LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

DRAFT GUIDELINE FOR THE PHARMACOVIGILANCE SYSTEM IN LIBERIA

Date: MARCH 2013

Foreword

The LMHRA was established by an Act of Legislation on September 29, 2010 and one of its core mandates is to ensure that the medicines used in the Republic of Liberia are of Good quality, safe and efficacious.

Since the enactment of the LMHRA Act, the pharmaceutical industry has been growing very fast. To date, over one thousand (1000) products have been registered for the circulation in the Liberian market. These medicines, despite their obvious benefits, can also cause Adverse Drug Reactions (ADRs) which can be serious or even fatal. Most often these ADRs are preventable.

The Department of Pharmacovigilance & Medicines Information at the Liberia Medicines and Health Products Regulatory Authority (LMHRA) has been actively involved with PV System review and re-designing tools and guidelines for the detection and reporting of ADRs.
In 2013, the Guidelines for the National Pharmacovigilance System in Liberia were developed proceeded by sensitization of healthcare workers through the National Sensitization workshop in LMHRA. Several other tools were also re-looked at concurrently, including the form for reporting poor quality medicinal products, suspected ADR reporting form and ADR Alert Card.

This Guideline for the National Pharmacovigilance System in Liberia has been developed to complement and support the efforts of educating all healthcare workers on this important concept and enhance their efforts in ensuring that safe, efficacious and quality medicines are made available to all Liberians.

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Acknowledgement

This guideline has been drafted to promote the controlled reporting of the adverse effects resulting as a result of medication usage in the Republic of Liberia. The process began in 2013, barely three years after the Act establishing the Liberia Medicines and Health Products Regulatory Authority (LMHRA) was enacted in 2010 through evaluations from various stakeholders in order to develop safety administration of medicines.

I am particularly grateful to the Ministry of Health and Social Welfare (MOH/SW) for providing me access to health facilities in which medicines safety monitoring (Pharmacovigilance) is being carried out. It is through the surveillance in these facilities that the guideline has been developed.

Special thanks go to the World Health Organization-Liberia Offices; the Headquarters, Geneva and the Uppsala Monitoring Centre, Sweden, for their invaluable guidance in developing this guideline.

Acknowledgement is also made to the healthcare professionals trained at the Sensitization Workshop on Pharmacovigilance held by the Liberia Medicines & Health Products Regulatory Authority for their contribution. Without their concrete contribution, this document would not have been completed. Gratitude is extended to the Chairperson, Managing Director and all Members of the Liberia Medicines & Health Products Regulatory Authority Board and its hard working staff who offered valuable contributions towards developing and producing this document.

I would further like to sincerely thank all persons and groups that reviewed and made constructive comments and inputs to this draft guideline including Prof. Jacob A. Kolawole of the School of Pharmacy; Dr. Lloyd Matowe of Pharmaceutical Systems Africa; Pharm. Ezekiel F. Hallie, Asst. Professor of the School of Pharmacy; National Malaria Control Program (NMCP).

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Abbreviations

ACT	**:**	Artemisinin based Combination Therapy
ADR	**:**	Adverse Drug Reaction
CHT	**:**	County Health Team
NTLCP	**:**	National Tuberculosis & Leprosy Control Program
NMCP	**:**	National Malaria Control Program
DDFP	**:**	Drug Depot Focal Person
EDP	**:**	Essential Drugs Program
ICH	**:**	International Conference on Harmonization
MOH/SW	**:**	Ministry of Health & Social Welfare
LMHRA	**:**	Liberia Medicines & Health Products Regulatory Authority
NACP	**:**	National AIDS Control Program
OTC	**:**	Over the counter
PBL	**:**	Pharmacy Board of Liberia
PV	**:**	Pharmacovigilance
ESRP	**:**	Expert Safety Review Panel
UMC	**:**	Uppsala Monitoring Centre
UMC-A	**:**	Uppsala Monitoring Center - Africa
WHO	**:**	World Health Organization
WHO-CC	**:**	World Health Organization Collaborating Centers
NPC	**:**	National Pharmacovigilance Center
CIT	:	County Investigation Team
ECCT	**:**	Expert Committee on Clinical Trials

Definitions of Terms in Pharmacovigilance

Adverse Event/Adverse Experience - Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

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

Case Control Study - Study that identifies a group of persons with the unintended drug effect of interest and a suitable comparison group of people without the unintended effect. The relationship of a drug to the drug event is examined by comparing the groups exhibiting and not exhibiting the drug event with regard to how frequently the drug is present.

Clinical Trial - A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the objective of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases: I to IV. Phase IV trials are studies performed after marketing of the pharmaceutical product. They are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance.

Cohort Study - A study that identifies defined populations and follows them forward in time; examine their rates of disease. A cohort study generally identifies and compares exposed patients to unexposed patients or to patients who receive a different exposure.

Complementary/Alternative Medicine - These terms are used interchangeably with traditional medicine in some countries. They refer to a broad set of healthcare practices that are not part of that country's own tradition and are not integrated into the dominant health care system. They have not usually been tested in specified clinical indications by an objective scientific discipline.

Drug/Medicine - Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug/medicinal product is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information.

Drug Alerts - The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator or from a regulator to the public.

Lack of Efficacy - Unexpected failure of a drug to produce the intended effect as determined by previous scientific investigation.

National Pharmacovigilance Center - A single, governmentally recognized center (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze and give advice on all information related to drug safety.

Pharmacoepidemiology - The study of the use and effects of drugs in large numbers of people.

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

Prescription Event Monitoring - A system created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified drug.

Record Linkage - Method of assembling information contained in two or more records, e.g., in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

Side Effect - Any unintended effect of a pharmaceutical product occurring at doses normally used in humans, 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 event and the quality of the information.

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

Unexpected Adverse Reaction - An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

List of Tables

Table description

List of figures

Figure description **Page number**

TABLE OF CONTENTS

1.0 Introduction

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other possible drug-related problems with the view to early detection of unknown adverse reactions and interactions, increase in frequency of known adverse reactions and identification of risk factors and possible mechanisms underlying adverse reactions. Medicines have significant benefits to our lives and lead to significant reduction in morbidity and mortality. However, even though they are generally seen as having beneficial effects, all medicines (including their excipients e.g. coloring agents, lubricants, preservatives, etc.), have a potential for producing adverse or unwanted effects no matter how skillfully they are used.

The Liberia Medicines & Health Products Regulatory Authority (LMHRA) is charged with the responsibility of ensuring the availability of safe, efficacious and good quality medicines to all residents of Liberia. To attain the objective, the LMHRA with collaborating partners (other institutions in Liberia) has been implementing strategies aimed at ensuring that products used in Liberia are safe, efficacious, of good quality and are supplied and handled by qualified personnel.

Safety and efficacy surveillance of medicines has in the past not received the required attention. To address this, the LMHRA has developed a guideline for the **National Pharmacovigilance System in Liberia.** The Pharmacovigilance system is necessary for the prevention of drug-related illnesses, early detection and assessment of adverse drug reactions and to minimize the financial costs associated with preventable adverse events. The role out of a Pharmacovigilance system is an indication of the Ministry's commitment to safeguarding the Health of all Liberians.
The guideline for the National Pharmacovigilance System in Liberia is to guide healthcare workers on the operations of the Pharmacovigilance system. It gives an overview of what Pharmacovigilance is, how to detect and classify ADRs and the structural organization of the system in Liberia. It also describes the reporting system to the National Pharmacovigilance Center and its expected outcomes. The information obtained will guide policy particularly on the inclusion of products into the list for essential drugs and/or standard treatment guidelines.

Amongst its many functions as spelt out in The Liberia Medicines & Health Products Regulatory Authority (LMHRA) in Liberia, along with other collaborating partners (MOH/SW, PBL, LMDC, School of Pharmacy, etc.), is charged out with the mission to regulate and control the pharmaceutical services and ensure accessibility, quality, efficacy and safety of human and veterinary medicines, herbal, medical devices and health products. With this in mind, the LMHRA has developed this guideline for healthcare workers and the public at large on detecting and reporting Adverse Drug Reactions and poor medicinal products.

The purpose of this guideline is to help healthcare providers to participate in the process of continuous surveillance of safety and efficacy of the pharmaceutical products used in clinical practice, thus to help achieve the ultimate goal to make safer and more effective treatment available to patients. All healthcare workers are encouraged to actively participate in Pharmacovigilance and to report all suspected adverse drug reactions to help safeguard the health of the Liberian populace.

The ultimate purpose of ADR reporting and monitoring is to reduce risks associated with drug prescribing and administration and to improve patient care, safety and treatment outcomes.

This guideline addresses specifically the issues on what to report, why to report, when to report, where to report and how to report.

1.1 How are ADRs classified?

A classification of ADRs reveals how they are related and draws attention to the common factors involved in the cause of reactions within the same group, thus enabling similar steps to be taken to treat or prevent them. Adverse Drug Reactions are categorized as either Type A or Type B reactions in this method of classification.

a. Type A (augmented) adverse drug reactions

These reactions are the result of an exaggerated, but otherwise normal pharmacological action of a drug given in the usual therapeutic doses. Type A reactions are largely predictable on the basis of a drug's known pharmacology.

They are usually dose-dependent and although their incidence and morbidity in the community is often high, their mortality is generally low. Examples include bradycardia with adrenoceptor antagonists, haemorrhage with anticoagulants, or drowsiness with benzodiazepine anxiolytics.

b. Type B (bizarre) adverse drug reactions

These reactions are totally aberrant or unusual effects that are not to be expected from the known pharmacological actions of a drug when given in the usual therapeutic doses to a patient whose body handles the drug in a normal way.

They are usually unpredictable and are not observed during conventional pharmacological and toxicological screening programs. Although their incidence and morbidity are low, their mortality may be high. Examples include malignant hyperthermia of anesthesia, acute porphyria, and many immunological reactions.

1.2 What is Pharmacovigilance?

WHO defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems.

1.3 What is the importance of Pharmacovigilance?

The information collected during the pre-marketing phase of drug development is inevitably incomplete with regard to possible ADRs. This is mainly because:

a. Tests in animals are insufficient to predict human safety;
b. Patients used in clinical trials are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited;
c. By the time of licensing a product, exposure of less than 5000 human subjects to a drug allows only the more common ADRs to be detected;
d. At least 30,000 people need to be treated with a drug to be sure that you do not miss at least one patient with an ADR which has an incidence of 1 in **10,000** exposed individuals**;**
e. Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available; thus, post-marketing surveillance is important to permit detection of less common, but sometimes very serious ADRs.

1.4 What are the goals of Pharmacovigilance?

The ultimate goals of Pharmacovigilance are:

a. The Rational and safe use of medicines and health products
b. The assessment and communication of the risks and benefits of drugs on the market
c. Educating and informing patients on safety of medicines

1.5 What are the objectives of the Pharmacovigilance System?

The objectives of Pharmacovigilance are to:

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

1.6 Location of the National Pharmacovigilance Center

a. The National Pharmacovigilance Centre (NPC) is based within the
Liberia Medicines & Health Products Regulatory Authority (LMHRA)
VP Road, Tubman Boulevard
Old Road, Sinkor
1000 Monrovia, 10 Liberia
West Africa
Email: libmhra@gmail.com or jgoteh@gmail.com; d.sumo2013@gmail.com
Tel: 231 (0) 886 530270 / 886 562019

b. A panel of experts (Expert Safety Review Panel) under the LMHRA, provides technical expertise to the PV system, and make appropriate recommendations to the PV Coordinator and Managing Director of LMHRA. Specific Terms of References (TORs) for the PV Coordinator, ADR reporters and ESRP have been developed.

1.7 Who should report ADRs?

All health care professionals/workers, including clinicians, pharmacists, dentists, nurses, traditional medicine practitioners and the public at large are encouraged to report.

1.8 What is to be reported?

a. Report all suspected adverse reactions to allopathic (modern) medicines, traditional/alternative/herbal medicines, x-ray contrast media, medical devices and cosmetics.
b. Report product quality problems such as:
   - Color change
   - Incomplete pack
   - Separating of components
   - Suspected contamination
   - Powdering / crumbling
   - Questionable stability
   - Caking
   - Defective components
   - Molding
   - Poor packaging / poor labeling
   - Change of odor
   - Therapeutic failures
   - Mislabeling
   - Receiving expired medicines

1.9 What will the Pharmacovigilance System Cover?

The Pharmacovigilance System shall cover the entire country. This includes: the public, private and NGO / Mission healthcare providers in all parts of the country to cover:

a. All levels of healthcare, including the community based health care providers
b. All medicines used in the country
c. All disease conditions encountered in the country
d. All cadres and disciplines of healthcare workers
e. Any individual resident in Liberia, suspecting a reaction to a medicine

The Pharmacovigilance System shall work closely with MOH/SW and various health programs and organizations to develop an effective feedback mechanism that serves the patient safety needs of the healthcare system. The LMHRA shall also endeavor to develop close links and to harmonize with other Pharmacovigilance systems in the region, particularly within the West African Community (WAC) and West African Health Organization (WAHO).

1.10 What happens to my reported ADRs?

a. The information obtained from ADR reports will be used to promote safe use of medicines in the local, national and international levels.
b. The reports submitted will be entered into the national and international database of adverse drug reactions and be analyzed by expert reviewers on a regular basis. Findings or feedbacks from these reports will also be used to make recommendations to public health programs; and to take regulatory actions where applicable.

1.10.1 A well - completed and duly submitted ADR reported by health workers may result in:

a. Additional investigations into the use of medicines in Liberia
b. Appropriate changes in the package insert
c. Change the schedule of the medicine
d. Enhancing educational initiatives to improve the safe use of that medicine
e. Other regulatory and health promotion interventions as the situation may warrant including withdrawal / recall.

Figure 1: Thalidomide induced phocomelia - Birth - defects where babies were born without limbs or with serious deformities.

1.11 What are the benefits of these reports for my patients and me?

The health care provider and patient stand to benefit as:

a. Improvement on the quality of care offered to patients
b. Reduction of drug-related problems leading to better treatment outcome
c. Improved patient confidence in professional practice, hence professional growth
d. Improved knowledge
e. Access to feedback information on drug related problems reported within the country and internationally
f. Satisfaction for the fulfillment of a moral and professional obligation

1.12 Will reporting have any negative consequences on me?

a. The adverse drug reaction report **does not** constitute an admission that you or any other health professional or the drug contributed to or caused the event in any way.
b. The outcome of the report, together with any important or relevant information relating to the reaction you have reported, will be communicated to you as appropriate.
c. The details of your report are stored in a confidential database at the National Pharmacovigilance Center in LMHRA and the analyzed report will be sent to the Uppsala Monitoring Center (UMC).
d. The names of the reporters or any other health professionals named on the report and the patient will be removed before any details about a specific adverse drug reaction is used or communicated to others.
e. The information obtained from your report will not be used for commercial purposes. It is only meant to improve our understanding and use of medicines in Liberia.

1.13 Why are health professionals in the best position to detect and report on ADRs?

a. The effectiveness of a National Pharmacovigilance Program is directly dependent on the active participation of health professionals. They are in the best position to report suspected ADRs observed in their everyday patient care, because they are the people who **diagnose, prescribe, dispense and monitor patients' response to the medicines.**

a. All healthcare providers should report ADRs as part of their professional responsibility, even if doubtful about the precise relationship with the given medication.
b. You can reduce suffering and save thousands of patients' lives by doing just one thing: **REPORTING ALL SUSPECTED ADVERSE DRUG REACTIONS including lack of effect.**

1.14 How do I recognize ADRs in my patient?

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

1.14.1 Take a proper history and do a proper examination of patient

A full drug and medical history should be taken.

a. An ADR should be your first differential diagnosis at all times!
b. Ask if this adverse reaction can be explained by any other cause; e.g. patient's underlying disease, other drugs including over-the-counter medicines or traditional medicines, toxins or foods
c. It is essential that the patient is thoroughly investigated to decide what the actual cause of any new medical problem is
d. A drug-related cause must be considered, especially when other causes do not explain the patient's condition.

1.14.2 Establish time relationships by asking and answering the following questions:

a. Did the ADR occur immediately following the drug administration?
Some reactions occur immediately after the medicine has been given while others take time to develop. The time from start of therapy to the time of onset of the suspected reaction must be logical.

1.14.3 Carry out a thorough physical examination with appropriate laboratory investigations if necessary:

a. Remember: only a few drugs produce distinctive physical signs
b. Exceptions include fixed drug eruptions, steroid-induced dermal atrophy, acute extra-pyramidal reactions
c. Laboratory tests are important if the drug is considered essential in improving patient care or if the laboratory tests results will improve management of the patient.
d. Try to describe the reaction as clearly as possible- Where possible, provide an accurate diagnosis

1.14.4 Effect of Dechallenge and Rechallenge should be determined

a. Dechallenge (withdrawal of the suspected drug) Positive dechallenge is the improvement/resolution of ADR when the suspected drug is withdrawn in a strong, though not conclusive indication of drug-induced reaction.
b. Rechallenge (re-introducing the suspected drug after a dechallenge)
Rechallenge is only justifiable when the benefit of re-introducing the suspected drug to the patient overweighs the risk of recurrence of the reaction, which is rare. In some cases the reaction may be more severe on repeated exposure. Rechallenge requires serious ethical considerations.

1.14.5 Check the known pharmacology of the medicine

a. Check if the reaction is known to occur with the particular suspected drug as stated in the package insert or other reference.

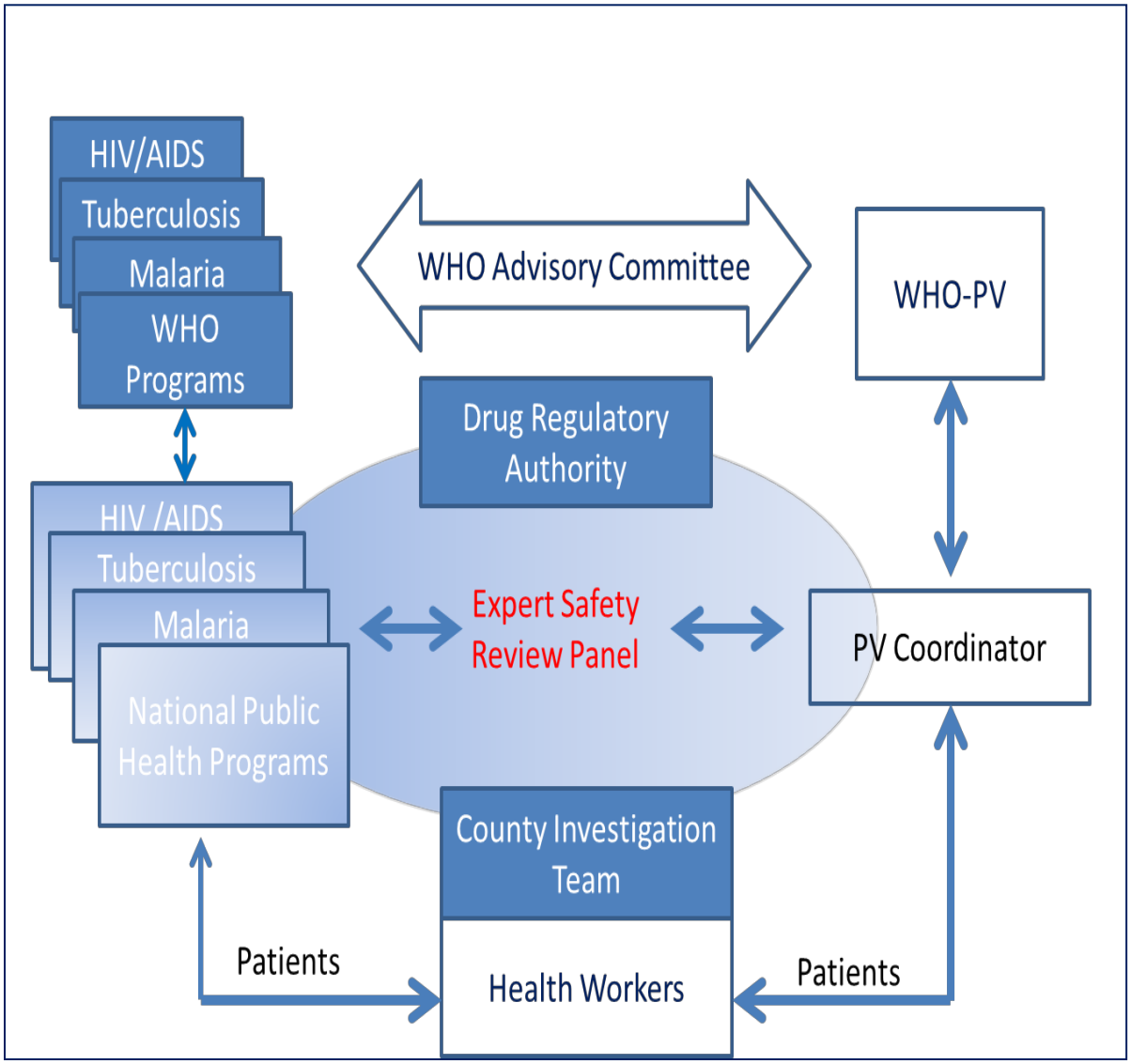
b. Remember, if the reaction is not documented in the package insert, it does not mean that the reaction cannot occur with that particular suspected medicine.

2.0 Structure and flow of information coordination

1. The PV Centre will link to the national health system through the County Health
2. Teams (CHT), specifically the County Investigation Team (CIT) and the County Pharmacists.
3. The CIT may be required at times to form a district investigation team to investigate 'signals' and reports of ADRs in consultation with the LMHRA.
   You are asked to **report ALL suspected adverse experiences with medications**, especially those where the patient outcome is:
   a. Death
   b. Life-threatening (real risk of dying)
   c. Hospitalization (initial or prolonged)
   d. Disability (significant, persistent or permanent)
   e. Congenital anomaly
   f. Required intervention to prevent permanent impairment or damage

   Report even if:
   a. You are not certain if the drug caused the reaction
   b. You do not have all the details
4. In the public health facilities reporters will forward their reports to the PV focal persons who will forward them to the NPC.
5. The NGO and private sectors would report either to the DPS or directly to LMHRA.
6. The County pharmacists (DPS) shall oversee the entire system to ensure that it runs smoothly and shall also provide necessary supervision to the districts.
7. Specific sentinel sites/systems will be established, as required under authority of the LMHRA, to carry out any or all of the following:
   a. Detailed investigations to gather specific data
   b. Specific Pharmacoepidemiology studies/analysis
   c. Verification of specific reports / claims.
8. The data received will be entered and analyzed at the National Pharmacovigilance Centre at the LMHRA, supported by the Expert Safety Review Panel (ESRP).
9. The LMHRA will review the reports received from all sources, and advise on or take the appropriate action.
10. Feedback to all levels of the system will be the responsibility of NPC.
11. The PV system will be based on the WHO data collection software '*VigiFlow*', which will be adapted as appropriate to meet the needs of the system.
    The PV system shall be linked to the WHO Monitoring Centre for ADRs, based in Uppsala, Sweden

Figure 2: Flow of Information Coordination



3.0 Tools for Pharmacovigilance

This Pharmacovigilance guideline provides the standard process for managing the Pharmacovigilance system, and provides, in the annexes, the basic tools prescribed by LMHRA. These include:

a. Suspected Adverse Drug Reaction Form
b. ADR Severity Assessment Scale
c. Causality Assessment Scale
d. Patient Alert Card
e. Criteria for issue of a Patient Alert Card
f. Checklist for investigation procedure by DIT

The Suspected ADR Form is the tool by which all suspected ADRs shall be reported. It has been designed to be short, simple and easy to fill and at the same time be able to collect important details pertaining to the suspected ADR. The form shall be the principal tool to collect data and for all reference purposes.

The severity of a reaction shall be judged according to the: **ADR Severity Assessment Scale**. This scale categorizes each ADR broadly into 'Mild', 'Moderate', 'Severe' and 'Fatal'.

The assessment of causality in a report is made easy using a **Causality Assessment Scale** which is a structured tool for determining the likelihood of a causal relationship between drug exposure and adverse events. The four main considerations incorporated in a scale are:

1. The association in between drug administration and event time
2. **Pharmacology** - including current knowledge of nature and frequency of adverse reactions
3. Medical or pharmacological **plausibility** - signs and symptoms, laboratory tests, pathological findings, mechanism
4. Likelihood or **exclusion** of other causes

Thus, with causality assessment, we can assess various levels of certainty whether a Suspected drug has indeed caused a specific adverse drug reaction.

The **Patient Alert Card** is a card that alerts all health care professionals that the bearer of the card has experienced a serious ADR. The card also helps the patient to learn of his or her serious ADR. The card is expected to be carried by the patient at all times on him- or herself and be presented to his clinician, dentist, nurse, pharmacist, community health worker at the time of consultation. This will help the health care professionals identify the patient's drug-related co-morbidity and prevent the same (or similar) drug reactions. The issue of an Alert Card is based on the **Criteria for issue of a Patient Alert Card**.

The **Poor Quality Medicinal Product Reporting Form** is a mechanism by which institutions and health care professionals can alert the NPC in LMHRA of problems encountered with the medicines supplied to or used by them. The form has been designed to incorporate the most common pharmaceutical problems encountered and assist the LMHRA in addressing the same.

The **Checklist for Investigation Procedure by DIT** has been designed to be a quick reference for the District Investigation Team to help gather more pertinent information regarding a specific

suspected ADR. This way, all necessary data will be collected and further research can be carried out. All health care professionals are encouraged to use these tools as indicated and continuously provide positive criticisms on their improvement to the NPC in LMHRA.

The LMHRA, in consultation with various stakeholders, will review these guidelines and tools periodically, to ensure that they continue to meet the goals of the PV system. Users are urged to provide feedback to the NPC in the LMHRA on the suitability and practicability of these tools.

4.0 ADR Monitoring within the Pharmacovigilance System

Monitoring of Adverse Drug Reactions will occur at all levels:

a. Individual patients who suspect a reaction to a medicine or other substance, will report to the nearest health care provider
b. Patients may also call the National Pharmacovigilance Center directly, through a dedicated number
c. At all health facilities, healthcare workers shall provide the necessary treatment to patients suspected of having an ADR
d. The healthcare worker shall record details of the suspected ADR on the ADR notification form, and forward the report to the facility in-charge
e. The facility in-charge shall forward the forms on a weekly basis to the CIT / DIT
f. The DIT consolidates the ADR notification forms received from the district, and forwards them to the NPC every two weeks or on an ad hoc basis in an emergency.
g. The NPC shall receive all ADR reports and enter them into the PV National database and later in *VigiFlow* for onward submission to *VigiBase*/*VigiLyze*.
h. report will also be forwarded to the PV Expert Review Panel for technical analysis and appropriate recommendations.
i. The NPC shall provide appropriate feedback to the CIT / DIT
j. The NPC shall initiate any follow-up investigations in conjunction with CIT/District Investigation Team

5.0 Roles and Responsibilities

The entire system of Pharmacovigilance works with the support of each healthcare provider, the regulatory bodies, the pharmaceutical industries, other stakeholders and the public at large. Hence, each of these has an important role to play and responsibility to bear:

5.1 Patient / Public

Patients to report any unacceptable, unexpected or suspected adverse effect of medicine dispensed to them.

5.2 Health Care Worker

Patient awareness of possible serious reactions, and development of a culture to report reactions to clinics, will be essential for any Pharmacovigilance system. Health facility staff provides an essential link in the detection of ADRs at the periphery of the health care system. The healthcare worker's roles in the PV system are:

a. Patient education
b. Detection and appropriate clinical management
c. Reporting
d. Documentation- to maintain accurate documents
e. Investigation, where necessary
f. Patient feedback

DIT - District Investigation Team (DIT)

a. Receive reports from health centers and send ADR reports from district to NPC on a monthly / weekly basis or on an ad hoc basis in an emergency.
b. Facilitate investigations initiated by NPC, where necessary

5.3 County Pharmacist

The two most important roles of the county pharmacist are:

a. Coordinate all activities of pharmacovigilance in the county
b. Along with staff from the National Pharmacovigilance Center, provide hands-on training of all county health care workers.

5.4 County Investigation Team (CIT)

The County Investigation Team (CIT) plays a central role in monitoring ADRs. The team ideally will comprise clinicians, pharmacists as well as the head nurse or matron of the facility. They are responsible for following-up routinely all suspected ADRs reported from all health facilities within their county. They also play an important role in the collaboration and encouragement of reporting by hospital staff. Detailed follow-up of suspected drug reactions would be used to define causality. The CIT Coordinator will coordinate the investigations, report to the NPC and contribute to public education on drug safety. They hence will:

1. Investigate suspected ADR reports from within the county with support from The NPC in LMHRA
2. Follow- up suspected drug reactions and ensure appropriate clinical management
3. Provide relevant reports to LMHRA PV Center.

The findings of investigations and the conclusions of the expert review panel (see below) in terms of causality and actions to be taken will be fed back to the reporters and patients by the CIT or other designated individuals.

5.5 Liberia Medicines and Health Products Regulatory Authority (LMHRA)

Once recommendations are received from the expert panel, the LMHRA will take responsibility for any regulatory action with respect to the implicated medicinal product/s. These actions will be officially communicated to the drug manufacturers, who have liability for the drug. The National Pharmacovigilance Center in LMHRA will:

a. Receive reports from CIT, DIT and all other sources
b. Develop and maintain National ADR database
c. Detect ADR signals and take necessary actions on received reports
d. Support CIT and DIT to investigate relevant ADR reports
e. Send ADR reports to UMC
f. Provide feedback to the users on reported ADRs through quarterly newsletters
g. Establish and provide secretariat for the Expert Safety Review Panel
h. Advocacy, Training and Education
i. Provide support to whole system (CIT, DIT and health facilities)
j. Communication / IEC
k. Implement appropriate regulatory framework.

5.6 Expert Safety Review Panel

The national expert safety review panel shall consist of the National PV Coordinator, a clinical pharmacologist, a physician, a pharmacoepidemiologist, an obstetrician, a pediatricians and a pharmacist. Moreover, a) the Panel shall review all ADR Report Forms

and conduct causality assessments and b) any additional investigations required by the panel or decisions made shall be communicated to the CIT and DIT by the NPC of the LMHRA.

Any conclusions and recommendations arising from the assessment of such reports by the expert safety review panel shall be reported to the relevant departments / programs within the Ministry of Health & Social Welfare (e.g. Malaria Control Program, National AIDS Control Program, TB Program etc); the CIT, DIT and the health facilities involved and the patient (where appropriate).

5.7 Public Health Programs (NACP, NMCP, NTLCP, etc.)

a. Provide public information during the launch of new drug regimens.
b. Take responsibility for ensuring training of health facility staff in use of new drugs.
c. When necessary, program members may be called upon by the LMHRA and Expert Safety Review Panel in determining the risk-benefit assessment of suspected drugs in order to update treatment guidelines and initiate new training and communications to health providers and the general public.
d. Resource mobilization
e. Ad hoc members of Expert Safety Review Panel
f. Education, training and advocacy.

5.8 Pharmacovigilance Sentinel Sites

It is recognized that the National Pharmacovigilance System will collect, as a passive method, a wide variety of data on ADRs. However, some specific '*programmatic*' interests may not be met. Therefore sentinel sites may be chosen for active data collection, its analysis, interpretation and investigation into specific drug - related outcomes. By nature of this event case control studies and other methods maybe required to collect relevant information.

The protocols for such sentinel sites shall be developed in conjunction with LMHRA, and where necessary gain the necessary scientific ethical clearance and consent of approved Ethics Committees, Institutional Review Boards and the Expert Committee on Clinical Trials (ECCT) at the LMHRA.
The data shall be made freely available, on a regular basis, to the Department of Pharmacovigilance and Medicines Information at the LMHRA. The Liberia Medicines and Health Products regulatory Authority remains responsible for all aspects of Pharmacovigilance but may work with an appropriate partner to set up relevant sentinel sites.

5.9 Pharmaceutical Industries

Drug manufacturers have a responsibility to share post-marketing surveillance data and periodic safety update reports with public sector agencies. They may also be called upon to meet the costs of specific investigations and/or regulatory actions affecting their products. Hence, they:

a. Provide information to LMHRA on ADRs
b. Implement directives of the LMHRA
c. Fund Pharmacovigilance activities and other investigations on their products.

5.10 Technical Support

Technical support for design and implementation of the PV system shall come from WHO, MSH, USAID, Global Fund and other meaningful stakeholders.

a. The Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring will be contacted to provide methodological support, analyses rates and risk-benefit profiles, and will inform the National Pharmacovigilance Centre of signals.
b. The World Health Organization will support international expert panels to review periodically the safety profile of all medicines and provide technical guidance and possibly training support to national programs.

6.0 Training, Roll-out and Capacity Building

Staff working at peripheral health facilities shall require training on the Pharmacovigilance System. Adverse drug reactions are not well understood and, in many countries, are seldom detected.
Attention to monitoring also may be neglected, and thus staff need to be made aware that ADR monitoring is a part of good clinical practice. Training and capacity building is required to ensure that staff understand new prescribing practices for new drugs, the correct dosage regimen, and how treatment failures are defined. Alongside this, they need to be taught to detect ADRs, know where to refer the patients, and accurately complete the ADR reporting form. Clinical guidance for improved recognition of adverse reactions is required. Staff will need to feel confident in reporting and assisting the District and County Investigation Teams. Motivation to continue monitoring over a longer time period may lapse and the PV System may require introduction of incentives together with training to sustain the activities. Common concerns and barriers to reporting by health care personnel will need to be addressed and clarified in such training activities (e.g. fear of blame etc).

In the initial stage the training is planned as:

a. A rapid cascade followed by a continuous training (with other training programs to reach out to all) for:
    i. County Pharmacists
    ii. Clinicians
    iii. Pharmacists/pharmaceutical technologists
    iv. Nurses
    v. Clinical officers
    vi. Dispenser
b. Mission sector to carry out its own training, under supervision and collaboration of the NPC in the LMHRA
c. LMHRA will achieve this with various programs as the system:
    i. Will be integrated with other on-going training in the health sector
    ii. Should be inculcated into pre-service training of health care workers at all levels
    iii. Will use Continuous Medical Education (CME) programs through professional associations such as Pharmaceutical Association of Liberia (PAL), Liberia Medical & Dental Council (LMDC), etc.

7.0 Basic Principles of Efficient Reporting

a. In-time reporting
   i. Report the suspected adverse drug reaction as soon as it occurs-the report involves less work and is more accurate
   ii. Send the report quickly to the National Pharmacovigilance Center

b. Strong suspicion and follow-up
   i. Continue your strong suspicion of the drug-induced illness in the same patient and in other patients
   ii. Keep a vigil for signs and symptoms that may now enhance or exclude the possibility of a drug induced event
   iii. All follow-up / supplementary information should be documented and submitted to the LMHRA with "FOLLOW-UP REPORT" clearly indicated on the top right corner of the form.
   iv. Make sure that the patient names and IP/OP numbers are the same.
   v. It is very important that follow-up reports are accurately identified and linked to the original report.
c. If the above information is missing, the report may not be useful
d. Remember to fill in all information accurately and in clear legible writing

Table 1: ADR Severity Assessment Scale

The severity of a reaction shall be judged according to the: "ADR Severity Assessment Scale". This scale categorizes each ADR broadly into 'Mild', 'Moderate' and 'Severe', and 'Fatal'

MILD	a. The ADR requires no change in treatment with the suspected drug b. The ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required c. No increase in length of stay.
MODERATE	a. The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required. b. Increases length of stay by at least one day c. The ADR is the reason for admission.
SEVERE	a. The ADR requires intensive medical care b. The ADR causes permanent harm to the patient
FATAL	The ADR either directly or indirectly leads to the death of the patient.

Table 2: Causality Assessment Card

Causality term	Assessment criteria
Certain	a. Event or laboratory test abnormality, with plausible time relationship to drug intake b. Cannot be explained by disease or other drugs c. **Response** to withdrawal plausible (pharmacologically, pathologically) d. Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) e. Rechallenge satisfactory, if necessary
Probable / Likely	a. Event or laboratory test abnormality, with reasonable time **relationship to drug intake** b. Unlikely to be attributed to disease or other drugs c. Response to withdrawal clinically reasonable d. Rechallenge not required
Possible	a. Event or laboratory test abnormality, with reasonable time relationship to drug intake b. Could also be explained by disease or other drugs c. Information on drug withdrawal may be lacking or unclear
Unlikely	a. Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) b. Disease or other drugs provide plausible explanations
Conditional / Unclassified	a. Event or laboratory test abnormality b. More data for proper assessment needed, or c. Additional data under examination
Unassessable / Unclassified	a. Report suggesting an adverse reaction b. Cannot be judged because information is insufficient or contradictory c. Data cannot be supplemented or verified

Table 3: Patient Alert Card

REPUBLIC OF LIBERIA
LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)
DEPARTMENT OF PHARMACOVIGILANCE & MEDICINES INFORMATION
VP ROAD, TUBMAN BOULEVARD, OLD ROAD, SINKOR
1000 MONROVIA, 10 LIBERIA
TEL: (+231) 777 281 914 email: pv@lmhra.com

ADVERSE DRUG REACTION ALERT CARD

Patient Name or Initial:.....
Age: ..... **Gender:** .....
Date Issued: ..... **Address:** .....
Suspected Drug(S): .....
Description of Reaction: …..…….....
Other comments (if any): .....
……

Please carry this card with you at all times and remember to produce it to your health care professional at each time of consultation.

Table 4: Criteria for Issuance of a Patient Alert Card

The criteria for the issuance of Patient Alert Card are as follows:

The alert card is given to:

a. Patients who are hypersensitive / allergic / intolerant to a particular drug
b. Patients who developed a 'near-fatal' reaction to any particular drug
c. Patients who have had a drug-induced morbidity to any drug
d. Patients who have had hospital admission due to an ADR to any drug
e. Patients who developed an ADR which caused increase in the health care expenditure

Table 5: Checklist for Investigation Procedure for DIT

Step	Actions
1) **Confirm information in Report**	Obtain patient's medical file (or other clinical records) Check details about patient and event from medical file and document information Obtain any details missing from suspected ADR reporting form Identify any other cases that need to be included in the
2) **Investigate and collect data: About patient:**	History of drug used (including over-the-counter and traditional medicine) Medical history, including prior history of similar reactions or Allergies Family history of similar events
a. About the event	History, clinical description, any relevant laboratory results about the suspected ADR and diagnosis of the event Treatment, whether hospitalized, and outcome
b. About the suspected drug(s)	Brand name, generic name, batch/lot numbers drug(s): Date of manufacture, date of expiry Name of manufacturer and supplier Conditions of storage at facility and expiry date Investigate the local health facility
c. About the people	Whether others received the same drug and developed illness (assess health facility ledgers) Whether others had same or similar illness (may need case definition); if so exposure of cases to suspect drug(s)
3) **Assess the service by asking about:**	Drug storage and prescription Details of training in diagnosis and treatment 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? Occasionally, laboratory tests may help
6) **Conclude investigation**	Assess causal association to suspected drug/s Complete suspected ADR Investigation Form 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)

Table 6: Feedback Form

Liberia Medicines & Health Products Regulatory Authority (LMHRA)
Department of Pharmacovigilance & Medicines Information
VP Road, Tubman Boulevard, Old Road, Sinkor
1000 Monrovia, 10 Liberia
West Africa

Tel: +231 886530270 **email: libmhra@gmail.com Website: www.libmhra.org**

For any comments, inclusions and exclusions, please fill this form and send it to the above mentioned address. This will assist in improving this guideline in its subsequent editions.

Table 7: Poor Quality Medicinal Products Reporting Form

REPUBLIC OF LIBERIA

LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY (LMHRA)

DEPARTMENT OF PHARMACOVIGILANCE & MEDICINES INFORMATION

VP ROAD, TUBMAN BOULEVARD, OLD ROAD, SINKOR

1000 MONROVIA, 10 LIBERIA

WEST AFRICA

TEL: (+231) 886530270 EMAIL: libmhra@gmail.com WEBSITE: www.libmhra.org

FORM FOR REPORTING POOR QUALITY MEDICINAL PRODUCTS

Name of Facility : _____ District Name: _____County: _____

Facility Address: _____ Facility Telephone: _____

PRODUCT IDENTITY							
Brand Name				Generic Name			
Batch/lot number		Date of manufacture		Date of Expiry		Date of Receipt	
Name of Manufacturer				Country of origin			
Name of distributor/ supplier		Distributor / supplier's Address					

PRODUCT INFORMATION (Tick appropriate box)	COMPLAINT (Tick appropriate box/boxes)
☐ Oral Tablet / Capsules	☐ Color Change
☐Oral Suspension / Syrup	☐ Separating
☐ Injection	☐Powder / Crumbling
☐ Diluents	☐ Caking
☐ Powder For Reconstitution Of Suspension	☐ Molding
☐ Powder for Reconstitution of Injection	☐ Change of odor
☐ Eye Drops	☐ Mislabeling
☐ Nebulizer Solution	☐ Incomplete Package
☐ Cream / Ointment / Limens / Past	☐ Other: _____
☐ Other _____	

Describe complaint in detail:

STORAGE CONDITION

Does the product require refrigeration?	☐ Yes	☐ No	Other detail (if necessary)
Was product available at facility?	☐ Yes	☐ No	
Was product dispensed and returned by client?	☐ Yes	☐ No	
Was product stored according to manufacturer LMHRA recommendation?	☐ Yes	☐ No	

Comments (if any)

Name of Reporter:	Contact Number:
Job Title:	Signature:
Email Address:	Date:

Once completed, please send copy of this form to above address

Pictorial representations of some well-known ADRs

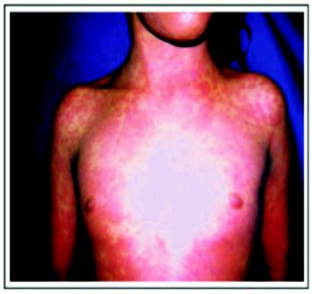


Figure 3: Phenobarbital hypersensitivity syndrome - *Extensive eruption of exanthematous pattern with erythema and infiltration involving the entire trunk and arm.*

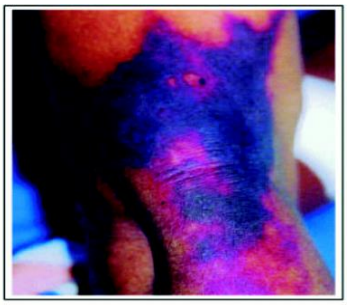


Figure 4: Stevens Johnsons Syndrome – *An immune-complex-mediated hypersensitivity (allergic) condition. It is a severe expression of the condition known as erythema multiforme.*
Note the inflammation of the skin and mucous membranes.

Figure 5: Propylthiouracil hypersensitivity vasculitis - o*bserve the ecchymosis with central cutaneous necrosis in the arm.*

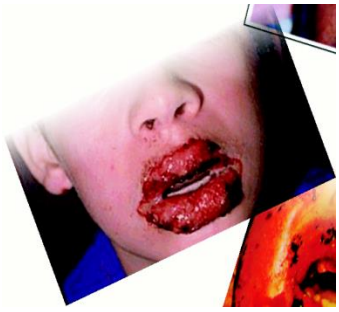


Figure 6: Toxic Epidermal Necrolysis *- the most severe condition associated with immune complex hypersensitivity. This condition involves multiple large blisters that coalesce, followed by a sloughing of most of the skin and mucous membranes*

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