also be encouraged to report ADRs.

**The Adverse Drug Reaction Report**

The information obtained from reports shall be collated, entered into the national adverse drug reaction database and analysed by Medicines Committee. The knowledge of the detected signals for new ADRs that were not known before will be used to promote safe use of medicines on a local, national and international level. It is therefore important to complete the form accurately because the information may offer the following benefits:

- Additional investigations into the use of the medication/vaccine/remedy in Malawi,
- Educational initiatives to improve the safe use of the medication,
- Appropriate package insert changes to include the potential for the reactions reported,
- Changes in the scheduling or manufacture of the medicine to make the medicine safer,
- Other regulatory and health promotion interventions as the situation may warrant including change in supply status or complete withdrawal of the medicine.

**Benefits of ADR Reports**

- Improvement on the quality of care offered to patients.
- Reduction of drug related problems leading to better treatment outcome.
- Improved patient confidence in professional practice and consequently professional growth.
- Improved patient compliance to the treatment.
- Access to feed back information on drug related problems reported within the country and internationally.
- Satisfaction for the fulfilment of a moral and professional obligation.

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

**Will Reporting Have Any Negative Consequences On The Health Worker Or The Patient?**

- The adverse drug reaction report shall not constitute an admission that the health worker or any other health professional or the drug contributed to or caused the reaction in any way. The health worker at the primary reporting level shall counsel the patient to counter any negative connotations that may lead to non-compliance.
- The outcome of the report, together with any important or relevant information relating to the reaction reported, will be communicated as appropriate.
- The details of the report will be stored in a confidential database and may be shared locally and international. Malawi as a Member Stat, being supported by WHO has an obligation to report ADRs.
- The names of the reporter and the patient will be deleted before any details about a specific adverse drug reaction are used or communicated to others.
- The information obtained from the report will not be used for commercial purposes. However, the information may be disclosed if it is in the interest of the general public.

The information is only meant to improve the understanding and use of the medicines in Malawi. ADR reports shall not be used in a court of law under any circumstances.

**The Success of the Pharmacovigilance System**

The effectiveness of a National Pharmacovigilance System is directly dependent on the active participation of all health professionals and the general public for information giving. Health professionals are in the best position to report suspected ADRs observed in their day-to-day patient care, because they diagnose, prescribe, dispense and monitor the patients' response to the medicines, medical products and vaccines.

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.

Health workers can reduce suffering and save patients' lives by doing just one thing: reporting suspected adverse drug reactions including lack of medicinal effect.

**How to Recognize ADRs**

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

7. Take a proper history and do a proper examination of the patient including:
    a. A full drug and medical history should be taken.
    b. Ensure that the medicine ordered is the medicine received and actually taken at the dose advised, by the patient.
8. Verify that the onset of the suspected ADR was after the drug was taken, not before and analyze carefully the observation made by the patient.
9. Determine the time interval between the beginning of drug treatment and the onset of the event.
    a. Did the ADR start immediately follow the drug administration?
    b. Some reactions occur immediately after the medicine has been given, while others take time to develop. The time from the start of therapy to the time of onset of the suspected reaction must be logical.
10. Evaluate the suspected ADR after discontinuing the drugs or reducing the dose and monitor the patient's status. If appropriate, restart the drug treatment and monitor recurrence of any adverse events.
11. Analyse the alternative causes (other than the drug administered) that could on their own have caused the reaction.
    a. Can this adverse reaction be explained by other causes e.g. patient's underlying disease, other drugs including over the counter medicines or traditional medicines; toxins or foods supplements?

6. Use relevant up-to-date literature and personal experience as a health worker on drugs and their ADRs and verify if there are previous conclusive reports on this reaction. The National Pharmacovigilance and Drug Information Centres will be very important resources for obtaining information on ADRs. The manufacturer of the drug can also be a resource to consult for information on the drug safety.

    a. Is the reaction known to occur with the particular drug as stated in the package insert or other references?
    b. If the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular medicine.

7. Report any suspected ADRs to the person nominated for ADR reporting in the hospital or directly to the National Pharmacovigilance Centre

**Causality Classification**

In order to assess the likelihood that the suspected adverse reaction is actually due to the medicine, WHO has provided a list of causality assessment criteria for deciding on the contribution of the medicine towards the adverse event. The criteria are in annex 4.

In most cases there is some level of uncertainty as to whether the drug is directly responsible for the reaction. Many of the questions above may remain unanswered or may be contradictory; however this should not dissuade the health worker/reporter from reporting the reaction. A well documented report which includes information about all the above mentioned questions can provide the system with the first signal of a previously unknown problem.

**What Should Be Reported**

It is important to report all adverse drug reactions even if you do not have all the facts or are uncertain that the medicine is definitely responsible for causing the reaction. What is required is to report all suspected adverse drug reactions. In many cases it will be impossible for an individual health worker to prove that the reaction was indeed caused by a particular drug. However, collection of reports from several health workers in different parts of the country will assist in making decisions on the possibility of associations between drugs and particular adverse drug reactions.

For monitoring purposes, adverse drug reactions to be reported shall include all responses to medicines used in human which are harmful and unintended, including lack of efficacy, and which occurs at any dose including the normal, overdose, or abuse of medicines.

- For "new" drugs: report all suspected reactions, including minor ones;
- For established or well-known drugs: report all serious or unexpected/unusual ADRs;
- Report if an increased frequency of a given reaction is observed;
- Report all suspected ADRs associated with drug-drug, drug-food or drug-food supplements interactions (including herbal and complimentary products);
- Report ADRs in special fields of interest such as drug abuse and drug use in pregnancy and during lactation;
- Report when suspected ADRs are associated with drug withdrawals;
- Report ADRs occurring from overdose or medication error;
- Report when there is a lack of efficacy or when suspected pharmaceutical defects are observed;
- Report reactions suspected of causing death, danger to life, admission to hospital, prolongation of hospitalization or birth defects.

**REPORT ALL SUSPECTED ADVERSE REACTIONS THAT YOU CONSIDER OF CLINICAL IMPORTANCE IMMEDIATELY!**

**Product Quality Problems Should Be Reported**

Report product quality problems such as:

- Suspected contamination.
- Questionable stability e.g. changes in "normal" colouring.
- Poor packaging or labelling.
- Therapeutic failures.
- Expired batches.

## Prevention of ADRs

Some ADRs are unavoidable and cannot be prevented. However, most ADRs can be prevented by following the basic principles of rational use of medicines that are described as follows:

## Guidelines for Prevention of ADRs

1. ***Use only appropriate medicines.***
2. ***Use medicines according to the standard treatment guidelines.***
3. ***Use text books and other reference materials providing information on drug reactions and interactions.***
4. ***Take extra care when you prescribe drugs known to exhibit a large variety of interactions and adverse reactions (anticoagulants, hypoglycaemics, and centrally acting drugs) with careful monitoring of patients with such reactions.***
5. ***Beware of the interaction of drugs with certain foods, alcohol and household chemicals.***
6. ***Review regularly the entire drugs used by patients, taking special notice of those bought without prescription. (over the counter, herbal preparations).***
7. ***Be particularly careful when prescribing for children, the elderly, the pregnant and nursing women, and the seriously ill patients especially with hepatic and renal diseases. Careful ongoing monitoring is essential in these patients.***
8. ***If patients show signs or symptoms not clearly explained by the course of their illness, think of adverse drug reaction.***
9. ***If you suspect an adverse reaction, consider stopping the drug or reducing the dosage as soon as possible and notify the adverse drug reaction to the National Pharmacovigilance Centre or the nearest hospital.***
10. ***Advice patients to obtain medications only from approved sources.***

## Some Basic Principles of Efficient Reporting

(a) **Timeliness of Reporting.**

- The ADR should be reported soon after it occurs. A recent ADR is easier to report upon (less work is involved) and the report is more likely to be accurate. The completed report should be sent to the National Pharmacovigilance Centre immediately, preferably within one week.
- If possible, the decision to report whilst the patient is still with the health worker should be taken, so that s/he can easily be questioned about the ADR and all the details filled on the reporting form at once.

**(b) Integrity/Reliability of Suspect Judgment**

- If any supplementary data is obtain later, e.g. if the same patient develops the reaction again, or if something happens which increases your suspicion or seems to exclude the reaction, please send in a supplementary note immediately.

**(c) Completeness/Eligibility of Report**

- Only reports with some minimal standards of adequacy of information should be submitted. Four (4) pieces of information constitute this minimum. They are:

    (a) An identifiable source of information.
    (b) An identifiable patient.
    (c) An identifiable drug.
    (d) An identifiable suspected reaction.

If any of these essential elements is missing, then such a report is unreliable and may not be useful. Reports of an alleged adverse drug reaction without any other details concerning the patient or the drug(s) should not be sent. Please write legibly.

**HOW THE INFORMATION WILL FLOW**

Both spontaneous and active reporting shall be encouraged as appropriate. Though it is cheaper to institute spontaneous reporting, the yield is normally low. Every effort will be made to motivate health workers to report ADRs.

**Spontaneous Reporting**

The definition of spontaneous reporting is a system whereby case reports of adverse drug reactions are voluntarily submitted by health professionals and pharmaceutical companies to the National Pharmacovigilance Centre.

***Public health care system***

The patients/public shall be encouraged to report ADRs to the nearest health centre or hospital. From the health centres the completed ADR forms will be submitted within one week to the District Health Officer (DHO). The DHO who will be a member of the District Investigation Team may delegate this responsibility to the District Pharmacist (DP).

The District Pharmacist, a member of the DIT, will compile the district reports and submit monthly reports to the National Pharmacovigilance Coordinator.

The National Pharmacovigilance Coordinator, the secretary of the Medicines Committee, will update the ADR database and analyze the data for possible signals. Initially a locally developed database will be utilized, which shall be changed to WHO "Vigiflow". The National PV Coordinator will submit the national PV report quarterly to the Medicines Committee for review. When the requirements for registration by the WHO Collaborating Centre for International Drug Monitoring (*the* Uppsala Drug Monitoring Centre, Sweden) shall be met, the National Pharmacovigilance Coordinator shall initiate/pursue the registration process with UMC.

The Medicines Committee shall review the national PV reports and make recommendations to the Pharmacy, Medicines and Poisons Board.

The PMPB will take appropriate decisions and actions. These decisions will be communicated to the respective PHP, Medical Associations, UN Agencies (WHO and UNICEF), other partners, the public and Manufactures/Suppliers.

***Private sector***

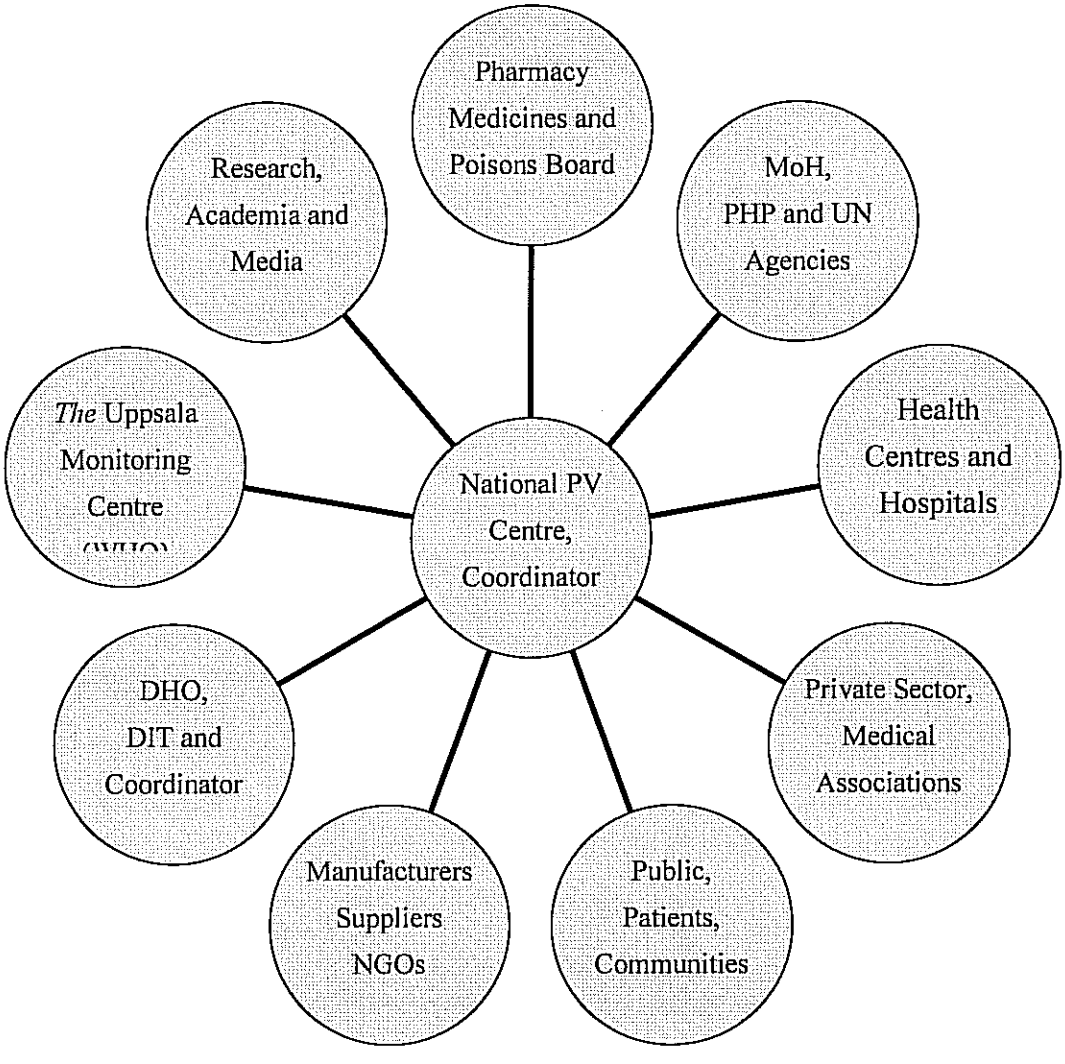
The private hospitals, clinics and NGOs will send completed ADR forms to the National Pharmacovigilance Coordinator or respective District Health Officer. These will then be treated as above.

**Active ADR reporting**

The PHP sentinel sites shall report ADRs to the National Pharmacovigilance Coordinator or the nearest DHO. From there the process will be as above.

Research and Academia/Learning Institutions shall report ADRs to the National Pharmacovigilance Coordinator or the nearest DHO. From there the process will be as above.

**Information Flow Chart**




**How to Report ADRs**

The reporter shall utilize the ADR reporting form. Reporting forms shall de distributed through the public health facilities by the Essential Drug programme (EDP) during their routine activities. Forms will also be sent to private clinics and hospitals; Pharmacies; and Drug Stores. Other institutions that may wish to receive reporting forms directly may indicate so.

A copy of a reporting form is enclosed in these guidelines. Completed ADR forms should be sent to:

The Registrar,
Pharmacy, Medicines and Poisons Board (PMPB),
Attention the Pharmacovigilance Coordinator,
Off Chilambula Road, Lilongwe Old Town,
PO Box 30241,
Lilongwe 3, MALAWI.

**REMEMBER!**
**The success of the pharmacovigilance system depends on accurate reporting and prompt delivery of the completed forms.**

**Pharmacovigilance Tools**

1. Pharmacovigilance guidelines
2. Adverse Drug Reaction Form
3. ADR Severity Assessment Chart
4. DIT Investigation Checklist
5. Causality Assessment Chart
6. Pharmacovigilance Glossary

## ANNEXES

### Annex 1: Adverse Drug Reaction Form

### Annex 2: ADR Severity Assessment

| Criteria | Severity |
|---|---|
| Mild | • ADR does not require change of drug.<br>• Drug should be withheld or discontinued or changed.<br>• No antidote is required |
| Moderate | • Suspected drug should be withheld or discontinued.<br>• Antidote should be administered.<br>• Admission to hospital required |
| Severe | • Intensive medical care required.<br>• Permanent damaged caused. |
| Fatal | • Directly or indirectly caused death. |

**Annex 3: DIT Investigation Checklist**

| CHECKLIST FOR INVESTIGATION PROCEDURE | |
|---|---|
| **Step** | **Actions** |
| **1) Confirm** information in the report | • Obtain patient's medical file (or other clinical records).<br>• Check details about patient and event from medical file and document information.<br>• Obtain any details missing from SAE Report Form.<br>• Identify any other cases that need to be included in the investigation. |
| **2) Investigate** and collect data:<br>About the **patient:** | • History of drug use (including over the counter and traditional medicine).<br>• Medical history, including prior history of similar reactions or allergies.<br>• Family history of similar events. |
| About the **event:** | • History, clinical examination, relevant laboratory results about the SAE<br>• Diagnosis of the event.<br>• Treatment, whether hospitalized, and outcome. |
| About the **suspected drug(s):** | • Conditions of storage at facility and expiry date. |
| About **other people:** | • Whether others received the same drug and developed illness (assess health facility ledgers).<br>• Whether others had similar illness (may need case definition); if so exposure of cases to suspect drug(s).<br>• Investigate the local health facility. |
| **3) Assess** the **service** by:<br>**asking** about: | • Drug storage and prescription.<br>• Details of training in diagnosis and treatment.<br>• Number of therapies greater than normal. |
| **4) Formulate** a working hypothesis: | • On the likely/possible cause(s) of the event. |
| **5) Test** working hypothesis | • Does case distribution match working hypothesis?<br>• Occasionally, laboratory tests may help. |
| **6) Conclude** investigation | • Assess causal association to suspected drug/s.<br>• Complete SAE Investigation Form.<br>• Take corrective action, and recommend further action. |

| | |
|---|---|
| **7) Assess outcome of actions/lack of actions taken** | • Assess impact of any corrective action taken (where appropriate. |

## Annex 4: Causality Assessment

### Causality Categories

| Causality Term | Category |
|---|---|
| Certain | • Specific clinical and laboratory phenomenon.<br>• Time elapsed between administration of the drug and occurrence of the event plausible.<br>• Cannot be explained by concomitant disease or any other drug or chemical.<br>• Response to withdrawal of the drug clinically plausible.<br>• Recurrence following re-challenge with same drug alone. |
| Probable/ Likely | • Specific clinical and laboratory phenomenon.<br>• Time elapsed between administration of the drug and occurrence of the event plausible.<br>• Cannot be explained by concomitant disease or any other drug or chemical.<br>• Response to withdrawal of the drug clinically plausible.<br>• Re-challenge did not occur or results unknown. |
| Possible | • Time elapsed between administration of the drug and occurrence of the event plausible.<br>• Unknown outcome of drug withdrawal.<br>• No information on the withdrawal of the drug.<br>• No information on presence or absence of other medicines. |
| Unlikely | • Time elapsed between administration of the drug and occurrence of the event not plausible.<br>• Withdrawal of drug made no difference. |
| Unclassifiable | • Inadequate data available.<br>• More data required for a proper assessment, or the additional data is under examination. |
| Unassessable | • Report suggesting an adverse reaction.<br>• Judgement not possible because information is insufficient or contradictory.<br>• Report cannot be supplemented or verified. |

**Note!**

In most cases there is some level of uncertainty as to whether the drug is directly responsible for the reaction. Many of the questions above may remain unanswered or may be contradictory; however this should not dissuade health workers from reporting the reaction. A well-documented report which includes information about all the above-mentioned questions can provide the first signal of a previously unknown problem.

## Annex 5: Pharmacovigilance Glossary

Glossary is the terms used in pharmacovigilance.

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

**Adverse (Drug) Reaction (ADR)**
A response 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. (WHO, 1972). An adverse drug reaction, contrary to an adverse event, is characterized by the suspicion of a causal relationship between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

**Biological products**
Medical products prepared from biological material of human, animal or microbiologic origin (such as blood products, vaccines, insulin).

**Causality assessment**
The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms.

**De-challenge**

The withdrawal of a drug from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.

***Drug*** or ***medicine*** is 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.

**Efficacy**

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

**Essential Medicines**

Essential medicines are those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.

**Generic (Multi-Source Product)**

The term 'generic product' has somewhat different meanings in different jurisdictions. Generic products may be marketed either under the non-proprietary approved name or under a new brand (proprietary) name. They are usually intended to be interchangeable with the innovator product, which is usually manufactured without a license from the innovator company and marketed after the expiry of patent or other exclusivity rights.

**Harm**

The nature and extent of actual damage that could be caused by a drug. This should not to be confused with risk.

**Herbal Medicine**

Includes herbs, herbal materials, herbal preparations and finished herbal products.

**Medical Error**

"An unintended act (either of omission or commission) or one that does not achieve its intended outcomes." Leape, Lucien.

**Member Countries**

Countries which comply with the criteria for, and have joined the WHO Programme for International Drug Monitoring.

**National Pharmacovigilance Centres**
Organisations recognised by governments to represent their country in the WHO Programme (usually the drug regulatory agency). A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety.

**Over The Counter (OTC)**
Medicines which are available for purchase without a prescription.

**Pharmaco-epidemiology**
Study of the use and effects of drugs in large populations.

**Pharmacology**
Study of the uses, effects and modes of action of drugs.

**Pharmacovigilance**
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

**Poly-pharmacy**
The concomitant use of more than one drug, sometimes prescribed by different practitioners.

**Post-marketing**
The stage when a drug is generally available on the market.

**Pre-marketing**
The stage before a drug is available for prescription or sale to the public.

**Prescription Only Medicine (POM)**
Medicinal product available to the public only on prescription.

**Prophylaxis**

Prevention or protection.

**Rational Drug Use**
An ideal of therapeutic practice in which drugs are prescribed and used in exact accordance with the best understanding of their appropriateness for the indication and the particular patient, and of their benefit, harm effectiveness and risk.

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

**Regulatory Authority**
The legal authority in any country with the responsibility of regulating all matters relating to drugs.

**Serious Adverse Event or Reaction**
A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Is life-threatening.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: The term "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.

**Side Effect**
Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug.

**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 a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.

**Spontaneous Reporting**
System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

**Vigibase**
The name for the WHO International ADR Database.

**Vigiflow**
VigiFlow (formerly called Vigibase Online) is a sophisticated case report management system created by the UMC, complying with GxP requirements.

**Vigisearch**
This is a custom search service offered by the UMC to third-party inquirers for which several types of standard presentation are available.

**Vigimed**
E-mail conferencing facility, exclusive to member countries of the WHO Programme for International Drug Monitoring.

## Annex 6: Terms of Reference for Medicines Committee

The Medicines Committee is mandated by the PMBP Pharmacy Act. The mandate that are relevant to pharmacovigilance are to:

1. Develop and review Adverse Drug Reaction (ADR) Reporting Forms for Pharmacovigilance system.
2. Institute Drug Post Marketing Surveillance systems.
3. Develop, adopt and institute guidelines for product recall of medicinal

products which are not safe, of low quality and not efficacious and a system for disposal of such products as well as expired drugs from various institutions.

The membership of the committee comprises:

- Community Pharmacist.
- Director of Central Medical Store (CMS) (A Pharmacist).
- Medical Practitioner (Paediatrician).
- Member from Medical Council of Malawi.
- An expert in Veterinary Medicine from Department of Animal Health.
- A nurse and midwife from Nurses & Midwives Council of Malawi.

It is recommended that for pharmacovigilance purposes, the following members shall be co-opted during the quarterly pharmacovigilance expert safety and reviews:

a) Obstetrician/Gynaecologist Specialist;
b) Physician;
c) PHP Manager (s);
d) Representative from School of Pharmacy;
e) College of Medicine;
f) Public Health Specialist;
g) Director of HTSS (Pharmaceuticals);
h) Consumer Association of Malawi
i) National Pharmacovigilance Coordinator.

The Terms of Reference (ToRs) above are compound and shall be broken down to the following activities:

a) Review reports referred by the National Pharmacovigilance Coordinator or PHP Managers;
b) Assess safety issues from reports of serious ADRs and cumulative data;
c) Assess safety issues that, although not serious, may affect adherence;
d) Assess reports that may suggest lack of efficacy and determine the likely cause;
e) Recommend further follow up and investigations when indicated;
f) Recommend appropriate action to the National Pharmacovigilance Coordinator, PHP Managers or PMPB.
g) Create awareness to the media and general public.

## Annex 7: Terms of Reference for National Pharmacovigilance Centre

The National Pharmacovigilance Centre (NPC) shall play a significant role in increasing public awareness of issues relevant to the safety of medicines. The medical practitioners and patients shall be provided with information about the benefits, harm and effectiveness of medicines. The NPC will also deal with real or contrived medicine scare crises.

On day-to-day basis the National Pharmacovigilance Centre shall be responsible for the following activities:

- Promoting increased public awareness of issues relevant to safety of medicines.
- Promoting the reporting of adverse reactions.
- Collecting case reports of adverse reactions.
- Clinically evaluating case reports.
- Collating, analyzing, and evaluating patterns of adverse reactions.
- Distinguishing signals of adverse reactions for "noise".
- Recommending or taking regulatory action in response to findings supported by good evidence.
- Initiating studies to investigate significant suspect reactions.
- Alerting prescribers, manufacturers and the public to new risks of adverse reactions.
- Sharing reports with WHO program for International Drug Monitoring.
- Supervising the work of the National Pharmacovigilance Coordinator
- Providing technical training and managerial support for all pharmacovigilance activities.

**Annex 8: Terms of Reference for National Pharmacovigilance Coordinator**

The National Pharmacovigilance Coordinator shall be a staff member of the PMPB. S/he shall function as the focal point for the National Pharmacovigilance System. Ideally this shall be a full-time position. The responsibilities of the National Pharmacovigilance Coordinator shall include:

a) Coordination, communication, integration, training and supervision of the Pharmacovigilance related activities of the District Investigation Teams.
b) Serve as member and secretary of the Medicines Committee.

c) Responsible for developing the pharmacovigilance system.
d) Responsible for the collection and storage of all reports of adverse reactions.
e) Responsible for coordination and communication between the National Pharmacovigilance Centre, the District Investigation Teams, the PMPB, the PHP, the Ministry of Health, international PV centres, and the pharmaceutical manufacturers or suppliers.
f) Ensure harmonization of pharmacovigilance in public health with other national pharmacovigilance activities,
g) Promote the reporting form, and develop a national database for signal generation.

The coordinator shall have the necessary facilities for carrying out his or her duties. S/he shall ensure that the ADR reports are processed appropriately for assessment by the Medicines Committee.

**Annex 9: Terms of Reference for DIT**

The District Health Officer as the head of the District Health Management Team shall constitute the District Investigation Team and call the DIT meetings on monthly basis. The District Pharmacist shall be the DIT Coordinator and secretariat. The membership of the DIT shall comprise:

a) District Health Officer,
b) District Nursing Officer,
c) District Vetenery Officer,
d) District Environmental Health Officer,
e) Representative of the Christian Health Association of Malawi,
f) District Pharmacist,
g) PHP specific Coordinator.

The terms of reference of the DIT shall be:

1) Review all district ADR reports.
2) Decide which reports need further investigation on the basis of:
   a) Integration of pharmacovigilance into Public Health Programmes;
   b) Seriousness (including all deaths);
   c) Severity; exposure to medicine during pregnancy;
   d) Apparent signals of new reactions;
   e) Patterns of suspected reactions which although not serious, may affect adherence and the success of the programme.

3) Submit all ADR reports to the National Pharmacovigilance Coordinator for processing and review by the Medicines Committee on monthly basis.
4) Create awareness to the media and general public on drug safety.

## Annex 10: Terms of Reference for DIT Coordinator

The DIT Coordinator shall:

1. Coordinate the investigations.
2. Develop and submit ADR reports to the National Pharmacovigilance Coordinator on monthly basis.
3. In case of serious event s/he shall communicate the information to the National Pharmacovigilance Coordinator immediately.
4. Contribute to the education of health workers and the public on medicine safety.
5. Communicate the findings of investigations and conclusions of the Medicines Committee, in terms of causality and actions to be taken, to the reporter and patients.

## Annex 11: Roles and Responsibilities of Key Stakeholders

It is the responsibility of **everyone** to report ADRs.

### Patient/Public

Improving the awareness of the public on possible ADRs shall be conducted on regular basis, so that they develop a culture of reporting reactions to the health workers at the various levels of health delivery system. An essential IEC/BCC package for pharmacovigilance system strengthening shall be produced and disseminated.

### Traditional Health Practitioners

Although Traditional Health Practitioners (THPs) are outside the formal health sectors, may not necessarily be literate, and may have reservations about referring patients to health facilities, they have significant contacts with seriously ill patients. It is recommended that all efforts be made to promote awareness of THPs through local channels of communication. It is envisaged that good communication could enable traditional healers to encourage patients visiting them with suspected ADRs to return to the public health facilities.

### Health Centre Level

Health workers from public health centre level and outpatient departments of various hospitals both public and private shall be expected to detect, investigate, manage and

report ADRs. Before scaling up pharmacovigilance, all health workers at these levels shall be trained on detection and reporting of ADRs.

a) As part of good clinical practice, health workers will educate and counsel patients about ADR, to improve patient confidence and promote adherence.
b) Methods need to be developed to encourage health workers to persuade patients to return to their clinics, complete ADR report forms routinely.
c) Incentives may need to be devised which motivate participation, until it will become well established and recognised to be a routine duty and part of good clinical practice.

- If ADR is suspected, the health workers should complete ADR form,
- Completed ADR Forms should be forwarded to the DIT Coordinator immediately, to prevent any delay with the follow up investigation.
- The health worker should immediately refer patients with life-threatening illnesses to the nearest hospital. The referral note should mention that ADR is suspected and the completed ADR form should be sent with the patient.
- Ideally the ADR form will be filled in duplicate so that one copy can be kept in the patient's hospital records and the other submitted to the DIT.

**District Investigation Team**

District Investigation Team (DIT) shall play a major role in monitoring adverse reactions and training the health workers in their respective districts.

1. The DIT shall ensure adequate supply and distribution of ADR forms, e.g. through the Essential Drug Program's (EDP) regular drug supply.
2. Play an important role in the collaboration and encouragement of reporting by hospital staff.
3. At the hospital level, the health workers shall notify the Hospital Pharmacist or the DIT Coordinator on ADRs.
4. The clinician in-charge of the patient may complete the initial ADR form. Alternatively the DIT coordinator may complete the ADR forms by obtaining information from the doctor or other attending health workers about the reaction.
5. In certain clinical settings, the clinical team may further investigate any patient exhibiting abnormal laboratory results, which could be drug-related, such as agranulocytosis or neutropenia. Information from laboratory investigations shall be used to assist with causality rating.
6. The DIT shall decide on which reports need further investigation on the basis of seriousness, exposure to medicines during pregnancy, apparent

signals of new reactions which may affect adherence and success of the program.

**DIT Coordinator**

The DIT Coordinator shall:

a. Contribute to public and clinic staff education on drug safety.
b. Be responsible for follow up of all ADR reports.
c. Review all reports forms on weekly basis; and complete a District Investigation Team report on ADRs.
d. Conduct home visits to obtain further information and to ensure that the patient has recovered from the adverse reaction.
e. Conduct investigations using the checklist to ensure completeness of the investigation.

**Antenatal Clinics and Delivery Services**

- As part of the general pharmacovigilance system, it will be important to report congenital abnormalities for women visiting the health facilities for delivery and postnatal care.
- Congenital abnormalities should be reported to the DIT for their necessary follow up. To implement the pharmacovigilance aspects related to pregnancy outcomes collaboration is needed with the national MoH programme responsible for Making Pregnancy Safer.
- At the time of registration of the mother into the pregnancy-monitoring programme, information shall be collected on the drug exposure, maternal disease status, and other factors that may affect pregnancy outcome.
- A pregnancy registry will be developed to estimate magnitude of risk associated with exposure in relation to abortions, stillbirth, congenital abnormalities, low birth weight, maternal deaths and neurodevelopment milestones of the newborn.
- District Investigation Team will visit the mother and infant immediately after the expected delivery date. During this visit, general information regarding the delivery will be obtained and the newborn will be examined for major or minor congenital anomalies. An additional visit will take place 6 months later for assessment of developmental milestones.

National Pharmacovigilance Coordinator

1. The National Coordinator shall be responsible for developing pharmacovigilance system, collection and storage of all ADRs reports/forms, and coordinates communications with the PMPB, MoH and the WHO Uppsala Monitoring Centre, international centres and pharmaceutical manufacturers/suppliers.
2. The Coordinator shall be ensure harmonization of pharmacovigilance in public health with other national PV activities, promote reporting form, and

develop national database for signal generation. S/he shall have facilities to carry out the duties.

- S/he will ensure that ADR reports are processed appropriately for assessment by the Medicines Committee especially if the reports:
    - Selected by DIT for further investigation
    - Considered to be a signal of a new ADR
    - Summarized reports requiring reaction profile of the medicine

**National Pharmacovigilance Centre**

The National Pharmacovigilance Centre will be responsible for:

1. Promoting the reporting of adverse reactions;
2. Collecting case reports of adverse reactions;
3. Clinically evaluating case reports;
4. Collating, analysing and evaluating patterns of adverse reactions;
5. Distinguishing signals of adverse reactions;
6. Recommending regulatory action in response to findings supported by good evidence;
7. Initiating studies to investigate significant suspect reactions;
8. Alerting prescribers, manufacturers and the public to new risks of adverse reactions;
9. Sharing their reports with the WHO Programme for International Drug Monitoring.
10. Increasing public awareness of issues relevant to the safety of medicines.
11. Supporting clinical practice and the development of public health policy.
12. Responding to real or contrived medicine scare crises.

**Pharmacy, Medicines and Poison's Board**

PMPB shall be responsible for:

1. Taking regulatory action in respect to the implicated medicinal product/s.
2. Communicating the actions to the drug manufacturers/suppliers liable for the drug.
3. Submitting all local and internationally derived safety information to the National Pharmacovigilance Coordinator.
4. Performing risk assessment, consider options for regulatory action and inform WHO UMC on action taken.

**Medicines Committee**

- The Medicines Committee as a national expert panel shall be responsible for:

1. Reviewing all ADRs report and conducting causality assessments.
2. Performing additional investigations required by the MC.

**Pharmaceutical manufacturers**

The pharmaceutical manufacturers should be recognised as partners in the national pharmacovigilance programme. The drug manufacturers shall be responsible for sharing post-marketing surveillance data and periodic safety update reports with public sector agencies.

**Public Health Programmes**

1. The PHPs shall assist with public information during the launch of new drug regimens.
2. Together with the Essential Drugs Programme, they will take responsibility for ensuring training of health facility staff in use of new drugs/vaccines.
3. When necessary, PHP members may be called upon by the PMPB and MC in determining the risk-benefit assessment of suspect drugs.
4. Update respective treatment guidelines and initiate new training and communications to health care providers and the general public.

**Media**

The media are included within the listing of responsible agencies because of their important role in passing correct information on to the public. Good communication between the MC and the media will increase the likelihood of informed media coverage. The media shall be responsible for:

1. Providing the public with informed information on drug safety.
2. Communicating with professional organizations, health care professionals and workers for evidence-based information.

International Support

1. International agencies, such as the WHO, will support PHPs throughout the process of development of new drugs, registration and deployment at population level guided by a well-developed risk management plan to allow continuous assessment of drug safety.
2. The Uppsala Monitoring Centre of the WHO shall collect international ADR reports, provide methodological support, analyses rates and risk-benefit profiles, and inform national pharmacovigilance programmes of new SAE signals.
3. The WHO (Essential Drugs and Medicines & Malaria Control Department) shall support international expert panels to review periodically the safety profile of drugs and provide technical guidance and possibly training support to national essential drug programmes and PH programmes.

**References**


1. A Practical Handbook on the Pharmacovigilance of Antimalarial Medicines.
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3. Safety Monitoring of Medicinal products – Guidelines for Setting Up and Running a Pharmacovigilance Centre (WHO UMC).
4. The Safety of Medicines in Public Health Programmes – Pharmacovigilance an Essential Tool (WHO UMC 2006).
5. Guidelines for Adverse Drug Reaction (ADR) Reporting, Drug Administration and Control Authority (DACA) Addis Ababa, Ethiopia.
6. The United Republic Of Tanzania, Ministry of Health, Guidelines for Monitoring and Reporting Adverse Drug Reactions – Prepared By TFDA, January 2006.
7. Aide Me moiré for a National Strategy for Safe Drugs and their Appropriate Use.
8. Glossary of Terms used in Pharmacovigilance.

Form No. xx

**MINISTRY OF HEALTH**
**PHARMACY, MEDICINES AND POISONS BOARD**
**Off Chilambula Road, Lilongwe Old Town**
**P. O. BOX 30241 Lilongwe 3, MALAWI**
**Tel: ..... Email: .....**

# SUSPECTEC ADVERSE DRUG REACTION REPORTING FORM

## A. PATIENT DETAILS

| | |
|---|---|
| Patient Registration No. | Name of Health Institution |
| Patient Physical Address | District |
| Postal Address | |
| Age in years ☐ Sex M ☐ F ☐ Weight in Kg ☐ | |

## B. DESCRIPTION OF ADVERSE DRUG REACTION AND OUTCOME OF EVENT

Date/time of onset of ADR (dd/mm/yy)/(Hr/Min) .....

Condition/Diagnosis.....

Description of actual drug reaction (use overleaf for additional information) .....

Seriousness of ADR

Hospitalization needed ☐ Disability caused ☐ Life Threatening ☐

Congenital abnormality ☐ Fatal ☐ (date of death.....) Minor ☐

(Specify) .....
Action taken .....

## C. ALL MEDICINES IN USE (Include OTC, Traditional, Herbal and Cosmetics); Use asterisk (*) For The Suspect Medicine

| Name of Medicine(s)/Vaccine | | Strength and Batch Number | Dosage and Route | Date treatment started | Date treatment stopped | Reason/Indication for use |
|---|---|---|---|---|---|---|
| Brand Name and Expiry date | Generic Name and expiry date | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Source of suspected medicine(s)Hospital/ Clinic ☐ Private Pharmacy ☐ Traditional healer ☐ Vendor ☐

Other: specify. .....

## D. OTHER RELEVANT INFORMATION

Known allergies (specify) ☐ Pregnancy (trimester) ☐ Alcohol use ☐ Tobacco use ☐ Renal disease ☐

☐ ☐

Strictly Confidential

Hepatic disease  Other medical conditions  (specify) .....

## E. Report compiled by

Name of health personnel .....
Designation..... Phone .....

Signature..... Date..... Email: .....

## F. NOTES TO THE REPORTER OF ADR

1. *ADR reporting is very critical for a well managed drug supply system and in particular for the promotion of safe use of medicines. All reporters must actively participate in the pharmacovigilance system.*
2. *All drugs suspected to cause ADR must be reported (medicines and vaccines.)*
3. *Identities of Patients and Reporter will remain strictly confidential and shall not be used in a court of law for whatever reasons.*
4. *All reports will be evaluated by Medicines Committee.*
5. *All significant outcomes of the evaluated reports will be shared widely by the Pharmacy, Medicines and Poisons Board.*
6. *Completed forms should be forwarded immediately to the above address the nearest the District Health Officer*
7. *If referral is possible (e.g. from the Health Centre), the completed ADR form should accompany the patient.*

**REMEMBER: YOU CAN REDUCE THE SUFFERING AND SAVE PATIENTS LIVES BY REPORTING SUSPECTED ADVERSE DRUG REACTIONS IMMEDIATELY**

## G. DISPATCH OF COMPLETED FORM: ADDRESS

**THE REGISTRAR**
**PHARMACY, MEDICINES AND POISONS BOARD**
**Attention: Pharmacovigilance Coordinator**
**PO Box 30241, Lilongwe 3**

Fax No 01 755 204  Phone 01 755165/166  E-mail admin@pmpb.malawi.net