	Title: A GUIDE FOR SAFETY MONITORING OF MEDICINES IN SIERRA LEONE	
Rev No: 01	**Doc No: PBSL/GL/004**	Version no. 02
Issue date: 15 Feb 2021	**Effective date: 17 Feb 2021**	Approved by: Registrar

PHARMACY BOARD OF SIERRA LEONE

PMB 322

CENTRAL MEDICAL STORES COMPOUND

NEW ENGLAND VILLE

FREETOWN

	Title: A GUIDE FOR SAFETY MONITORING OF MEDICINES IN SIERRA LEONE	
Rev No: 01	**Doc No: PBSL/GL/004**	Version no. 02
Issue date: 15 Feb 2021	**Effective date: 17 Feb 2021**	Approved by: Registrar

Contents

INTRODUCTION

The World Health Organization has defined Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The ultimate goal of pharmacovigilance is to improve the safe and rational use of medicines, thereby improving patient care and public health

The Agency therefore has developed PBSL Guide for Safety Monitoring of Medicines in Sierra Leone to ensure safety of medicinal products that it regulates

They provide detailed guidance for Healthcare Professionals, Consumers, as well as for Marketing authorization holders on establishing and maintaining a pharmacovigilance system including its quality management, pharmacovigilance system master file, adverse reaction reporting, risk management, post authorization safety studies, risk communication and pharmacovigilance audit

The PBSL Guide for Safety Monitoring of Medicines in Sierra Leone describes the obligations of the Marketing Authorization Holders to set up a system for pharmacovigilance in order to collect, collate and evaluate information about suspected adverse reactions of products it puts into the Sierra Leone market. The ultimate goal is to ensure that medicinal products put into the Sierra Leone market are safe and effective, and continue to provide a satisfactory balance between their benefits and risks.

These guidelines have been developed with reference mainly from the European Medicines Agency's , Ghana FDA, South Africa regulatory agency, USFDA guidelines for Good Pharmacovigilance Practices (GVP), which currently provide the most comprehensive

description of best practices in safety monitoring and reporting for marketing authorization holders.

OBJECTIVE

These guidelines are intended to help all stakeholders comply with all aspects of safety monitoring of medicines in Sierra Leone

SCOPE

These guidelines provide detailed guidance for marketing authorization holders on establishing and maintaining a pharmacovigilance system including its quality management, pharmacovigilance system master file, adverse reaction reporting, risk management, post authorization safety studies, risk communication and pharmacovigilance inspections.

GLOSSARY

ADVERSE DRUG REACTION	A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.
ADVERSE EVENT/ADVERSE EXPERIENCE	Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign

	(including an abnormal laboratory finding for example), symptom or disease temporarily associated with the use of the medicine.
AUDIT	A systematic, disciplined, independent and documented process for obtaining audit evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled
BOARD	Means Pharmacy Board of Sierra Leone (PBSL)
CONSUMER	Is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, or relative of a patient.
DATA LOCK POINT	For a periodic safety update report (PSUR), the date designated as the cut-off date for data to be included in a PSUR. For a periodic benefit-risk evaluation report (PBRER), the date designated as the cut-off date for data to be included in a PBRER, based on the international birth date.
DEVELOPMENT INTERNATIONAL BIRTH DATE	Date of first approval (or authorisation) for conducting an interventional clinical trial in any country (see ICH-E2F Guideline, Volume 10 of the Rules Governing Medicinal Products in the EU).

DRUG	A drug is a pharmaceutical product, used in or on the human body for the prevention (prophylaxis) mitigation, diagnosis and or treatment of disease, or for the modification of physiological function. This definition includes prescribed medicines, over-the counter medicines, vaccines, herbal medicines, traditional medicines and biologicals (including blood and blood-related products e.g. sera, plasma) and cosmetics, medical devices and nutritional agents.
DRUG ABUSE	Drug abuse is a persistent or sporadic, intentional excessive use of medicines, which is accompanied by harmful physical or psychological effects.
EXPEDITED REPORTING	This is the immediate reporting and in not more than 7 calendar days, of a serious adverse reaction to the Board.
HEALTHCARE PROFESSIONAL	Healthcare professional is defined as a medically-qualified person such as a physician, pharmacist, dentist, nurse, coroner, or as otherwise specified by local regulations

IDENTIFIED RISK	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. An important identified risk is an identified risk that could have an impact on the benefit-risk of the product or have implications for public health. What constitutes an import risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally any risk that is likely to be included in the contraindications or precautions section of the product information should be considered important. Examples include: • an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data; • an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group on a parameter of interest suggests a causal relationship; • an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions. In a clinical trial, the comparator may be placebo, an active substance or non-exposure

IMPORTANT IDENTIFIED RISK AND IMPORTANT POTENTIAL RISK	An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.
INTERNATIONAL BIRTH DATE	The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world (see GVP Annex IV, ICH-E2C(R2) Guideline).
LINE LISTING	A line listing provides key information but not necessarily all the details customarily collected on individual cases. Reactions are classified by body system for the most serious-presenting sign or symptom. The headings usually included are: ☐ Country of occurrence ☐ Source (e.g. spontaneous, clinical trial, literature, regulatory authority)

	☐ Age ☐ Gender ☐ Dose(s) of suspected medicine(s) ☐ Formulation and/or route of administration, batch number when applicable ☐ Duration of treatment (prior to event); time to onset ☐ Description of reaction (as reported) ☐ Patient outcome (e.g. fatal, resolved, etc.) ☐ Comment (if relevant)
LOCAL DISTRIBUTOR OR LOCAL AGENT	A person or company authorized by the Board to manufacture, import, receive as donation, distribute or sell a medicinal product in Sierra Leone.
LOCAL REPRESENTATIVE	The company or legal entity that represents the MAH in Sierra Leone and performs functions delegated by the MAH.
MANUFACTURER	A person or a body who sells a product under their own name, or under a trademark, design, trade name or other name or mark owned or controlled by the person or the body, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the product, or for

	assigning to it a purpose, whether those tasks are performed by that person or on
MARKETTIG AUTHORIZATION HOLDER	A person or company authorized by the Board to manufacture, import, receive as donation, distribute or sell a medicinal product in Sierra Leone.
MISSING INFORMATION	Information about the safety of a medicinal product which is not available at the time of submission of a particular risk management plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace. Examples of missing information include populations not studied (e.g. pregnant women or patients with severe renal impairment) or where there is a high likelihood of off-label use period.
NEW SAFTEY INFROMATION	New safety information with respect to a drug, means information derived from a clinical trial, an adverse event report, a post-approval, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system; or other scientific data deemed appropriate — (A) a serious risk or unexpected serious risk associated with use of the drug that may be based on a new analysis of existing information since the drug was approved, since the risk

	management plan (RMP) was required, or since the last assessment of the approved RMP for the drug; or (B) the effectiveness of the approved RMP for the drug obtained since the last assessment.
OFF LABEL USE	A chemical or biologically Active Pharmaceutical Ingredient (API) that has not previously been registered as an ingredient of any pharmaceutical product Off label use of a medicine is use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling of the medicinal product.
PERIODIC BENEFIT RISK EVALUATION REPORT	An update of the world-wide marketing experience of a medicinal product at defined times with focus on formal evaluation of benefit in special population at defines times during post-registration
PERIODIC SAFETY UPDATE REPORT	A regular update of the world-wide safety experience of a medicinal product at defined times during post-registration period
PHARMACOVIGILANCE	The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

PHARMACOVIGILANCE SYSTEM MASTER FILE	A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products
POST AUTHORIZATION SAFETY STUDIES	Any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.
PAES	
POTENTIAL RISK	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. An example is toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies. An important potential risk is a potential risk that could have an impact on the benefit-risk of the product or have implications for public health. What constitutes an import risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health. Normally any risk that

	is likely to be included in the contraindications or precautions section of the product information should be considered important
QUALITY OF A PHARMACOVIGILANCE SYSTEM	All characteristics of the pharmacovigilance system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance.
QUALIFIED PERSON RESPOSIBLE FOR PHARMACOVIGILANCE	An individual named by the Marketing Authorization Holder (MAH) and approved by the Board as the person responsible for ensuring that the company's MAH meets its legal obligation in accordance with PBSL PV regulatory obligations in Sierra Leone.
QUALITY REQUIREMENTS	Those characteristics of a system that are likely to produce the desired outcome, or quality objectives.
QUALITY SYSTEM OF A PHARMACOVIGILANCE SYSTEM	The organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management
RISK MANAGEMENT PLAN(RMP)	A systematic approach and set of pharmacovigilance activities and interventions designed to identify,

	characterize, prevent or minimize risks relating to medicinal products, and the assessment of effectiveness of those intervention and how these risks will be communicated to the Board and the general population
SAFETY CONCERN	An important identified risk, important potential risk, or important missing information
SERIOUS ADVERSE DRUG EXPERIENCE	Serious adverse drug experience is an adverse drug experience that — (A) results in — (i) death; (ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form); (iii) inpatient hospitalization or prolongation of existing hospitalization; (iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or (v) a congenital anomaly or birth defect; or (B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A**).**
SIDE EFFECT	It is any unintended effect of a pharmaceutical product

	occurring at doses normally used in human, which is related to the pharmaceutical properties of the drug." Such effects may or may not be beneficial. Side effects are related to the known properties of the drug and can often be predicted. It must be stressed that in pharmacovigilance, we are interested in all drug related reactions, this includes side effects and suspected adverse drug reactions. Healthcare professionals must therefore report all drug related problems to the NPC.
SERIOUS RISK	Serious risk means a risk of a serious adverse drug experience.
SIGNAL	A Signal refers to "Reported information on a possible causal relationship between an adverse event and a drug; the relationship being known 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.

SIGNAL OF A SERIOUS RISK	means information related to a serious adverse drug experience associated with use of a drug and derived from — (A) a clinical trial; (B) adverse event reports; (C) a post-approval study; (D) peer-reviewed biomedical literature; (E) data derived from the post-market risk identification and analysis; (F) other scientific data deemed appropriate by the Board.
SPONTANEOUS REPORT OR SPONTANEOUS NOTIFICATION	Unsolicited communication by a patient, a consumer or healthcare professional to the Board, marketing authorization holder or local representative or an organization that describes a suspected adverse reaction in a patient, a consumer who is given one or more medicines and which is not derived from a study or any organized data collection systems where adverse event reporting is actively sought.

SUBSTANTIAL AMENDMENT TO THE STUDY PROTOCOL	Amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, the study population, the sample size, the study design, the data sources, the method of data collection, the definitions of the main exposure, outcome and confounding variables or the statistical analytical plan as described in the study protocol.
UNEXPECTED ADVERSE REACTION	It is an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization or expected from the characteristic of the drug”**.**
UNEXPECTED SERIOUS RISK	Unexpected serious risk means a serious adverse drug experience that is not listed in the labelling of a drug, or that may be symptomatically or pathophysiologically related to an adverse drug experience identified in the labelling, but differs because of greater severity, specificity, or prevalence.

ACRONYM

ADR	Adverse Drug Reaction
AE	Adverse Event
CAP	Corrective Action Plan
CAPA	Corrective and Preventive Action
CIOMS	Council for International Organizations of Medical Sciences
DIBD	Development International Birth Date
DLP	Data Lock Point
DSUR	Development Safety Update report
GVP	Good Pharmacovigilance Practices
IBD	International Birth Date
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
IT	Information technology
LBD	Local Birth date
MA	Marketing Authorization
MAH	Marketing Authorization Holder
NCE	New Chemical Entity

NPC	National Pharmacovigilance Centre
PASS	Post Authorization Safety Studies
PAES	Post Authorization Efficacy studies
PBRER	Periodic Benefit -Risk Evaluation Report
PBSL	Pharmacy Board of Sierra Leone
PSMF	Pharmacovigilance Systems Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PV	Pharmacovigilance
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
SMPC	Summary of Product Characteristics
SR	Summary Report
WHO	World Health Organization

SECTION 1

Detecting & Reporting Adverse Drug Reactions

Background/Introduction

1.1 Modern medicines have brought significant benefits to our lives offering reduction in morbidity and mortality due to disease. It is also apparent that the improving health status of an increasing number of the Sierra Leonean population can be attributed to medicines. However, even though medicines are generally seen as beneficial, all medications including the excipients (e.g. preservatives, coloring agents, lubricants etc.) in medicines are capable of producing adverse or unwanted effects.

In order to effectively safeguard the health of Sierra Leoneans, The Pharmacy Board of Sierra Leone (PBSL) is at the forefront of activities designed to ensure that all medicines used in Sierra Leone are safe, efficacious and of good quality. Furthermore, the Board has been crusading against substandard and falsified pharmaceuticals and is leading the fight against counterfeiting of all regulated products.

It is hoped that all health care professionals will take an active interest in pharmacovigilance and report any suspicion of adverse drug reactions to the NPC. This way, we will make Sierra Leone and the world a safer place as far as the use of medicines and other regulated products are concerned. Remember, even one seemingly inconsequential report may be lifesaving, if the suspicion for the drug causing the ADR is acted upon. As such, any report may give an early warning to us all.

Drug safety monitoring gained worldwide attention following the thalidomide incident in the 1960s. Thalidomide was a drug given to pregnant women to prevent "morning sickness". The babies born to some of these women were badly deformed and it took a while before the link between the deformed babies and the drug was made. Once this link was

established the drug was banned and regulatory authorities all over the world became aware of the fact that seemingly safe drugs could have potentially serious adverse effects. The World Health Organization (WHO) therefore called for close monitoring of the adverse effects of all drugs. By continuous monitoring of all drugs used in Sierra Leone, it is possible to detect drugs causing unwanted ADRs and to control them. This can only be done effectively if healthcare professionals and patients report all suspected ADRs to the NPC.

OBJECTIVES

1.2

- Raise awareness on the magnitude of drug safety problems
- Convince health professionals that the reporting of ADRs is their professional and moral obligation.
- Aid health professionals in becoming vigilant in the detection and reporting ADRs and other drug induced problems.
- Promote early detection of drug safety problems in patients
- Improve selection and rational use of drugs by health professionals
- Reduce medicine induced morbidity and mortality
- Promote rational and safe use of medicines.
- Educate and inform the patients.
- Contributing to the protection of patients' and public health.
- Identification of predisposing risk factors and possible mechanisms underlying adverse reactions

- Estimation of quantitative aspects of risk benefits analysis and dissemination of information needed to improve drug prescribing, drug dispensing and drug regulation.

SCOPE OF THE GUIDELINE

1.3 This guideline provides definitions of the main terms used in pharmacovigilance, gives a broad educational overview of pharmacovigilance in general and the organisation of the Drug Safety Monitoring Programme, situated within the National Pharmacovigilance Centre (NPC) of the Pharmacy Board of Sierra Leone. It describes who can report suspected cases of ADRs to the NPC, how to report and what to report. It also explains what happens after reports are sent and the benefits of a strong pharmacovigilance system to the reporting practitioner, the patient and the nation.

1.4 REQUIREMENTS

1.4.1 HOW MEDICINE SAFETY IS ASSURED?

All drugs undergo a significant amount of testing and evaluation before marketing to ensure their effectiveness as well as safety. Marketed medicines undergo trials in animals (pre-clinical testing) and humans (clinical trials) to establish their efficacy, safety, and quality

1.4.1.1 PRE-MARKETING EVALUATION

Pre-marketing evaluation involves animal studies and clinical trials in human. Studies in two or more animal species are conducted to test whether the drugs are harmful and whether they may for instance induce cancer, damage and malformations in the unborn child etc. Once scientists are sure that a drug is safe, they start studies in human beings and these studies are known as clinical trials.

Pre-marketing clinical trials take place in three phases (I, II and III). These trials are studies on the effects of drug on humans under rigorously controlled conditions. All clinical trials will assess safety of the drug in question. A brief description of each phase of clinical trial is given below:

- **Phase I** –Single or multiple dose studies in healthy volunteers, using low doses of the drug. Subsequently, large doses and multiple sequence are evaluated.
- **Phase II** –Efficacy is the primary objective of phase II trials, but safety is also continuously monitored and evaluated.
- **Phase III**- Evaluations of efficacy and safety in large number of patients

1.4.1.2 POST-MARKETING SURVEILLANCE (PMS)

It is not possible to identify all of the safety –related problems that may exist with a new drug during pre-market testing and evaluation. PMS activity is the responsibility of regulators, pharmaceutical companies, marketing authorization holders (MAHs) and healthcare professionals in Sierra Leone and they must work together to continuously monitor the safety and quality of medicines after they have been licensed and when necessary swift and appropriate actions should be taken to protect patients.

One of the most common methods of PMS is spontaneous reporting using approved ADR reporting forms. In Sierra Leone, the NPC issues spontaneous reporting forms, which health care professionals should use to report any suspected ADRs.

1.4.2 MEDICINE ASSOCIATED PROBLEMS

1.4.2.1 THE MAGNITUDE OF THE PROBLEM

It has been demonstrated by a number of studies that medicine-induced morbidity and mortality is a major problem to which health care professionals and the general public are becoming increasingly aware. It has been estimated that ADRs are the 4th to 6th largest cause of death in the USA (1). Studies conducted in developed countries have shown that hospital admissions due to ADRs in some countries was about or more than 10% (2-4)

Norway	11.5%
France	13.0%
UK	16.0%

Even these startling figures do not represent the whole picture. These studies generally excluded ADRs caused by other drug related problems such as overdose, drug abuse, misuse, poisoning, medication errors and therapeutic failures.

In addition, treatment of ADRs imposes a high financial burden on health care. Some countries spend up to 15-20% of their hospital budget dealings with drug complications and socio-economic motive that urgently need addressed (5).

1.4.2.2 WHAT IS THE SIZE AND SEVERITY OF THE ADR PROBLEM IN SIERRA LEONE?

While no studies have comprehensively assessed the burden of ADRs on health care, it is likely that the problem is considerable in Sierra Leone. There is very limited information available on ADRs. However, the National Medicines Policy recognizes the need for a Drug Safety Monitoring Programme in Sierra Leone to deal with widespread irrational medicines use, including, preference for injections, misuse of antibiotics and other prescription

medicines, unstandardized use of orthodox and traditional/herbal medicines and extensive self-medication.

The circulation of substandard and counterfeit medicines in Sierra Leone, lack of independent information on medicines other than that from the pharmaceutical industry and the irrational use of medicines, compound the likelihood of a higher incidence of ADRs. Effective Pharmacovigilance activity will enable Sierra Leone to develop a good record keeping habit and build a useful safety information database that will improve the quality of health care offered to the patient.

1.4.3 WHY IS ADVERSE DRUG RECATION REPORTING NEEDED IN SIERRA LEONE?

1.4.3.1 HOW VOLUNTARY REPORTING OF ADRS CAN PREVENT NEW MEDICINES TRAGEDIES FROM DEVELOPING

It took many decades before the deleterious effects of **aspirin** on the gastro-intestinal tract became apparent and almost as long before it was recognized that the protracted abuse of **phenacetin** could produce renal papillary necrosis and 35 years elapsed before it became clear that **amidopyrine** could cause agranulocytosis, and several years before the association of phocomelia with **thalidomide** became obvious.

Withdrawals from the Market as a result spontaneous reporting

Generic Name (Brand Name)	Reason for withdrawal	Year of marketing	Year of withdrawal
Bromfenac (Duract)	Serious hepatotoxic effect	1997	1998
Encainide (Enkaid)	Excessive Mortality	1992	1991

Temafloxacin (Omniflox)	Hemolytic Anaemia	1992	1992
Benoxaprofen (Oraflex)	Liver Necrosis	1982	1992
Mibefradil (Posicor)	Multiple Drug Interaction	1997	1998
Terfenadine (Seldane)	Fatal Cardiac Arrhythmias	1985	1998
Over 153 Drug Products withdrawn from the Sierra Leone Market	Substandard/Poor Quality	1998	2017
Rofecoxib (Vioox)	Severe cardiovascular Events	1999	2004

1.4.3.2 HOW VOLUNTARY REPORTING ON ADRS CAN INFLUENCE LABELLING

There are many examples of the importance of ADRs reporting in the improvement of information in labelling of many effective pharmaceutical products (new possible ADRs, contraindications, dosage etc.). **Cyclophosphamide** has been on the market for several years in many countries. In January 2001 there were some new reactions included in the

labels: Stevens Johnson syndrome and toxic epidermal necrolysis; they were not included in the Physician Desk Reference (PDR) 1995.

For example:
EPIDERMAL NECROLYSIS
ERYTHEMA MULTIFORME
STEVENS JOHNSON SYNDROME
Losartan was marketed in the USA since 1995. Some of the new reactions that have been discovered after launch and included in the PDR are:
VASCULITIS
PURPURA ALLERGIC
(incl. HENOCH-SCHOENLEIN PURPURA)
ANAPHYLACTIC SHOCK ANAPHYLACTOID REACTION
Levofloxacin was launched in the USA in 1997. In February 2000 the label torsade de pointes was included.

1.4.3.3 WHY POSTMARKETING SURVEILLANCE AND REPORTING ADR IS NEEDED?

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

- ❖ Tests in animals are insufficient to predict human safety;
- ❖ 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;

❖ By the time of licensing, exposure of less than 5000 human subjects to a drug allows only the more common ADR to be detected;

❖ 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 expose individuals (6);

❖ 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. Therefore, health professionals worldwide should report on ADRs as it can save lives of their patients and others.

1.4.3.4 WHY PHARMACOVIGILANCE IS NEEDED IN EVERY COUNTRY?

The information which we receive on adverse effects of medicines in other countries may not be relevant or applicable to Sierra Leone due to various differences that may influence patient response including;

- Diseases and prescribing practices;
- Treatment seeking behavior e.g. self-medication;
- Genetics, diet, traditions of the people e.g. high carbohydrate and fat diet, kola nut consumption etc.;
- Dug manufacturing processes which influence the quality and composition;
- Drug distribution and use, including indications, dose, storage and availability of pharmaceuticals.

- The use of traditional and complementary medicines (e.g. herbal remedies) which may pose specific toxicological problems, when used alone or in combination with other medicines; and
- Racial differences.

Data derived from within the country may have greater relevance and educational value and can assist PBSL to make evidence-based decisions. Information obtained in one county (e.g. the country of origin of the medicine) may not be relevant to other parts of the world, where circumstances may differ.

It is essential that doctors, pharmacists, nurses, community health officers and other health professionals support a monitoring system for the safety of medicines in Sierra Leone in order to prevent unnecessary suffering and decrease the financial loss sustained by the patient due to ADRs and the inappropriate or unsafe use of medicines and the overall burden on the health care system and national economy.

The PBSL is committed to improving medicine safety through adverse drug reaction monitoring in Sierra Leone. The national Pharmacovigilance centre of PBSL shall make the spontaneous reporting forms available at all times. Health professionals are expected to report adverse reactions, lack of effect and other medicines problems on a daily basis as a professional moral obligation.

1.4.4 SPECIFIC RESPONSIBILITIES

1.4.4.1 Pharmacy Board of Sierra Leone

- Should establish a pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medicinal products authorised.
- Continually monitors the safety profile of the products available in Sierra Leone.
- Takes appropriate action where necessary.
- Monitors the compliance of Manufacturers and Marketing Authorisation Holders with their obligations with respect to pharmacovigilance.
- Ensures that Marketing Authorisation Holders implement, when appropriate, Risk Management Plans to effectively monitor and manage risks associated with the safety of their products
- Ensures that pharmacovigilance data are shared between stakeholders, health programmes and internationally.
- Collect and evaluate risk-benefit balance on medicinal products, monitor safety profile, take appropriate actions, monitor health care professional (HCP) and MAH.
- Have an established pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medicinal products.
- Constitute an Expert Committee on Drug Safety and Clinical Trials to carry out the safety assessment of medicinal products among others things such as providing scientific opinion for clinical trials monitoring by the Board and whose terms of reference shall be:

- ✓ The committee shall review pharmacovigilance or medicine safety information and related data on all pharmaceuticals, biologicals and other regulated products on the Sierra Leone market;
- ✓ upon request, the expert committee will make recommendations to the Board regarding actions the Board may take to resolve issues or concerns related to post-approval product safety, quality and efficacy;
- ✓ the committee will also recommend to the Board appropriate product information labelling update; recall or withdrawal products as may be necessary;
- ✓ regularly review and advise the Board on the clinical trials structure in the country and make recommendations regarding its maintenance and enhancement;
- ✓ perform causality assessment and issue reports on adverse event in relation to clinical trials and also for adverse drug reaction reports from routine clinical care;
- ✓ make recommendations to the Board regarding actions the Board may take to resolve issues or concerns related to the conduct of clinical trials including the need to halt or suspend a clinical trial;
- ✓ recommend publication of case reports, as well as its risk or benefit assessments in medical and scientific journals with prior consent of the sponsor;
- ✓ recommend educational programmes and topics for pharmacovigilance and also for investigators aimed at enhancing reporting of adverse effect or event and improving compliance with Good Clinical Practice as recommended by the

International Conference on Harmonization Guidelines and Helsinki Declaration;

- ✓ advise the Board periodically on the review of applications and guidelines for clinical trials, Good Clinical Practice and pharmacovigilance issued by the Board;
- ✓ recommend to the Board approval of clinical trials;
- ✓ evaluate final reports of clinical trials that have been approved by the Board;
- ✓ advise the Board on matters relating to Good Clinical and Laboratory Practice (GCLP) inspections; and
- ✓ perform any other functions that are supplementary to the attainment of the objectives of the Committee.

The membership of the Expert Committee should reflect areas of expertise and specialisation as the case maybe, such as:

1. General Medicine 2. Clinical Pharmacy 3. Clinical Pharmacology 4. Pharmacology/Toxicology 5. Epidemiology 6. Herbal Medicine 7. Pathology 8. Industrial Pharmacy/Quality Control/Quality Assurance 9. Biostatistics 10. Paediatrics/Child Health 11. Public Health

1.4.4.2 Patient/consumers

Patients/consumers should report any suspected ADR to PBSL, Pharmaceutical Companies, MAH, HCP as soon as possible even if they are not sure of a causal relationship. If PBSL, pharmaceutical companies and MAH receives any ADR report from a consumer, the consumer should be advised to seek medical attention from their healthcare provider. All consumer reports should however be documented as for any other type of report and

should be taken into account when overall safety assessments are made. Consumers should be encouraged to report any suspected adverse reaction within 7 days.

1.4.4.3 Healthcare professionals

Healthcare professionals are encouraged to report all adverse reactions received from consumers /patients. Spontaneous reports must be submitted within seven days to PBSL. Reports can also be sent directly to the manufacturers or MAH. During contacts with patients, attempts should be made to obtain information sufficient to ascertain the nature and seriousness of the event. Additional follow-up or medical confirmation may not be necessary for apparently non-serious and expected adverse reactions. On the other hand, if the event is serious/or unexpected, reasonable additional efforts should be made to contact the treating doctor or have the consumer provide the relevant medical documentation to allow for risk assessment and signal detection.

Health care professionals should be encouraged to be involved in active surveillance activities such as prescription event monitoring as PV is one of their key responsibilities

1.4.4.4 Local Representative or Marketing Authorization Holders

An appropriate system of safety monitoring shall be put in place by each Local Representative or Marketing Authorization Holder of registered products in order to assume responsibility and liability for products on the market and to ensure that appropriate action can be taken when necessary. In addition to spontaneous reporting for new drugs, the Local Representative or the Marketing Authorization Holder shall put in place pharmacovigilance measures to actively monitor the safety of the product in clinical practice

during the first registration life-cycle or for a period to be determined by PBSL. The Board may also request for formal post authorization safety study when necessary.

For drugs, the Local Representative or the Marketing Authorization Holder shall permanently and continuously have at his disposal an appropriately Qualified Person Responsible for Pharmacovigilance resident in Sierra Leone. **See PBSL Guideline for Requirements for selecting a QPPV for more details.**

1.4.5 GUIDE TO REPORTING

1.4.5.1 WHO SHOULD REPORT ADVERSE DRUG REACTION?

All health care professionals/workers, **including doctors, dentists, pharmacists, pharmacy technicians, nurses, community health officers, traditional medicine practitioners and other health professional**s are requested to report all suspected adverse reaction to medicines including allopathic medicines, vaccines, biotherapeutics, X-ray contrast media, medical devices, cosmetics, traditional and herbal remedies, chemical agents, nutritional agents etc. **This includes all health care institutions such as primary, secondary and tertiary healthcare facilities and public health programmes (HIV/AIDS control programme, tuberculosis and leprosy control programme, neglected tropical diseases programme, national malaria control programme, reproductive health programme, expanded programme on**

It is vital to report an ADR to the national Pharmacovigilance centre of PBSL even if you do not have all the facts or are uncertain that the medicine is definitely responsible or 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 medicine. However, collection of reports from several health workers in different parts of the country will assist in making an association between the medicine and a particular adverse reaction.

immunization etc), patients/consumers, MAH and Manufacturers.

1.4.5.2 WHAT TO REPORT

For all medicinal products the following should be reported:

- Suspected Adverse Drug Reactions (ADRs) resulting from non-prescription and prescription medicines (including biological products and radiopharmaceutical products).
- Adverse reactions resulting from herbal medicinal products and food supplements, medical devices, cosmetics and household chemical substances.
- For "new" medicines - report all suspected reactions, including minor ones
- For established or well-known medicines - report all serious or unexpected (unusual) suspected ADRs and minor ones.
- Drug abuse, drug overdose, drug interactions (drug-drug, drug-food, drug-food supplements)
- Adverse reactions occurring in a recipient of blood or blood components
- Suspected ADRs associated with drug withdrawals.
- Adverse events resulting from products used during phase IV clinical studies.
- Report ADRs in special fields of interest such as drug use in pregnancy and lactation
- Sub-standard and falsified medical products (SF products)
- What product quality problems should I report?
    - ✓ Suspected contamination
    - ✓ Questionable stability
    - ✓ Defective component

- ✓ Poor packaging or labeling
- ✓ Therapeutic failures or lack of therapeutic effect
- ✓ Expired batches

- Medication error
  - **Medication errors examples:**
    - ✓ Omissions – any prescribed dose not given
    - ✓ Wrong dose dispensed or administered – too much or too little
    - ✓ Extra dose given
    - ✓ Given wrong medicine
    - ✓ Wrong dose interval
    - ✓ Wrong administration route – administration of a medicine by a different route or in a different form from that prescribed
    - ✓ Wrong time for administration
    - ✓ Not following warning' advice when administering. Take with or after food.
    - ✓ Prescribed or administrated of a medicine to which the resident has a known allergy
    - ✓ Dispensed or administrated an expiry date medicine
    - ✓ Un-prescribed medicine — dispense or administrate authorized medicine to a patient.

  - The following are key medication error incidents one should look for during drug safety monitoring; 1) Prescribing error 2) Dispensing error 3) Medication preparation error 4) Administration error 5) Monitoring error
  - Medication error can be detected in clinical practice via the following methods;

1. ***Incident report review***: It is commonly use and is based on voluntary reporting of incidents by HCPs, patients or parents of patients.
2. ***Patient chart review***: It encompasses concurrent or retrospective medical record review including, but not limited to, medical records, discharge summaries, pharmacy data bases and laboratory data.
3. ***Direct observation***: This method consists of the administration of medicines at the patient's own bedside in order to detect any difference between what the patients receive and the medical prescription.
4. ***Intervention by Health Care Professionals***: This method is efficient for detecting medication error during the prescription process and also for intercepting errors before they affect the patient. This method is use for detecting not only medication error but also adverse drug events.
5. ***Adverse drug event trigger tools:*** The trigger tool uses an efficient sampling technique to identify potential adverse events through an audit of medical records. Each tool includes a limitted number of triggers that signal the most common types of adverse events or those that are most likely to cause serious harm. Triggers are included based on a literature review, expert opinion and testing for feasibility. When a trigger is found, the chart is reviewed to determine whether an adverse event has occurred.

All suspected ADRs should be reported even if the reporter thinks there is no causal relationship between the medicinal product and the reaction, except when the reporter is absolutely sure. All ADRs that occur in all health care institutions and public health programmes such as Malaria, HIV/AIDS, Leprosy/Tuberculosis, EPI, Neglected Tropical Diseases, Reproductive and Child Health, School Health Programme, Nutrition should be reported. Thus, all suspected adverse reactions of clinical importance should be reported.

1.4.5.3 HOW DO I REPORT AN ADR TO THE NPC OF PBSL?

1.4.5.3.1 Submitting your ADR report to PBSL

To report an ADR or other drug-related problems complete an ADR form (Appendices 1&2). ADR forms are available at all tertiary, secondary and primary healthcare facilities at central and district levels, private hospitals, surgeries, clinics, pharmacies and drug stores nationwide. Other institutions that may wish to receive reporting forms directly may indicate so. All Health Facilities should have an Institutional Contract Person(s) (ICP) for Pharmacovigilance. If you are unable to send your filled ADR form directly to the NPC at PBSL headquarters or to our Regional Offices, please give your ICP for onward submission to the Pharmacy Board of Sierra Leone. Appendix 3 give details for our regional offices.

You can download the adverse drug reaction form from our website www.pharmacyboard.gov.sl or report online by clicking the Report an adverse drug reaction on the PBSL website and submit your **report (Click or go to this link for online reporting- http://www.pharmacyboard.gov.sl/ContactUs/ReportAdverseDrugReaction.aspx)**. The National Pharmacovigilance Centre can be contacted on mobile: 025282886 or e-mail: drugsafety@pharmacyboard.gov.sl.

Applicants may use their in-house reporting forms in-house reporting forms, provided all the necessary data elements are included on the forms in a readable format and the form also complies with the CIOMS 1 format.

The form should be completed in as much details possible and returned to the address above.

Thank you for supporting the Pharmacy Board of Sierra Leone in the Drug Safety Monitoring Programme. Information provided will contribute to the improvement of drug safety and therapy in Sierra Leone.

1.4.5.3.2. Confidentiality

With respect to **confidentiality** of ADR Reports any information related to the reporter and patient must be kept strictly confidential.

1.4.5.3.3 Follow-up information

Any **follow-up information** for an ADR that has already been reported as an initial report can be sent on another ADR form or on a supplementary sheet. This can also be communicated by telephone, fax or e-mail if convenient. To match this information with the original report, indicate that it is follow-up information, the date of the original report and the report case number if known. It is very important that follow up reports are identified and linked to the original report.

1.4.5.3.4 Duplicate report

For **duplication of report**, if the Local Representative or Marketing Authorization Holder is aware that a person has reported a reaction of one of its products directly to the Board, the Local Representative or Manufacturer/ Marketing Authorization Holder should still report the adverse reaction informing PBSL that the report is a duplicate of a previous report. In such a situation, the Local Representative or Marketing Authorization Holder shall provide all the available details making appropriate references to the information provided by the initial reporter, in order to aid identification of the duplicate.

1.4.5.3.5 Information to be provided on the Reporting Form

1. Patient information:

— patient identifier (patients initial)
— age at time of event or date of birth
— gender
— weight

- Pregnancy status
- Name of Health facility

2. Suspected medication(s):

— name (INN and brand name)
— dose, frequency & route used
— Start and end dates of drug administration
— Therapeutic indication
— batch number
— expiration date
— Route of administration and details of manufacturer
— concomitant medical products and therapy dates

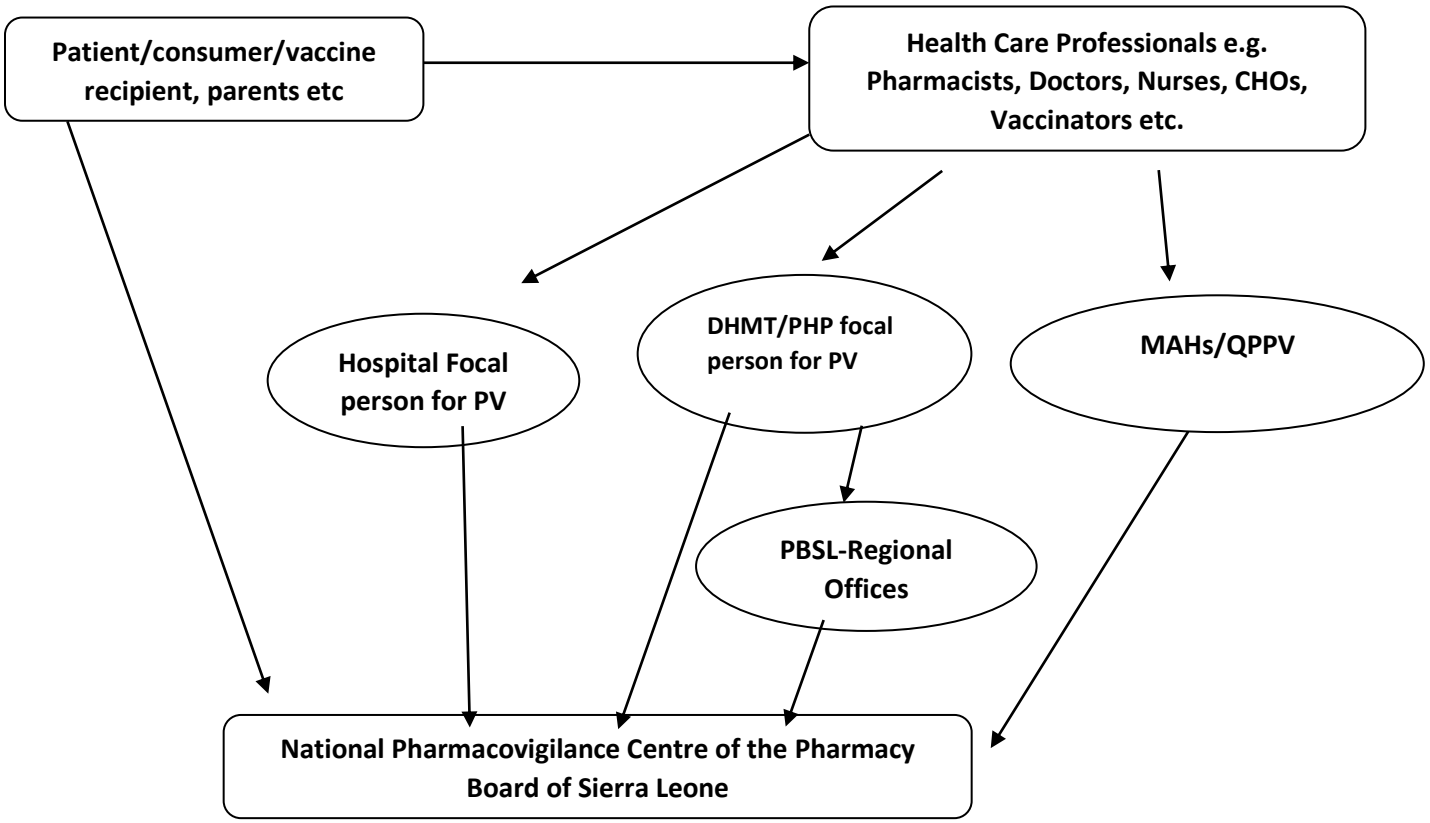
3. Adverse event or product problem:

— description of event or problem
— date of event
— date of this report
— relevant tests/laboratory data (if available)
— other relevant patient information/history
— event abated after use stopped or dose reduced
— outcomes attributed to adverse event

4. Reporter:

— name, address, email and telephone number
— specialty and occupation

1.4.5.3.6. Information flow for reporting adverse drug reaction in Sierra Leone



KEY:

CHO: Community Health Officer

DHMT: District Health Management Team

MAHs: Market Authorization Holders

PBSL: Pharmacy Board of Sierra Leone

PHP: Public Health Programme

QPPV: Qualify Person for Pharmacovigilance

PV: Pharmacovigilance

1.4.5.3.7 WHAT WILL HAPPEN TO MY ADVERSE DRUG REACTION REPORT?

The information obtained from your report shall be used to promote the safe use of medicines on a local, national and international level. Your reported case will be entered into the national adverse drug reaction database and analyzed by expert reviewers. A well-completed adverse drug reaction reporting form submitted by you could result in one or more of the followings;

- Additional investigations into the use of the medication in Sierra Leone
- Educational initiatives to improve the safe use of the medication
- Appropriate package inserts or product label changes
- Improvement on the quality of care offered to patients.
- Reduction of drug related problems leading to better treatment outcomes
- Improved patient confidence in professional practice and consequently professional growth.
- Improved knowledge.
- Access to feedback information on drug related problems reported within the country and internationally.
- 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 withdrawal

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

1.4.5.3.8 WILL REPORTING HAVE ANY NEGATIVE CONSEQUENCES ON THE HEALTH WORKER OR THE PATIENT?

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. 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. The details of your report will be stored in a confidential database in Sierra Leone and the analyzed report sent to the Uppsala Monitoring Centre (UMC)-World Health Organization Global Database.

The information obtained from your report will not be used for commercial purposes. The information is only meant to improve our understanding and use of medicines in Sierra Leone. ADR reports cannot be used in a court of law under any circumstances.

1.4.5.3.9 WHY HEALTH PROFESSIONALS ARE IN THE BEST POSITION TO DETECT AND REPORT ADRs?

The effectiveness of the Drug Safety Monitoring Programme is directly dependent on the active participation of health professionals. Health professionals are in the best position to report suspected ADRs observed in their everyday practice, because they are the people who diagnose, prescribe, dispense and monitor patients' response to medicines.

All health care providers should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the given medication.

You can reduce suffering and save thousands of patients' lives by doing just one thing:

Report suspected adverse drug reaction

1.4.5.3.10 HOW DO I RECOGNIZE ADRS IN MY PATIENT?

Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. However, the following step-wise approach may be helpful in assessing possible drug-related ADRs:

1. Ensure that the medicine ordered is the medicine received and actually taken by the patient at the dose advised;
2. Verify that the onset of the suspected ADR was after the drug was taken, not before and discuss carefully the observation made by the patient;
3. Determine the time interval between the beginning of drug treatment and the onset of the event;
4. 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.
5. Analyse the alternative causes (other than the drug) that could on their own have caused the reaction;
6. Use relevant up-to-date literature and personal experience as a health professional on drugs and their ADRs and verify if there are previous conclusive reports on this reaction.

The National Pharmacovigilance Centre and Drug Information Centres are very important resources for obtaining information on ADR. The manufacturer of the drug can also be a resource to consult;

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

In order to assess comprehensively the likelihood that the suspected adverse reaction is actually due to the medicine, the WHO-UMC has provided a list of causality assessment criteria for deciding the association of the medicine towards the adverse event.

These criteria are defined as follows:

Certain

- Clinical event, lab test abnormality with plausible time relationship to medicine intake
- Cannot be explained by concurrent disease or other medicines/ chemicals
- Response to dechallenge – positive?
- Event must be definitive pharmacologically/immunologically
- Positive rechallenge (if performed).

Probable/Likely:

- Clinical event, lab test abnormality with reasonable time relationship to medicine intake
- Unlikely to be explained by concurrent disease, medicines/chemicals
- Clinically reasonable response to withdrawal (Dechallenge)
- Rechallenge not required

Possible

- Clinical event, lab test abnormality with reasonable time relationship to medicine intake
- Could also be explained by concurrent disease or other medicines or chemicals
- Information on drug withdrawal may be lacking or unclear

Unlikely:

- Clinical event, lab test with improbable time relationship to medicine intake
- Other medicines, chemicals and underlying disease provide plausible explanations

Inaccessible/Unclassifiable:

- Insufficient/contradictory evidence, which cannot be supplemented or verified

Conditional/Unclassified:

- More data is essential for proper assessment or additional data are under examination.

1.4.6 DATA ANALYSIS

All safety information received at the NPC are subjected to benefit-risk assessment alongside causality assessment, signal management, categorisation based on severity and seriousness, preventability and predictability evaluations. Recommendations from these assessments maybe translated risk minimization actions and communicated as dear health professional letters, consumer alerts, dear investigator letter or used to inform medical

product recall, revocation of marketing authorization, update of summary of product characteristics and product labels as the case may be.

1.4.7 FEEDBACK AND REPORTING TIMELINES

1.4.7.1 FEEDBACK ON REPORTS RECEIVED

The Board shall acknowledge receipt of the adverse reaction report within 5 working days of receipt. The initial acknowledgement may be in the form of a telephone call or e-mail which may be followed by an official written acknowledgement letter. The feedback of evaluation of the adverse reaction reports shall be communicated to the reporter within 30 working days of such evaluation.

1.4.7.2 TIME OF REPORTING (TIMELINES)

Report the event soon after it occurs. A recent event is easier to report upon (i.e. less work is involved) and the report is more likely to be accurate. If possible, take the decision to report whilst the patient is still with you, so that he/she can easily be questioned (by you) about the event and all the details filled in at once on the reporting form.

Reporting by Healthcare Professionals

All serious suspected and serious unexpected adverse drug reactions associated with the use of any product in Sierra Leone should be reported to the Board within 7 calendar days. All other adverse drug reactions will be reported to the Board within a period of 28 days.

Summary of Timelines and Report Format

TYPE OF SAFETY REPORT	TIME FRAME FOR REPORTING	FORMAT
Local Reports:		PBSL Adverse Drug Reaction Reporting form (Appendix I)
Serious unexpected adverse reaction	7 days	
Serious expected adverse reaction	7 days	PBSL Adverse Drug Reaction Reporting form (Appendix I)
Non-serious expected and unexpected adverse drug reactions	28 days	PBSL Adverse Drug Reaction Reporting form (Appendix I)

1.4.6 CONFIDENTIALITY OF ADR REPORTS

Ensuring confidentiality of reports is paramount. Individual ADR reports should be kept confidential just as a patient's clinic information is kept unless otherwise required by a court of law. It is unethical to divulge patient information without their consent. Therefore, data analysis and reports on aggregate level should be unlinked to individual client's identifiers to preserve anonymity.

SECTION 2

PHARMACOVIGILANCE SYSTEM

Background

2.1 Pharmacovigilance (PV) systems are put in place to be used by the marketing authorisation holder (MAH) to fulfil the specific PV tasks and responsibilities designed to monitor the safety of marketed medicinal products and detect any change to their risk-benefit balance. The national PV centre of the Pharmacy Board of Sierra Leone is ISO 9001:2015 certified for quality management systems and likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities. For performing their pharmacovigilance activities, marketing authorisation holders, shall establish and use quality systems that are adequate and effective for this performance. By following the overall quality objectives in section 2.4.1.4 and the guiding principle in section 2.4.1.5.to meet the needs of patients, healthcare professionals and the public in relation to the safety of medicines, the application of the quality system should be adapted to how crucial each pharmacovigilance task is for fulfilling the quality objectives for each medicinal product covered by a quality system. The guidance on quality systems in this Module is consistent with the general principles of the ISO 9000 Standards on good quality management practices, specifically the ISO 9001:2015, standards on quality management systems, issued by the International Organization for Standardization (ISO). The general application of quality management to pharmacovigilance systems is described under section 2.4.1 in this guideline.

OBJECTIVE

2.2 To ensure the establishment and maintenance PV quality systems for MAHS

SCOPE

2.3 This guideline contains directions for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorisation holders.

2.4 REQUIREMENTS

2.4.1 Structures and processes

2.4.1.1 Pharmacovigilance system

A pharmacovigilance system is defined as a system used by an organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance [DIR Art 1(28d)]. A pharmacovigilance system, like any system, is characterised by its structures, processes and outcomes.

2.4.1.2 Quality, quality objectives, quality requirements and quality system

For the purpose of good pharmacovigilance practice (GVP), the quality of a pharmacovigilance system can be defined as all the characteristics of the system which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance. In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under section 2.4.1.4. Specific quality objectives and quality requirements for the

specific structures and processes of the pharmacovigilance systems are provided in the other PBSL PV guidelines as appropriate. The quality system is part of the pharmacovigilance system and consists of its own structures and processes. It shall cover organisational structure, responsibilities, procedures, processes and resources of the pharmacovigilance system as well as appropriate resource management, compliance management and record management.

2.4.1.3 Quality cycle

The quality system shall be based on all of the following activities:

- quality planning: establishing structures and planning integrated and consistent processes;
- quality adherence: carrying out tasks and responsibilities in accordance with quality requirements;
- quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; and
- quality improvements: correcting and improving the structures and processes where necessary.

2.4.1.4. Overall quality objectives for pharmacovigilance

The overall quality objectives of a pharmacovigilance system are:

- complying with the legal requirements for pharmacovigilance tasks and responsibilities;

- preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure;
- promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public; and
- contributing to the protection of patients' and public health.

2.4.1.5 Principles for good pharmacovigilance practices

With the aim of fulfilling the overall quality objectives in section 2.4.1.3., the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met.
- Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives.
- All persons within the organisation should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organisation should engage in continuous quality improvement following the quality cycle in section 2.4.1.3

- Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
- Good cooperation should be fostered between marketing authorisation holders, public health organisations, the national PV centre, patients, healthcare professionals, and other relevant bodies in accordance with the applicable legal provisions.

2.4.1.6. Responsibilities for the quality system within an organisation

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities. Their responsibility should include adherence to the principles defined in section 2.4.1.5. For the purpose of a systematic approach towards quality in accordance with the quality cycle (see section 2.4.1.3.), managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for:

- ensuring that the organisation documents the quality system as described in section 2.4.1.11;
- ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;

- ensuring that adequate resources are available and that training is provided (see section 2.4.1.7);
- ensuring that suitable and sufficient premises, facilities and equipment are available (see section 2.4.1.8);
- ensuring adequate compliance management (see section 2.4.1.9);
- ensuring adequate record management (see section 2.4.1.10);
- reviewing the pharmacovigilance system including its quality system at regular intervals in risk-based manner to verify its effectiveness (see section 2.4.1.12); and introducing corrective and preventive measures where necessary;
- ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to medicinal products within an organisation;
- identifying and investigating concerns arising within an organisation regarding suspected nonadherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- ensuring that audits are performed (see I.B.12.).

In relation to the management responsibilities described above, upper management within an organisation should provide leadership through:

- motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organisation; and

- assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

2.4.1.7. Training of personnel for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel (see section 2.4.1.6).

All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training. For marketing authorisation holders, this training shall relate to the roles and responsibilities of the personnel. Refer to PBSL Guideline for Marketing Authorisation Holders-Requirements for Qualified Person Responsible for Pharmacovigilance (QPPV)

The organisation shall keep annual training plans and records for documenting, maintaining and developing the competences of personnel. Training plans should be based on training needs assessment and should be subject to monitoring.
The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff

members of the organisation should receive and be able to seek information about what to do if they become aware of a safety concern.

There should be a process in place within the organisation to check that training results in the appropriate levels of understanding and conduct of pharmacovigilance activities for the assigned tasks and responsibilities, or to identify unmet training needs, in line with professional development plans agreed for the organisations as well as the individual staff members.

Adequate training should also be considered by the organisation for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of urgency, including business continuity (section 2.4.1.3), shall be provided by the organisation to their personnel.

2.4.1.8. Facilities and equipment for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see section 2.4.1.4.) and also be

available for business continuity .Facilities and equipment which are critical for the conduct of pharmacovigilance should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep the IT systems up-to-date accordingly.

2.4.1.9. Specific quality system procedures and processes

2.4.9.1.1 Compliance management by marketing authorisation holders

For the purpose of compliance management, marketing authorisation holders shall have specific quality system procedures and processes in place in order to ensure the following:

- the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder;
- the scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorisation or associated with occupational exposure;
- the submission of accurate and verifiable data on serious and non-serious adverse reactions to the Board within the legally required time-limits;
- the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals;

- effective communication by the marketing authorisation holder with the Board including communication on new or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisations measures, periodic safety update reports, corrective and preventive actions and post-authorisation safety studies;
- the update of product information by the marketing authorisation holder in the light of scientific knowledge;
- appropriate communication of relevant safety information to healthcare professionals and patients.

2.4.1.10. Record management

The organisation shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information. A record management system shall be put in place for all documents used for pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process. The record management system should support:

- the management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- timely access to all records;
- effective internal and external communication; and

- the retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

In addition, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports.

In this context, it should be ensured that the fundamental right to personal data protection is fully and effectively guaranteed in all pharmacovigilance activities in conformity with legal provisions. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data should be justified if identifiable personal data are processed only where necessary and only where the parties involved assess this necessity at every stage of the pharmacovigilance process. As part of a record management system, specific measures should therefore be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security and confidentiality. This should involve strict limitation of access to documents and to databases to authorised personnel respecting the medical and administrative confidentiality of the data.

There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

The record management system should be described in a record management policy.

2.4.1.11. Documentation of the quality system

All elements, requirements and provisions adopted for the quality system shall be documented in a systematic and orderly manner in the form of written policies and procedures, such as quality plans, quality manuals and quality records.

A quality plan documents the setting of quality objectives and sets out the processes to be implemented to achieve them. A procedure is a specified way to carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

In order to have a systematic approach, the organisation should define in advance:

- quality objectives specific to their organisations in accordance with the overall quality objectives provided under section 2.4.1.4 and the structure- and process-specific quality objectives; and
- methods for monitoring the effectiveness of the pharmacovigilance system (see section 2.4.1.12.).

The quality system shall be documented by:

- documents on organisational structures and assignments of tasks to personnel (see sections 2.4.1.11.1. and 2.4.11.2.);
- training plans and records (see section 2.4.1.7.);
- instructions for the compliance management processes (see section 2.4.1.9.)
- appropriate instructions on the processes to be used in case of urgency, including business continuity (see section 2.4.11.3.)];
- performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities;
- reports of quality audits and follow-up audits, including their dates and results.

Training plans and records shall be kept and made available for audit and inspection.

It is recommended that the documentation of the quality system also includes:

- the methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
- a record management policy;
- records created as a result of pharmacovigilance processes which demonstrate that key steps for the defined procedures have been taken;
- records and reports relating to the facilities and equipment including functionality checks, qualification and validation activities which demonstrate that all steps required by the applicable requirements, protocols and procedures have been taken;
- records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been

taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

2.4.1.11.1. Additional quality system documentation by marketing authorisation holders

In addition to the quality system documentation in accordance with 2.4.1.11., marketing authorisation holders shall document:

- their human resource management in the pharmacovigilance system master file (PSMF) (see Module II) ;
- job descriptions defining the duties of the managerial and supervisory staff;
- an organisational chart defining the hierarchical relationships of managerial and supervisory staff;
- instructions on critical processes (see section 2.4.1.11.3.) in the pharmacovigilance system master file (PSMF) (see Module II); and
- their record management system in the pharmacovigilance system master file (PSMF) (see Module II).

It is recommended that the documentation of the quality system additionally includes the organisational structures and assignments of tasks, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks.

2.4.1.11.2. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

- continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;
- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from the Board, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between marketing authorisation holders and the Board, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk benefit balance of products for the aim of safe and effective use of medicinal products;

- keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the Board;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

Business continuity plans should be established in a risk-based manner and should include:

- provisions for events that could severely impact on the organisation's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
- back-up systems for urgent exchange of information within an organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders and the Board.

2.4.1.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

Processes to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include:

- reviews of the systems by those responsible for management;
- audits;
- compliance monitoring;

- inspections;
- evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use in patients.

The organisation may use performance indicators to continuously monitor the good performance of pharmacovigilance activities in relation to the quality requirements.

The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system (see section 5.1.11.) at regular intervals, with the frequency and the extent of the reviews to be determined in a risk-based manner. Pre-defined programmes for the review of the system should therefore be in place. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

Risk-based audits of the quality system shall be performed at regular intervals to ensure that it complies with the requirements for the quality system, the human resource management, the compliance management, the record management and the data retention and to ensure its effectiveness. Audits of the quality system should include audit of the pharmacovigilance system which is the subject of the quality system. In relation to the pharmacovigilance system of a marketing authorisation holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent

to the management responsible for the matters audited. The report should include the results of audits of organisations or persons the marketing authorisation holder has delegated tasks to, as these are part of the marketing authorisation holder 's pharmacovigilance system.

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall be taken where necessary.

SECTION 3

PHARMACOVIGILANCE SYSTEM MASTER FILE

3.1 BACKGROUND

The Pharmacovigilance Site Master File (PSMF) shall be located either at the site in the Sierra Leone where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Sierra Leone where the qualified person responsible for pharmacovigilance operates. It is a requirement of the marketing authorisation application that summary information about the pharmacovigilance system is submitted to the Board. This Module provides detailed guidance regarding the requirements for the PSMF, including its maintenance, content and associated submissions to the Board.

3.2 OBJECTIVE

To describe the pharmacovigilance system and support/document its compliance with the requirements and to also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorisations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by the Board.

3.3 SCOPE

This guidance concerns the requirements for the PSMF and is applicable for any medicinal product authorised for use in the Sierra Leone, irrespective of the marketing authorisation procedure. The required content and management of the PSMF applies

irrespective of the organisational structure of a marketing authorisation holder, including any subcontracting or delegation of activities, or their location. The content of the PSMF should reflect global availability of safety information for medicinal products authorised in the Sierra Leone, presenting information on the pharmacovigilance system applied at global, regional and local levels.

3.4 REQUIREMENTS

3.4.1. Summary of the applicant's pharmacovigilance system

Marketing authorization holders are required to submit a summary of their pharmacovigilance system which shall be included in the marketing authorisation application and which shall include the following elements in module 1.8.1 of the dossier:

- proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance;
- the contact details of the qualified person;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the required tasks and responsibilities
- a reference to the location where the PSMF for the medicinal product is kept.

3.4.2 Location, registration and maintenance

The PSMF shall be located within Sierra Leone, either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates, irrespective of the format (paper-based or

electronic format file). At the time of marketing authorisation application, the applicant should submit the PSMF reference number.

Marketing authorisation holders shall continue to ensure that their PSMF are up-to-date, including the information about the qualified person responsible for pharmacovigilance (QPPV), name and contact details (telephone and fax numbers, postal address and email addresses). Upon a change in the QPPV or location of the PMSF information, PSMF shall be updated by the marketing authorisation holder immediately and no later than 30 working days, and to allow continuous supervision by the Board.

The required location information for the PSMF is a physical office address of the marketing authorisation holder. Where the PSMF is held in electronic form, the location stated must be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location.

3.4.3 Transfers of responsibilities for the pharmacovigilance system master file

The pharmacovigilance system may change with time. Transfer or delegation of responsibilities and activities concerning the master file should be documented and managed to ensure that the marketing authorisation holder fulfils their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the PSMF should also be notified to the QPPV in order to support their authority to make improvements to the system.

The types of changes that should be routinely and promptly notified to the QPPV are:

- Updates to the PSMF or its location that are notified to the Board;

- The addition of corrective and/or preventative actions to the PSMF (e.g. following audits and inspections). The QPPV should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance;
- Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
- Changes in arrangements for the provision of the PSMF to the Board;
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies or the addition of territories.

Any recipient QPPV should explicitly accept the following changes in writing:

- Transfer of responsibility for a pharmacovigilance system to a QPPV.

The QPPV should be in a position to ensure and to verify that the information contained in the PSMF is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility

3.4.4 The representation of pharmacovigilance systems

The PSMF, shall describe the pharmacovigilance system for one or more medicinal products of the marketing authorisation holder. For different categories of medicinal

products, the marketing authorisation holder may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate PSMF. Those files shall cumulatively cover all medicinal products of the marketing authorisation holder for which a marketing authorisation has been issued or an authorisation has been granted.

- It is anticipated that there will be circumstances where a single marketing authorisation holder or local agent may establish more than one pharmacovigilance system e.g. specific systems for particular types of products, manufacturers (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more than one marketing authorisation holder or local agents. In either case, a single and specific PSMF shall be in place to describe each system.
- A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.
- Where a pharmacovigilance system is shared by several marketing authorisation holders each marketing authorisation holder is responsible ensuring that a PSMF exists to describe the pharmacovigilance system applicable for his products. For a particular product(s) the marketing authorisation holder may delegate through written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the marketing authorisation holder is responsible. In this case the PSMF of the marketing authorisation holder may cross refer to all or part of the PSMF managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the marketing authorisation holder and the authorities. The marketing authorisation holder should be able to assure the content of the

referenced file(s) in relation to the pharmacovigilance system applicable to their product(s). Activities for maintaining the PSMF in a current and accessible state can be delegated.

- Where applicable, a list of all PSMFs held by the same marketing authorisation holder shall be provided in the annex; this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).
- When delegating any activities concerning the pharmacovigilance system and its master file, the marketing authorisation holder retains ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to the Board upon request. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions and management, as well as to govern the conduct of pharmacovigilance should be in place.
- When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own PSMFs. Accessibility of the PSMF to all the applicable marketing authorisation holder(s), and its provision to the Board should be defined in written agreements. It is vital that marketing authorisation holder(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

3.4.5 Content and structure of the pharmacovigilance system master file

The PSMF shall include documents to describe the pharmacovigilance system. The content of the PSMF should reflect the global availability of safety information for medicinal products authorised in Sierra Leone. The main principle for the structure of the content of

the PSMF is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the Annexes. It is accepted that, where no marketing authorisation (and master file) previously existed in Sierra Leone, there may be information that cannot be initially provided, for example, compliance information, however, descriptions of what will be implemented should be provided instead.

3.4.5.1 Cover page

The name of the MAH or Local Representative. The date of preparation and last update (version) and reference number.

3.4.5.2 Section 1: Administrative Information

A signed statement that the Local Representative or the Marketing Authorization Holder (MAH) has the necessary means to fulfill the tasks and responsibilities as stated in PBSL Guide for Safety Monitoring of Medicines is Sierra Leone.

3.4.5.3. Section 2- Qualified person responsible for pharmacovigilance (QPPV)

For the QPPV, contact details shall be provided in the marketing authorisation application. The information relating to the QPPV provided in the PSMF shall include:

- a description of the responsibilities and job description guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;

- curriculum vitae with the key information on the role of the qualified person responsible for pharmacovigilance, including proof of registration and certification as a QPPV in Sierra Leone;
- contact details;
- a signed contract between the Local Representative or the MAH and the QPPV
- details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance; and
- a list of tasks that have been delegated by the qualified person for pharmacovigilance shall also be included in the Annexes. This should outline the activities that are delegated and to whom, and include the access to a medically qualified person if applicable.
- The details provided in relation to the QPPV should also include:
  - ✓ the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance (including registration and certification as a QPPV in Sierra Leone).
  - ✓ The contact details supplied should include name, postal address, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorisation holder address.
  - ✓ If the QPPV is employed by a third party, even if the usual working address is an office of the marketing authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

3.4.5.4. Section 3-Organisational structure of the marketing authorisation holder

A description of the organisational structure of the marketing authorisation holder relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance departments and the relationship(s) between organisations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties.

Specifically, the PSMF shall describe:

- The organisational structure of the marketing authorisation holder(s) or local agent, showing the position of the QPPV in the organisation.
- The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation study management, and management of safety variations to product particulars.
- Diagrams showing the organizational charts will be helpful and preferred.
- Any pharmacovigilance related activities performed by third parties
- Description of co-marketing agreements and contracts of pharmacovigilance activities, if any.
- List of product(s) for which the QPPV is responsible

3.4.5.5. Section 4-Sources of safety data

- Flow diagrams and Inflow of adverse reaction reports and safety information and description of the stages involved in the processing of ICSRs including the timelines for submission to the Board should be provided.
- Outflow of safety data to regulatory authorities including the Board should also be indicated.
- For the purposes of inspection and audit of the pharmacovigilance system, sources of safety data, including but not limited to spontaneous reports, sources include data arising from study sources, including any studies, registries, surveillance or support programmes sponsored by the marketing authorisation holder through which ICSRs could be reported. MAHs should be able to produce and make available a list of such sources to support inspection, audit and QPPV oversight.

3.4.5.6. Section 5-Computerised systems and databases

- The location, functionality and operational responsibility for computerised systems and databases used to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the PSMF.
- The validation status of key aspects of computer system functionality should also be described;
  - the change control,
  - ✓ nature of testing,
  - ✓ back-up procedures and

- ✓ electronic data repositories vital to pharmacovigilance compliance should be included in summary, and
- ✓ the nature of the documentation available described.

- For paper-based systems (where an electronic system may only be used for expedited submission of ICSRs), the management of the data, and mechanisms used to assure the integrity and accessibility of the safety data, and in particular the collation of information about adverse drug reactions, should be described.

3.4.5.7. Section 6- Pharmacovigilance processes

An essential element of any pharmacovigilance system is that there are clear written procedures in place. A description of the procedural documentation available (standard operating procedures, manuals, at a global and/or National level etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the PSMF.

Details of all the current standard operating procedures relating to pharmacovigilance which are expected includes but not limited to the following;

1. Archiving and retrieval
2. Corrective and Preventive Action (CAPA) processes for pharmacovigilance
3. Causality assessment, if applicable
4. Coding of Individual Case Safety Reports (ICSRs), if applicable
5. Communication of safety concerns to patients/consumers, healthcare professionals and the Board
6. Complaint handling

7. Deviation Documentation
8. Escalation of safety issues
9. Handling of Counterfeits
10. Internal audits
11. Literature searches (scientific and lay media)
12. Management of pharmacovigilance inspections
13. Manual handling of ICSRs, if applicable
14. ICSR collection, collation, follow up, assessment and reporting
15. Scheduling, production and submission of regulatory documents (e.g. PSURs/PBRERs, RMPs), if applicable
16. Signal generation
17. SOP for SOPs
18. Training
19. Implementation of safety variations to the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL), if applicable
20. Risk management system(s) and monitoring of the outcome of risk minimisation measures

The list, which may be located in the Annexes, should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified.

3.4.5.8. Section 7-Pharmacovigilance system performance

The PSMF should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The PSMF should include a description of the monitoring methods applied and contain as a minimum:

- An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 7-day and 28-day reporting over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by competent authorities like the Board regarding the quality of ICSR reporting, PSURs or other submissions;
- An overview of the timeliness of PSUR reporting to the Board (the annex should reflect the latest figures used by the marketing authorisation holder to assess compliance);
- An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and the Board's deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to risk management plan commitments, or other obligations or conditions of marketing authorisation(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance system shall be described and explained and a list of performance indicators must be provided.

3.4.5.9. Section 8-quality system

A description of the quality management system should be provided, in terms of the structure of the organisation and the application of the quality to pharmacovigilance. This shall include:

Document and Record Control

A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents.

Procedural documents

- A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc), the applicability of the various documents at global, regional or local level within the organisation, and the controls that are applied to their accessibility, implementation and maintenance.

- . A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed must be provided.

Training

- A description of the resource management for the performance of pharmacovigilance activities: – the organisational chart giving the number of

people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organisational structure

- A summary description of the training concept, including a reference to the location training files. Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports.
- Evidence of training should be available (certificate, attendance list, training materials etc)

Auditing

- Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex of the PSMF This list should describe the date(s) (of conduct and of report), scope and completion status of audits of third parties including Local Distributors.
- The PSMF shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the criteria for major or critical findings must be indicated. The audit report must be documented within the quality system; in the PSMF it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with

the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In case corrective and preventative action plan(s) have not yet been agreed for a particular audit or finding, the PSMF should include the note required and stating that "corrective and preventative action plan(s) are to be agreed". In the annex, in the list of audits conducted, those associated with unresolved notes in the PSMF, should be identified. The note and associated corrective and preventative action(s), shall be documented in the PSMF until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified

- The addition, amendment or removal of the notes must therefore be recorded in the logbook. As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

3.4.5.10. Section 9-Annex to the PSMF

An annex to the PSMF shall contain the following documents:

- A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s);

- ✓ For marketing authorisations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs.
- ✓ Where pharmacovigilance systems are shared, all products that utilise the pharmacovigilance system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organised per MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the purpose of complying with the Board's pharmacovigilance requirements
- A list of contractual agreements covering delegated;
- A list of tasks that have been delegated by the qualified person for pharmacovigilance;
- A list of all completed audits, for a period of five years, and a list of audit schedules;
- Where applicable, a list of performance indicators;
- Where applicable, a list of other PSMFs held by the same marketing authorisation holder or local agents; This list should include the PSMF number(s), and the name of MAH of the QPPV responsible for the pharmacovigilance system used. If

the pharmacovigilance system is managed by another party that is not a marketing authorisation holder, the name of the service provider should also be included.

- Updated training materials and records of the training should be provided including assessment of the effectiveness of the training programmes
- Pharmacovigilance agreement between the MAH/Local Representative and the Local Distributor(s)
- A logbook. Other change control documentation should be included as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change.

.

SECTION 4

REQUIREMENT FOR QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE

Background

4.1 Pharmacy Board of Sierra Leone (PBSL) is mandated to ensure that manufacturer' representatives or marketing authorisation holders (MAH) have a functional pharmacovigilance system in place so that they can assume responsibility and liability for their products on the market and to ensure that appropriate actions are taken when necessary. The manufacturer representative or MAH should ensure that all information that is important to the benefit-risk ratio of a product is reported promptly to PBSL in accordance with PBSL's PV regulatory obligations.

OBJECTIVE

4.2 To provide a guide for marketing authorisation holders in selecting a qualified person responsible for pharmacovigilance (QPPV).

SCOPE

4.3 This guideline covers the roles and responsibilities of the QPPV and MAH

4.4 REQUIREMENTS

4.4.1 THE ROLES AND RESPONSIBILITIES OF THE QUALIFIED PERSON FOR PHARMACOVIGILANCE (QPPV)

4.4.1.1 Qualifications of QPPV

4.4.1.1.1 The Qualified Person for Pharmacovigilance (QPPV) shall have a degree in pharmacy, medicine, or any other science discipline deemed acceptable by the Board.

4.4.1.1.2 The Board may also accept a person with a relevant scientific discipline with at least two years minimum experience with specific job function in the area of pharmacovigilance for designation as the QPPV

4.4.1.1.3 The QPPV should have received a formal training in pharmacovigilance recognized by the Board.

4.4.1.1.4. The QPPV should have knowledge of PBSL pharmacovigilance legislation and guidelines and

other international standards for Pharmacovigilance such as ICH E2A-F

4.4.1.2 Back-up QPPV

4.4.1.2.1 With the exception of Sub-section 4.4.1.1.4, the Back-up QPPV shall meet all the requirements of a QPPV. The Back-up QPPV shall however receive training in pharmacovigilance appropriate for his/her roles. In addition to the above the QPPV and the Back-up QPPV should have knowledge on applicable Sierra Leone safety monitoring legislation and guidelines and international standards for pharmacovigilance and also demonstrate (e.g. through qualifications and training) that he/she has knowledge of the key pharmacovigilance activities performed as part of the MAH's pharmacovigilance system and how to implement them.

4,4.1.3 Re-Designation of QPPV

4.4.1.3.1. The QPPV shall be eligible for the performance of the responsibilities assigned for a period of three (3) years after successfully completing the training programme described in Section 5.1.1.3.

4.4.1.3.2 The Board shall re-designate the QPPV for another three years upon application (Refer Appendix 5) and evidence of the underlisted conditions.

4.4.1.3.3. No pending Corrective Action Plan (CAP) after a Good Pharmacovigilance Practice (GVP) Inspection.

4.4.1.3.4 Good standing in the professional body/association the QPPV belongs to (e.g. Sierra Leone Medical and Dental Council, Pharmaceutical Society of Sierra Leone etc).

4.4.1.3.5 Participation in at least one pharmacovigilance conference OR training programme relevant to patient safety OR passing a written exam related to the QPPV roles administered by the Board.

4.4.1.4 Responsibilities of QPPV

The QPPV should have oversight of the pharmacovigilance system in relation to structure and proper functioning and be in a position to ensure that all responsibilities are performed well and to ensure in particular the following system components and processes, either directly or through supervision. The QPPV should reside in Sierra Leone.

4.4.1.4.1 The QPPV should act as a point of contact for the MAH on all matters relating to pharmacovigilance and safety of marketed products including pharmacovigilance inspections. He or she should be available during PV inspections.

4.4.1.4.2 Establishment and maintenance of a system which ensures that information about all suspected adverse drug reactions/ events which are reported to the personnel of the marketing authorization holder and to the medical representatives is collected, collated and assessed for onward submission to the Board.

4.4.1.4.3 The QPPV should have access to the pharmacovigilance system master file (PSMF) (see Module IV) and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility. All PSMFs submitted shall be accompanied by a declaration to be signed by the QPPV (Refer Appendix 6). The declaration should indicate that the QPPV has read the RMP and will ensure implementation of all activities outline in the RMP.

4.4.1.4.4 Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);

4.4.1.4.5 Prepare the following documents for submission to the Board:

4.4.1.4.5.1. Adverse Drug Reaction reports/ individual case safety reports (ICSRs)

4.4.1.4.5.2. Periodic Safety Update Reports (PSURs)/Periodic Benefit-Risk Evaluation Report PBRER), when necessary

4.4.1.4.5.3. Company-sponsored pre-and post-registration safety and efficacy study reports

4.4.1.4.5.4. Risk Management Plan (RMP). All RMPs submitted shall be accompanied by a declaration

to be signed by the QPPV (Refer Appendix 7). The declaration should indicate that the QPPV has

read the RMP and will ensure implementation of all activities outline in the RMP.

4.4.1.4.5.5. Line listing

4.4.1.4.5.6. Summary report

4.4.1.4.6 Ensure that any request from the Board for additional information deemed necessary for the evaluation of the risk–benefit afforded by a marketed product, is provided to PBSL promptly and fully. Inclusive of information on sales volume or prescriptions of the medicines concerned

4.4.1.4.7 Ensure safety monitoring oversight of the marketed products and any emerging safety concerns

4.4.1.4.8. Notify the Board within fourteen (14) days from the date he/she ceases to be QPPV for the MAH.

4.4.1.4.9 Act as a contact point for the Board on a 24-hr basis

The oversight by the QPPV referred to above should cover the functioning of the MAH PV system in all relevant aspects, including quality control and assurance procedures, SOPs, database operations, contractual agreements, compliance data (e.g. with respect to the quality, completeness and timeliness for expedited reporting and submission of PSURs), audit reports and training of personnel in relation to pharmacovigilance

4.4.1.5 Timelines for reporting (See appendix 8 for summary)

Local Representative or Marketing Authorization Holder shall submit all relevant information available at the time of initial notification of an adverse drug reaction report. Details including but not limited to post-mortem reports, relevant laboratory data may be attached when necessary. The original words/description (verbatim) used by the initial reporter to describe the adverse reaction should be provided. The medicine (or trade) name must be provided as reported by the initial reporter. Additional information, not available at the time of initial report, should be provided in the form of follow-up reports. The Local Representative or Marketing Authorization Holder is required to submit the name or initials, address and telephone number and qualification of the initial reporter on the adverse drug reaction report form.

Serious adverse reaction reports received by the Local Representative or the Marketing Authorization Holder shall be submitted to the Board within 7 calendar days. In case all the information needed is not available within 7 days, the Local Representative or Marketing Authorization Holder shall submit an initial report containing at least the minimum data elements required (i.e. patient details, suspected product details, reaction details and the reporter details) in order to meet the expedited reporting time frames. A follow-up report containing more detailed information should be submitted later as soon as this becomes available.

All non-serious suspected adverse drug reactions, occurring in Sierra Leone with any medicine, must be reported by the applicant within 28 calendar days on first notification.

Local Representative or Marketing Authorization Holder is required to **search widely referenced databases (e.g. Medline, Embase)** on weekly basis and submit any case

originating from Sierra Leone on registered products to the Board. Local Representatives or Marketing Authorization Holders are also required to search local scientific and medical journals not included in widely referenced databases on scheduled basis depending on the periodicity of such journals and submit any publication identified as coming from Sierra Leone on marketed products to the Board. Publications should be accompanied by a copy of the article. If the article describes identifiable patients, adverse reaction report(s) should be completed for each patient and the publication authors considered as the primary source.

Reports from lay press should be handled as spontaneous report; every attempt should be made to collect minimum information that constitutes a valid ICSR. The same timelines apply as for spontaneous reports.

Internet or Digital media under the management of MAH shall be screened regularly for adverse reaction reports and report to the Board within the specified timelines. Reports from noncompany sponsored internet sites or social media (e.g. Facebook, WhatsApp, Twitter, Instagram etc) should be assessed to determine whether minimum reporting criteria are met and these should also be treated as spontaneous reports.

All safety information that becomes available to the Local Representative or Marketing Authorization Holder as a result of follow-up activities should also be reported within 7 calendar days.

All Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in all **post authorization safety studies in Sierra Leone of which the Local Representative or Marketing Authorization Holder is aware** and includes the design and conduct of company-sponsored Post Marketing Surveillance (PMS) Studies (i.e Phase IV clinical trials) should be reported within 7 days. However, if the **post-authorization safety study is**

conducted by an investigator independent of the Local Representative or Marketing Authorization Holder (e.g. "investigator –initiated post authorization safety study"), the responsibility for reporting adverse reactions to the Board shall rest with the investigator and not the Local Representative or Marketing Authorization Holder.

Significant safety issues identified by the Local Representative or Marketing Authorization Holder as a result of ongoing review and analysis of all information (including foreign ADR reports) that is pertinent to the safety **or benefit-risk assessment of the product or action taken by a foreign regulatory agency**, including the basis for such actions shall be reported to the Authority within 7 days.

Foreign regulatory agency decisions to be communicated to the Board include:

Any matter relating to the safety of the product, withdrawal or suspension of availability of the product, the addition of a contraindication or the modification for safety reasons of an existing contraindication, warning or precaution statement in the approved product information.

Foreign individual case safety reports should not be submitted to the Board on a routine basis, but should be reported in the context of a specific safety issue or on specific request by the Board.

The applicant should advise the Board of any action relating to safety that has been taken by a foreign agency, including the basis for such action, within seven days of first knowledge.

Marketing Authorization Holders of both innovator and generic drugs are required to submit **PSUR/PBRER** to the Board at the time of renewal of the registration of the drug**. Refer to PBSL PSUR/PBRER Guideline for more details**.

See APPENDIX 8- Summary of Timelines and Report Format for more details

4.4.2 THE RESPONSIBILITIES OF THE MAH IN RELATION TO THE QPPV

The MAH should ensure that effective and efficient pharmacovigilance systems are in place so as to assure responsibility of its products being marketed in Sierra Leone and to take appropriate action when necessary. The Marketing Authorization Holder should always and uninterruptedly have at its disposal a fittingly Qualified Person Responsible for Pharmacovigilance domicile in Sierra Leone.

4.4.2.1 Responsibilities of the MAH

The MAH should:

4.4.2.1.1 Provide support to the QPPV in order for him/her to acquire comprehensive training in pharmacovigilance.

4.4.2.1.2 Ensure that there are effective and efficient processes, resources, communication mechanisms and access to all source of relevant information in place so that QPPV will be able to fulfil his/her responsibilities and tasks.

4.4.2.1.3 Ensure that full documentation is in place covering all procedures and activities of the QPPV.

4.4.2.1.4 MAH should ensure the implementation of appropriate mechanisms for the QPPV to be kept informed of emerging safety concerns and any other information with

respect to the risk-benefit ratio. This should include information from on-going or completed clinical trials and other studies that may be important to the products marketed in Sierra Leone by the MAH.

4.4.2.1.5 Assess risks with potential impact on the PV system and plan for contingency, including back-up procedures (e.g. in case of absence of personnel, adverse drug reaction database failure, failure of other hardware or software with impact on electronic reporting and data capture and analysis).

4.4.2.1.6 Ensure that the QPPV has sufficient authority to:

4.4.2.1.6.1 Implement changes to the MAH PV systems, structure and processes so as to promote and improve compliance;

4.4.2.1.6.2 Provide input into the RMP and the preparation of regulatory action in response to emerging safety issues or concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to patient and healthcare professionals).

4.4.2.1.6.3 Notify the Board within fourteen (14) days when the QPPV ceases to be an employee of the MAH or when his/her roles and responsibilities changes

4.4.2.1.6.4 Have written a contract with the QPPV.

4.4.2.2 Information to be submitted to the Board by the MAH

The MAH shall submit the following information to the Board relating to the QPPV.

4.4.2.2.1 Curriculum vitae including key information on the role of the QPPV

4.4.2.2.2 Contact details including but not limited to the name, telephone, and e-mail, postal and official working address

4.4.2.2.3 A detailed job description

4.4.2.2.4 Term of reference

4.4.2.2.5 Standard operating procedures (SOPs) for all PV activities

4.4.2.2.6 A list of tasks that have been delegated by the qualified person for Pharmacovigilance and to whom those tasks have been delegated.

4.5 SANCTIONS

The following regulatory sanctions shall be applied to the Manufacturer Representative or Marketing Authorization Holder in the case of non-compliance to the regulations in these guidelines:

4.5.2 The Board may issue a formal warning reminding Manufacturer representative or Marketing Authorization Holder of their Pharmacovigilance regulatory obligation.

4.5.3 The non-compliant Manufacturer Representative or Marketing Authorization Holder may be placed on high risk leading to additional monitoring and retraining.

4.5.4 The Board may consider making public a list of Manufacturer Representative or Marketing Authorization Holder found to be seriously or persistently non-compliant.

4.5.5 Urgent Safety Restriction

4.5.6 Variation of the Marketing Authorization

4.5.7 Suspension of the Marketing Authorization

4.5.8 Revocation of the Marketing Authorization

4.6 PENALTIES

Non-adherence to the requirements of these guidelines by Manufacturer representatives and Marketing Authorization Holder will result in the Board imposing penal sanctions.

SECTION 5

PHARMACOVIGILANCE INSPECTIONS

Background

5.1 In order to assure that manufacturer's representative and Marketing Authorization Holders comply with Pharmacovigilance obligations within Sierra Leone and to facilitate compliance, the Pharmacy Board of Sierra Leone (PBSL) shall conduct Pharmacovigilance inspections of companies. Inspections shall be carried out by inspectors mandated by PBSL to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorisation holder or any firm employed by the marketing authorisation holder to perform their pharmacovigilance activities. The result will be used to help the manufacturer representatives and Marketing Authorization Holders to improve compliance in relation to PV.

Pharmacovigilance inspection programmes will be implemented, which will include routine inspections scheduled according to a risk-based approach and will also incorporate "for cause" inspections, which have been triggered to examine suspected non-compliance or potential risk, usually with impact on a specific product(s).

The outcome of an inspection will be provided to the manufacturer's representative or marketing authorisation holder who will be given the opportunity to comment on any non-compliance identified. Any non-compliance should also be addressed by the manufacturer's representative or marketing authorisation holder in a timely

manner through the implementation of a corrective and preventive action plan and submission of a compliance report.

Information on the conduct and outcome of Pharmacovigilance inspections and follow-up and evaluation of the consequence may be made publicly available as part of the overall transparency of Pharmacovigilance activities.

The inspection will be conducted where Pharmacovigilance activities of the Local representative of Marketing Authorization Holders is located.

OBJECTIVE

5.2 To ensure that manufacturer's representatives and Marketing Authorization Holders (MAH) comply with PBSL Pharmacovigilance requirements and to ensure compliance with these obligations, the Board shall conduct Pharmacovigilance inspections.

SCOPE

5.3 This guideline contains direction on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the Sierra Leone and outlines the role of the different parties involved.

5.4 REQUIREMENTS

5.4.1 PHARMACOVIGILANCE INSPECTIONS

5.4.1.1 Objectives of Pharmacovigilance inspections

- To assess that the manufacturer's representative or marketing authorisation holder has personnel, facilities and mechanism in place to comply with PBSL PV requirements.
- To detect and document non-compliance which may be risky to public health
- To use the inspection results to ensure that PV obligations are enforced

5.4.1.2. Types of Pharmacovigilance inspections

Pharmacovigilance inspections will be done, which will include system and product – related, routine and "for cause", pre-authorisation, post-authorisation, announced and unannounced and re-inspections.

5.4.1.2.1 System and product-related inspections

Pharmacovigilance system inspections are done to review personnel, procedures and facilities that are in place and to assess their compliance with PV regulatory obligations. Product specific examples maybe be utilized in the assessment to illustrate the proper functioning of the PV systems.

Product –related PV inspections focuses on Pharmacovigilance issue that are product-related taking into consideration documentation, product –related activities. However, some aspects of the system that's related to the product may be assessed.

5.4.1.2.2 Routine and 'for cause" Pharmacovigilance inspections

Routine Pharmacovigilance inspections are scheduled before hand as part of the Board's inspection plan and it involves no specific trigger though it is risk analysis

based. The kind of inspection is mostly system-based although one or more products can be selected to demonstrate practically the proper functioning and compliance of the system.

For cause Pharmacovigilance inspection, there is a specific trigger and an inspection is necessary to examine the issue. This inspection will primarily focus on specific PV processes or assessment that identifies compliance issues and their impact on specific product. Full system inspection may also be conducted due to the trigger. For cause inspections may arise when, for example, one or more of the triggers listed below are identified:

- Risk-benefit balance of the product:
    - Suspension or product withdrawal without notifying PBSL
    - Delays or failure to identify or communicate a risk or a change in the risk-benefit ratio
    - Communication of information on PV concerns to the public without prior notification to PBSL.
- Reporting obligation (expedited or periodic)
    - Delays or omissions in reporting
    - Poor quality or incomplete report
    - Inconsistencies between reports and other source
- Requests from PBSL
    - Failure to provide the requested information or data within the deadline specified by PBSL

- Poor quality or inadequate provision of data to fulfil request for information from PBSL

- Fulfilment of commitments:
  - Concerns about the status or fulfilment of risk management plan (RMP) commitments
  - Delays or failure to carry out specific obligation relating to the monitoring of product safety, identified at the time of the marketing authorisation.

5.4.1.2.3 Pre-authorisation PV inspections

These are inspections conducted prior to the granting of marketing authorisation (MA). This kind of inspection is done to assess existing or proposed PV system in support of the MA application. They are not mandatory but maybe requested in specific situations. Due to product –specific safety concerns, it may be prudent to examine the applicant's ability.

- To implement product specific risk-minimisation activities, or
- To manage the routine safety monitoring for the product concern (e.g.-anticipated significant increase in adverse reaction reports where compared to previous products).

5.4.1.2.4 Post-authorisation inspection

These are inspections conducted after a marketing authorisation has been granted and are intended to determine whether the manufacturer's representative or MAH has complied with its regulatory obligations as stipulated by PBSL. This kind of inspection can be either 3.2.1 or 3.2.2 as mentioned above.

5.4.1.2.5. Announced and unannounced inspections

Usually inspections are done with prior notification to the MAH to ensure the availability of relevant documentation and personnel for the inspection. However, in some instance it may be prudent to do unannounced inspections or to announce an inspection at very short notice (e.g. when the announcement could potentially compromise the goal of the inspections or when the inspections is conducted in a short time frame due to urgent safety reasons.

5.4.1.2.6. Re-inspection

These inspections are conducted on a routine basis as part of a routine inspections programme. Risk factors will be assessed in order to prioritise re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate on going compliance with PV obligations. Early re-inspections may also be warranted when the MAH filed to implement appropriate corrective and preventive actions in response to an earlier inspection.

5.4.2. The inspection Programme

The Board will perform Pharmacovigilance inspections for manufacturer's representatives and MAHs based on using a risk-based approach. This will help to focus resources to improve the protection of public health where there is a potential risk.

Factors which may affect inspection scheduling may include but not limited to the following:

5.4.2.1 number of products issued marketing authorization by the Board;

5.4.2.2 product portfolio;

5.4.2.3 failure to provide details of the Qualified Person for Pharmacovigilance to the Board;

5.4.2.4 number of product with known safety risks:

5.4.2.5 non-compliance with the Board's reporting requirements

5.4.3 Inspection process

Pharmacovigilance inspections should be well planned, coordinated, conducted and reported on, follow-up and documented in accordance with prescribed inspection procedure.

Planning: Pharmacovigilance inspections planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. In order to ensure that the inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of an inspection programme.

A preliminary notification to the manufacturer's representative or the MAH about the scheduled inspections and pertinent documents to facilitate the inspection may be requested by the Board at least 21 days to the scheduled date of inspection. The date for the inspection will be agreed with the MAH.

The Board may request for the following documents prior to the inspection. This may include but

not limited to;

5.4.3.1. Curriculum vitae, job descriptions and training records for QPPV and any other

employee the Board considers relevant.

5.4.3.2. Contract between the manufacturer's representative or the MAH and the QPPV

5.4.3.3. Organization charts/organograms (with names and job titles);

5.4.4.4. Procedural documents (e.g. Standard Operating Procedures, working instructions,

Job descriptions, terms of reference etc.);

5.4.3.5. Standard training material and presentations;

5.4.3.6. Minutes of meetings specific to Pharmacovigilance

5.4.3.7. Individual adverse reaction cases files and adverse event reports;

5.4.3.8. Recent PSURs/PBRERs for marketed products;

5.4.3.9. Contacts and agreements with third parties and list of distributors;

5.4.3.10. Sierra Leone specific RMPs for selected products when applicable;

5.4.3.11. Line listings of adverse reaction reports;

5.4.3.12 Summary report of ADR

5.4.3.13 Pharmacovigilance System Master File (PSMF) to reflect Sierra Leone's Pharmacovigilance system including but not limited to human resource for pharmacovigilance, organizational chart for pharmacovigilance, job description of the QPPV and other staff involved in pharmacovigilance, information relating to the QPPV, SOPs and other work instructions. For details refer to Module IV.

5.4.4. Conduct of inspection:

The inspection may be conducted at the MAHs location, and if a third party is involved in any Pharmacovigilance activity, their site may also be inspected by the Board. The inspection will normally commence with an opening meeting and end with a closing meeting. The MAH has the right to choose which members of staff participate in these meetings but shall include the QPPV. Reporting and follow-up Deficiencies found during the Board's Pharmacovigilance inspection are graded as follow.

Critical: A deficiency in Pharmacovigilance systems, practices or processes that could either adversely affect the rights, safety or well-being of patients or that poses a potential risk to public health or that represents a serious violation or regulatory offence of the pharmacy and Drugs Act and the applicable PBSL guidelines.

Major: A deficiency in Pharmacovigilance systems, practices or processes that could either potentially adversely affect the rights, safety or well-being of patients or that could potentially pose a risk to public health or that represents a violation of the Pharmacy and Drugs Act and the applicable PBSL guideline

Minor: A deficiency in Pharmacovigilance systems, practices or processes that would not be expected to adversely affect the rights, safety or well-being of patients. Lots of minor non-compliance may add up to a major non-compliance.

In general, preliminary findings will be communicated at the closing meeting. An inspection report is then prepared and reviewed internally to ensure consistency of classification of deficiencies prior to issue of the final report. The report is sent to the MAH, usually within 30 working days of the site visit or the date of the provision of the last document requested. It should be noticed that the factual matter contained in the inspection report relates only to those things that the inspection team sees and hears during the inspection process.

5.4.5 Responding to Findings

Following the issue of the inspection report, the manufacturer's representative or MAH is requested to respond to any deficiencies identified and to provide the Board with an appropriate corrective action plan (CAP) within 14 working days or a deadline to be determined by the Board based on the magnitude of non-compliance identified and a corrective action report (CAR) within 45 working days on receipt of PV inspection report.

The manufacturer's representative or MAH may be required to provide report and where necessary evidence of the progress and completion of the action plan. There may be re-inspections at an appropriate time to verify the progress and success of these remedial actions.

Note that, in some circumstances, the manufacturer's representative of MAH may be required to take immediate action to address a critical or major finding, for the protection of public health and safety.

5.4.6 RECORD MANAGEMENT AND ARCHIVING

All Pharmacovigilance data should be maintained in a secure area (dedicated for that purpose) and the data should be stored to ensure:

- Limited access to data
- Protection of Information
- Easy retrieval

Documents must be stored in secured cabinets that will protect them from hazards (rodents flood, fire). Pharmacovigilance data should be stored throughout the life cycle of the product.

5.4.7 REGULATORY ACTIONS AND SANCTIONS

The following regulatory sanctions shall be applied in the case of non-compliance;

Non-compliant manufacturer representative or Marketing Authorization Holder may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.

5.4.7.1 The Board may issue a formal warning remaining manufacturer's representative or Marketing Authorization Holder of their Pharmacovigilance regulatory obligations.

5.4.7.2 The non-complaint manufacturer's Representative or Marketing Authorization Holder may be placed on high risk leading to additional monitoring and retraining.

5.4.7.3 Product recalls e.g. where important safety warnings have been omitted form product information;

5.4.7.4 Deferral of application for registration of product(s) or delays in approval of new products until corrective and preventive or actions have been implemented or the addition of safely conditions to new approvals.

5.4.7.5 The Board may consider making public a list of Manufacturers representative or Marketing Authorization Holder found to be seriously or persistently non-compliant

5.4.7.6 Urgent safety Restriction

5.4.7.7 Variation of the marketing Authorization

5.4.7.8 Suspension of the Marketing Authorization

5.4.7.9 Revocation of the Marketing Authorization

5.4.7.10 Amendment or suspension of clinical trials due to product-specific safety issue

5.4.7.11 Administrative penalties, usually in the forms of fines as stipulated in the fines schedule

5.5 PENALTIES

Non-adherence to the requirements of these guidelines by manufacturer Representatives and Marking Authorization Holders and will result in the Board imposing sanctions.

SECTION

6

PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER)

Background

6.1 This Guideline defines the recommended format and content of a PBRER and provides an outline of points to be considered in its preparation and submission.

When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials. Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited.

Moreover, patients in trials are closely monitored for evidence of adverse events. In clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed (e.g., severe liver injury). These factors underlie the need for continuing analysis of relevant safety, efficacy, and effectiveness

information throughout the lifecycle of a medicinal product – promptly, as important findings occur – and periodically – to allow an overall assessment of the accumulating data.

Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

While PSUR and PBRER may be used interchangeably in this guideline, it must be understood that these documents are different. Whilst, the primary objective of the PSUR is to provide a comprehensive picture of the safety of approved medicinal products with recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the PRBER provides a greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly. For additional information on the differences between the PSUR and PBRER reference is made to ICH E2C and ICH E2C (R2) guidelines respectively. PSURs/PBRERs are generally not requested routinely for generic products, herbal medicines and homeopathic medicinal products. Under this condition, the PSUR/PBRER shall be submitted only when there is a condition in the marketing authorisation which requested for this or when requested by the Board on the basis of safety concerns.

OBJECTIVE

6.2 The main objective of this PBRER guideline is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile.

The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:

- Summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- Summarising any important new efficacy/effectiveness information that has become available during the reporting interval; Periodic Benefit-Risk;
- Examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile; and
- Where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

When appropriate, the PBRER should include proposed action(s) to optimise the benefit-risk profile. Urgent safety information should be reported through the appropriate mechanism; the PBRER is not intended to be used to provide initial notification of significant new safety information or to provide the means by which new safety concerns are detected.

SCOPE

6.3 The main focus of each PBRER guideline is the evaluation of relevant new safety information from the available data sources, placed within the context of any pertinent efficacy/effectiveness information that may have become available since the International Birth Date (IBD), the date of the first marketing approval in any country in the world, or the Development International Birth Date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. All pertinent new safety and efficacy/effectiveness information discovered during the reporting interval should be discussed in the appropriate sections of the PBRER

6.4 REQUIREMENTS

6.4.1 Format and Presentation of PBRER/PSUR

The recommended format and content of the PBRER/PSUR, including table of contents, section numbering, and content of each section, is outlined below. The full ICH Guideline E2C and E2C(R2) format should be used for all PSUR and PBRERs respectively. When no relevant information is available or a PBRER section is not applicable, this should be stated.

The recommended table of contents, including section numbering, for the PBRER is provided below:

Title Page

Executive Summary

Table of Contents

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns
    - 5.1 Cumulative Subject Exposure in Clinical Trials
    - 5.2 Cumulative and Interval Patient Exposure from Marketing Experience
6. Data in Summary Tabulations
    - 6.1 Reference Information
    - 6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials
    - 6.3 Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources
7. Summaries of Significant Findings from Clinical Trials during the Reporting Period
    - 7.1 Completed Clinical Trials
    - 7.2 Ongoing Clinical Trials
    - 7.3 Long-Term Follow-up
    - 7.4 Other Therapeutic Use of Medicinal Product
    - 7.5 New Safety Data Related to Fixed Combination Therapies
8. Findings from Non-Interventional Studies
9. Information from Other Clinical Trials and Sources

10. Non-Clinical Data
11. Literature
12. Other Periodic Reports
13. Lack of Efficacy in Controlled Clinical Trials
14. Late-Breaking Information
15. Overview of Signals: New, Ongoing, or Closed
16. Signal and Risk Evaluation
    - 16.1 Summary of Safety Concerns
    - 16.2 Signal Evaluation
    - 16.3 Evaluation of Risks and New Information
    - 16.4 Characterisation of Risks
    - 16.5 Effectiveness of Risk Minimisation (if applicable)
17. Benefit Evaluation
    - 17.1 Important Baseline Efficacy/Effectiveness Information
    - 17.2 Newly Identified information on Efficacy/Effectiveness
    - 17.3 Characterisation of Benefits
18. Integrated Benefit-Risk Analysis for Approved Indications
    - 18.1 Benefit-Risk Context - Medical Need and Important Alternatives
    - 18.2 Benefit-Risk Analysis Evaluation
19. Conclusions and Actions
20. Appendices

SEE APPENDIX 13 FOR TIMELINE FOR SUBMISSION

6.4.2 Feedback

The Board shall acknowledge receipt of the report and preliminary evaluation comments communicated to the Local Representative or the Marketing Authorization Holder within 28 days of receipt of the report

SECTION

7

RISK MANAGEMENT PLAN (RMP)

Background

7.1 The decision to approve a drug is based on it having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, during the early post marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities like the Pharmacy Board of Sierra Leone.

Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective

pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

In relation to risk management of medicinal products, the Local representative/agent or Marketing Authorization Holder is responsible for:

- Ensuring that it constantly monitors the risks of its medicinal products issued with marketing authorization in Sierra Leone in compliance with relevant PV requirements and report the results of this, as required, to the Board;
- Taking all appropriate actions to minimize the risks of the medicinal product and maximize the benefits including ensuring the accuracy of all information by the company in relation to its medicinal products, and actively updating and promptly communicating it when new information becomes available.

OBJECTIVE

7.2 To aid in planning pharmacovigilance activities, especially in preparation for the early post-marketing period of medical products not limited to new chemical entities, biotechnology-derived products, vaccines etc. The main focus of this guideline is on the Safety Specification and Pharmacovigilance Plan that might be submitted at the time of marketing authorization.

This guideline describes a method for summarising the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval.

The aim of a risk management plan (RMP) is to document the risk management system considered necessary to identify, characterise and minimise a medicinal product's important risks. To this end, the RMP shall contain the following elements:

1. the identification or characterisation of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification');
2. the planning of pharmacovigilance activities to characterise and quantify clinically relevant risks, and to identify new adverse reactions (the 'pharmacovigilance plan');
3. the planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

SCOPE

7.3 This guideline is applicable to new chemical entities, biotechnology-derived products, and vaccines, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnologically-derived product) and for established products that are to be introduced to new populations or in significant new indications or where a new major safety concern has arisen.

For products with important identified risks, important potential risks or important missing information, the Pharmacovigilance Plan should include additional actions designed to address these concerns. For products for which no special concerns have

arisen, **routine pharmacovigilance practices** as described in ICH E2E should be sufficient for post-approval safety monitoring, without the need for additional actions (e.g., safety studies).

7.4 REQUIREMENTS

7.4.1 When a Risk Management Plan (RMP) should be submitted

RMP or an update, as applicable, may need to be submitted at any time during a product's lifecycle when requested by the Board or for products considered as New Chemical Entity, the RMP should be submitted as part of an application for marketing authorization.

A Risk Management Plan should be submitted:

7.4.1.1 with an application for:

- any product containing a New Chemical Entity
- a biotechnology-derived products or similar biological medicinal product
- a generic medicinal product where the reference product has a risk management plan and a safety concern requiring additional risk minimization activities has been identified with the reference medicinal product

7.4.1.2 with an application for pediatric use marketing authorization

7.4.1.3 with an application involving a significant change in marketing approval (for example: new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication, including a new

pediatric indication) unless it has been agreed with the Board that submission of RMP is not required

7.4.1.4 with an application for new fixed-dose combination applications irrespective of how long any of the ingredient(s) in the combination has been used as single agent.

7.4.1.5 generic medicinal products where the changes compared with the reference medicinal product suggest different risks

7.4.1.6 on the request of the Board (both pre-and post-authorization)

7.4.1.7 on the initiative of Marketing Authorization Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

7.4.2 Format and content of the RMP

The RMP consists of seven parts as listed below; certain parts specifically the Safety specification are subdivided into modules so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents s (e.g.PSURs). RMP part II modules generally follow the section titles in the Safety Specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan. See Table 1

Table 1: RMP parts and modules

Part	Module	Area
Part I		Product(s) overview
Part II		Safety specification
	Module SI	Epidemiology of the indication(s) and target

		population(s)
	Module SII	Non-clinical part of the safety specification
	Module SIII	Clinical trial exposure
	Module SIV	Populations not studied in clinical trials
	Module SV	Post-authorization experience
	Module SVI	Additional requirements for safety specification not discussed in ICH-E2E (e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error)
	Module SVII	Identified and potential risks
	Module SVIII	Summary of the safety concerns
Part III		Pharmacovigilance plan
Part IV		Plans for post-authorization efficacy studies
Part V		Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)
Part VI		Summary of the risk management plan
Part VII		Annexes

For detailed description of each part of the RMP and the format acceptable to the Board, the Local representative or the Marketing Authorization Holder shall refer to read GVP Module V – Risk management systems and ICH E2E. If the RMP is submitted as part of the marketing authorization application, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document.

7.4.3 Sierra Leone Specific Annex to the EU-RMP or other RMP

The Board recommends that where an existing global or EU-RMP is submitted, Sierra Leone Specific Annex shall be included to the EU-RMP. Sierra Leone Specific Annex is needed whenever there are differences between the Sierra Leonean implementation of the RMP compared to what is proposed in the EU-RMP or the global RMP. The Sierra Leone Specific Annex should identify any differences between the EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimization activities undertaken as reflected in the content of the EU Summary of Product Characteristics (SmPC) and the proposed Sierra Leone Product Information (PI), and the reasons for the difference. This will allow the Board to assess the appropriateness of the proposed RMP in the Sierra Leone environment.

7.4.4 Purpose of the Sierra Leone Specific Annex

The Sierra Leone Specific Annex should provide local specific information that is important in assessing the 'risk' in Sierra Leone (and therefore appropriateness of

proposed plans/activities), the relevance of pharmacovigilance and risk management activities in Sierra Leone, and identify and explain the reasons for any differences with activities planned in the EU or globally.

7.4.5 Content of Sierra Leone Specific Annex

This should include:

- Differences in indications between the European Union (EU) and Sierra Leone if applicable.
- Sierra Leone specific epidemiological information on the population to be treated if available (information relating to the size of the target population or any specifics that is needed to assess the safety of the use of the product in the Sierra Leone population).
- Sierra Leone information if available, on potential for medication errors or other risks.
- Applicability of EU activities to the Sierra Leone environment if no specific Sierra Leonean data will be collected.

7.4.6 Format of Sierra Leone Specific Annex

A recommended format for the Sierra Leone Specific Annex is as below.

- Introduction - Purpose of Sierra Leone Specific Annex
- Pharmacovigilance practice –

- ✓ Routine pharmacovigilance systems in Sierra Leone and Studies referenced in the RMP
- ✓ Describe involvement of Sierra Leone and applicability of global studies to the Sierra Leonean environment, or—if not applicable or relevant to the Sierra Leonean environment—include a justification.

- Risk minimization plan –
  - ✓ Address how risk minimization activities will be implemented and evaluated in Sierra Leone. If surveys or studies are referenced in the Sierra Leone Specific Annex, copies of outlines and protocols should be provided.
  - ✓ Provide a justification if activities in the EU are not to be implemented in Sierra Leone. Indicate how and when evaluation of risk minimization activities, including educational activities, will be undertaken. Marketing Authorization Holders are responsible for showing that the measures they are using to mitigate risk are working and, if not, what actions they will take to ensure effectiveness.
- Contact person for RMP-
  - ✓ This is be the person the MAH considers responsible for the implementation of the RMP activities in Sierra Leone, and will usually be the Qualified Person for Pharmacovigilance.

All RMPs submitted shall be accompanied by a declaration signed by the QPPV (Appendix 7). The declaration should indicate that the QPPV has read the RMP and will ensure implementation of all activities outlines in the RMP.

SECTION

8

SAFETY VARIATIONS

Background

8.1 The Board may require and, if necessary, order labeling changes if it becomes aware of new safety information that should be included in the labeling of the drug.

When a pharmaceutical product or medical device is approved by the Pharmacy Board of Sierra Leone (PBSL), it must be given an appropriate label, which contains information about the use of the product or device. The label is usually a package insert that is placed inside of the product, and includes detailed information about the clinical data, proper uses or "on-label uses," risks and benefits of a particular drug or device, and other information

that the Board requires. At times, after the Board has approved a product or device, subsequent testing or data has caused companies to revise a product label to include new uses for a product that were once considered "off-label," and to advise consumers and health care practitioners of new warnings and safety issues associated with a product or device.

8.1 OBJECTIVE

To ensure good practices for documentation and management of safety variations.

8.3 SCOPE

The guideline provides direction for the implementation of variations relating to the Summary of Product Characteristics and Package Leaflets (SmPCs/PLs). Variations leading to the revision of product information Where a variation leads to the revision of the summary of product characteristics, labelling or package leaflet, this revision shall be considered as part of that variation.

8.4 REQUIREMENTS

8.4.1 WHAT IS NEW SAFETY INFORMATION?

8.4.1.1. What Does New Safety Information Mean?

Is information derived from a clinical trial, an adverse event report, a post approval study (PASS or PAES), peer-reviewed biomedical literature, data derived from the post-market surveillance; or other scientific data deemed appropriate by the Board" about:

- "A serious risk or an unexpected serious risk associated with use of a drug that the Board has become aware of (that may be based on a new analysis of existing information) since the drug was approved, or
- "The effectiveness of the approved Risk Management Plan (RMP) for the drug obtained since the last assessment of RMP."

8.4.1.2. Sources of New Safety Information

Sources of new information, include, but not limited to the following:

- Routine monitoring of Adverse Event or Vaccine Adverse Event Reporting System
- Data mining of PBSL local safety database, either through routine practice or triggered by a specific issue
- Systematic data mining of all division products
- Safety-related data in a new drug/biologics' application or investigational new drug application
- The Board's PV inspections and investigations, including postmarket adverse drug experience inspections
- Medical literature submitted by marketing authorization holders (MAHs) or external stakeholders or identified by the Board's staff
- Submissions from a MAH, including but not limited to:

  — Periodic safety update reports (PSURs)/Periodic Benefit Risk Evaluation Report (PBRER),

— Reports of preclinical, toxicological, or pharmacokinetic studies, clinical trials, or observational studies

— RMP assessments

- Communications with foreign regulatory authorities regarding post-market analysis of adverse reactions associated with drugs approved in their countries
- Meta-analyses of safety information, or new analyses of previously submitted information

Once the Board has learned about the potential for new safety information, it may derive new safety information through various means, including, but not limited to, the following:

- A new analysis of existing information
- An assessment of the risks and benefits of the drug as it pertains to a new use of the drug, a new indication for the drug, or the use of the drug in a new population
- Information on the effectiveness of a previously approved RMP obtained since the last assessment.

8.4.2 HOW WILL THE BOARD EVALUATE THE NEW SAFETY INFORMATION?

The Board through its Risk Assessment and Signal Detection Team and or its Expert Committee on Drug Safety and Clinical Trials shall evaluate information that may be new safety information that should be incorporated into a drug's labeling.

8.4.2.1 Types of Safety Labeling Changes that shall be Required by the Board

The Board expects that information that meets the standard of new safety information that should be included in labeling, thereby triggering safety labeling changes, generally will include, but is not limited to, information that would be described in new or revised language in the following sections of the prescribing information:

- BOXED WARNINGS
- CONTRAINDICATIONS
- CAUTIONS
- WARNINGS AND PRECAUTIONS
- DRUG INTERACTIONS
- ADVERSE REACTIONS

The Board expects that information that results in changes made only to the ADVERSE REACTIONS section, but does not warrant inclusion in other sections of labeling (such as WARNINGS AND PRECAUTIONS), would not normally trigger required safety labeling changes. In addition, minor revisions to risk information that is already in the labeling (e.g., updating information about the well-known risk of neutropenia in the label of a cytotoxic chemotherapy drug or updating information about the well-known risk of hypoglycemia for an antidiabetic agent) may not trigger required safety labeling changes in all circumstances. The Board also anticipates that minor editorial changes to any part of the labeling would not trigger required safety labeling changes.

8.4.3. PROCEDURES FOR SAFETY VARIATIONS

8.4.3.1. How Will MAH notify the Board of Required Safety Labeling Changes?

Changes to safety aspects of approved labelling information including Summary of Product

Characteristics (SmPC), Patient Information Leaflet (PIL) and Prescribing Information must be notified to

the Board with the sample of the new labelling information for approval before implementation.

The request for the change should be submitted with the underlisted documentation:

- Covering letter addressed to the Registrar
- Tracked and clean versions of the document indicating the section where the change(s) have been affected.
- Evidence supporting the need for the change.

8.4.3.2. How Will the Board Notify MAH of Required Safety Labeling Changes?

Once the Board has determined that there is new safety information that should be included in labeling, the Board will send a safety labeling change notification letter (notification letter) to the MAH. The MAH will be notified and required to make the safety labeling changes.

The Board will include the following information in the notification letter:

- The source from which the new safety information was derived
- A brief description of what the new safety information is about (a serious risk or an unexpected serious risk associated with the use of the drug, or the effectiveness of the RMP
- Proposed labeling changes

8.4.3.3. How Should MAHs Respond to a Notification Letter?

After receiving notification of the required safety labeling changes, the MAH must either:

- submit details of proposed labeling changes to reflect the new safety information; or
- notify the Board that it does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted (a rebuttal statement).

8.4.3.4 Feedback

- Feedback on review of the safety variation will be communicated to the MAH within 90 working days from date of receipt
- When an applicant submits a rebuttal statement, the Board's review team will conduct a preliminary review of the rebuttal statement, and determine whether the Board accepts the MAH reasons why labeling changes are not warranted or whether the rebuttal statement requires further discussion, and proceed as follows:
  - ✓ If the Board accepts the MAH reasons why labeling changes are not warranted, the Board will promptly notify the MAH within 30 days of receipt of the rebuttal statement.
  - ✓ If the Board does not accept the MAH reasons why labeling changes are not warranted, the Board will initiate a discussion with MAH begin on the date the Board receives the MAH rebuttal statement and last no more than 30 days (unless an extension is warranted).

- ✓ Within 15 calendar days of the conclusion of the 30-day discussion (and any extension period, if applicable), the Board will proceed as follows:
  - ❖ If the Board and the MAH reach consensus on the reasons why labeling changes are not needed, the Board will notify the MAH
  - ❖ If the Board does not agree with the MAH rebuttal statement and the Board and the MAH cannot reach a consensus, the Board can order the MAH to make the required labeling changes with reasons.

8.4.4 When Should New Labeling Be Available?

The Board expects that new approved labeling will be available on the MAH's Web site within 15 days of approval. In addition, approved updates to labeling will be posted on the Board's Web site.

The Board acknowledges that incorporating labeling changes into printed material included in drug shipments usually requires more time than incorporating changes to a Web site. Therefore, such changes shall be affected within six months (unless an extension is warranted) on receipt of the Board's approval for the availability of labeling changes for printed package inserts, patient package inserts and SmPC.

8.4.5 Will Safety Labeling Changes Letters Be Disclosed?

Safety labeling changes notification letters may be posted on the Board's Web site to provide rapid communication to the public of a serious safety risk

SECTION

9

SAFETY COMMUNICATION

Background

9.1 Safety communication covers different types of information on medicines, including statutory information as contained in the product information (i.e. the summary of product characteristics (SmPC), package leaflet (PL) and the labelling of the packaging) and public assessment reports.

Although some principles in this apply to all types of safety communication, the Module itself focuses on the communication of 'important new safety information', which means new information about a previously known or unknown risk of a medicine which has or could have an impact on a medicine's risk-benefit balance and its condition of use.

OBJECTIVE

9.2 Safety communication aims at:

- providing timely, evidence-based information on the safe and effective use of medicines;
- facilitating changes to healthcare practices (including self-medication practices) where necessary;
- changing attitudes, decisions and behaviours in relation to the use of medicines;

- supporting risk minimisation behaviour;
- facilitating informed decisions on the rational use of medicines.

In addition to the above effective, high-quality safety communication can support public confidence in the regulatory system.

SCOPE

9.3 This Module provides guidance to marketing authorisation holders, competent authorities on how to communicate and coordinate safety information concerning medicinal products authorised in the Sierra Leone. Communicating safety information to patients and healthcare professionals is a public health responsibility and is essential for achieving the objectives of pharmacovigilance in terms of promoting the rational, safe and effective use of medicines, preventing harm from adverse reactions, minimising risks and contributing to the protection of patients' and public health.

9.4 REQUIREMENTS

Throughout the life cycle of the medicinal product information relating to the benefit-risk profile of the product may need to be communicated to stakeholders including, regulatory authorities and marketing authorization holders, patients and healthcare

professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

All Safety Communication issued by the Local Representative or the Marketing Authorization Holders, Manufacturers shall receive prior approval from the Board. Application for approval shall include a copy of the proposed communication, the medium of distribution and the targeted audience(s).

9.4.1 Target audiences

The primary target audiences for safety communication are patients, carers and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

- As primary target audiences, healthcare professionals play an essential role in ensuring that medicines are used as effectively and safely as possible. Effective safety communication enables them to take adequate actions to minimise risks and to give clear and useful information to their patients. This ultimately promotes patient safety and confidence in the regulatory system. Both healthcare professionals in clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concern at the same time.
- Patient, consumer and healthcare professional organisations can play a role as multipliers as they can disseminate important safety information to target audiences.
- The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public

perception and it is therefore important that the media receives safety information directly from the competent authorities like the Board in addition to the information they receive from other sources.

9.4.2 Content of safety communication

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information should not include any material or statement which might constitute advertising.

Therefore, safety communication should contain:

- important new or emerging information on any authorised medicinal product which has an impact on the medicine's risk-benefit balance under any conditions of use;
- the reason for initiating safety communication clearly explained to the target audience;
- any recommendations to healthcare professionals and patients on how to deal with a safety concern;
- when applicable, a statement on the agreement between the marketing authorisation holder and the Board on the safety information provided;
- information on any proposed change to the product information (e.g. the summary of product characteristics (SmPC) or package leaflet (PL));
- a list of medical literature references, when relevant or a reference to where more detailed information can be found, and any other background information considered relevant;
- where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

9.4.3 Means of safety communication

Relevant communication tools and channels should be considered when issuing a safety communication in order to reach the target audiences and meet their expectations. Different communication tools and channels are discussed below:

9.4.3.1. Direct healthcare professional communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important safety information is delivered directly to individual healthcare professionals by a marketing authorisation holder or the Board, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. DHPCs are not replies to enquiries from healthcare professionals.

A DHPC should be disseminated in the following situations when there is a need to take immediate action or change current practice in relation to a medicinal product:

- suspension, withdrawal or revocation of a marketing authorisation for safety reasons;
- an important change to the use of a medicine due to the restriction of an indication, a new contraindication, or a change in the recommended dose due to safety reasons;
- a restriction in availability or discontinuation of a medicine with potential detrimental effects on patient care.

Other situations where dissemination of a DHPC should be considered are:

- new major warnings or precautions for use in the product information;
- new data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- new evidence that the medicinal product is not as effective as previously considered;
- new recommendations for preventing or treating adverse reactions or to avoid misuse or medication errors with the medicinal product;
- ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC should encourage close monitoring of the safety concern in clinical practice and encourage reporting, and possibly provide information on how to minimise the potential risk).

The Board may disseminate or request the marketing authorisation holder to disseminate a DHPC in any situation where it considers it necessary for the continued safe and effective use of a medicinal product.

9.4.3.2. Communication materials from competent authorities targeted at healthcare professionals

The Board can issue safety communications targeting healthcare professionals directly. These are usually published on the website of the competent authority. These communications often complement other means for communicating a safety concern (e.g. a DHPC) and are issued around the same time. They contain the Board's recommendations

and advice for risk minimisation for healthcare professionals, and provide relevant background information. Adequate links to further information can be included (e.g. links to the product information of the concerned medicinal product(s) and, whenever possible, prescription and dispensing systems).

9.4.3.3 Documents in lay language to patients and the general public

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. It can also be an additional tool that healthcare professionals can use in their communication with patients. Lay language documents shall contain the Board's recommendations and advice for risk minimisation for patients, and be accompanied by relevant background information.

Lay language documents is useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference will be made to other communication materials on the topic to direct readers to where they can find further information.

9.4.3.4. Press communication

Press communication includes press releases and press briefings which are primarily intended for journalists. The Board may send press releases directly to journalists in addition to publishing them on its website. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the Board's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system.

Press releases may also be prepared and published by marketing authorisation holders. Their press releases should make reference to the regulatory action taken by the Board. Relevant ongoing reviews should be mentioned in any communication by the marketing authorisation holder.

Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public. Reference should therefore be made to related communication materials on the topic.

9.4.3.5. Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicinal products. The Board as well as marketing authorisation holders shall ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed.

9.4.3.6. Social media and other online communications

Online safety information may also be disseminated via social media and other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised. Communication practices should take into account emerging digital communication tools used by the various target audiences.

9.4.3.7. Bulletins and newsletters

Bulletins and newsletters provide at regular intervals information about medicines and their safety and effectiveness. These tools may serve as reminders of previous communications.

9.4.3.8. Inter-National Medicines Regulatory Authority (NMRA) communication

When one NMRA takes regulatory action on a particular safety concern, other authorities like the Board may also receive enquiries or may want to communicate on the same issue.

9.4.3.9. Responding to enquiries from the public

The Board and marketing authorisation holders should have systems in place for responding to enquiries about medicines from individual members of the public. Responses should take into account the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by the Board. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

9.4.3.10. Other means of communication

In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.

9.4.2 Effectiveness of safety communication

Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Where possible, mechanisms should be introduced in order to measure the effectiveness of the safety communication.

9.1 PENALTIES

Non-adherence to the requirements of these guidelines by manufacturer Representatives and Marking Authorization Holders and will result in the Board imposing sanctions.

SECTION

10

POST AUTHORIZATION SAFETY STUDIES

Background

10.1 A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. A PASS may be interventional or non-interventional. This Module concerns both interventional and non-interventional PASS, with a main focus on non-interventional ones. It does not concern pre-clinical safety studies.

PASS can be initiated, managed or financed by a marketing authorisation holder or local representative voluntarily as well as those conducted by a third party on behalf of the Local Representative or the Marketing Authorisation Holder or pursuant to an obligation imposed by the Board.

OBJECTIVE

10.2 The objectives of PASS are:

- to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product or class of medicinal products as appropriate, and investigate risk factors, including effect modifiers;
- to evaluate the risks of a medicinal product used in a patient population for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess patterns of drug utilisation that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g. collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);
- to measure the effectiveness of a risk management measures.

SCOPE

10.3 The guideline on PASS provide general guidance for: the transparency, scientific standards and quality standards of noninterventional PASS conducted voluntarily or pursuant to the Board's PV requirements. It also describes procedures whereby the Board may impose on a marketing authorisation holder or local representative an obligation to conduct a PASS.

10.4 REQUIREMENTS

10.4.1 When a PASS may be conducted

PASS may be requested by the Board and conducted by Local Representatives or MAHs under the following conditions:

- As a condition to the granting of the marketing authorization, or after the granting of a marketing authorization if there are concerns about the risks of the authorized medicinal product.
- As part of a marketing authorization granted under exceptional circumstances.
- Required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimization activities.
- PASS conducted voluntarily by the MAH.

10.4.2 Study protocol

PASS conducted in Sierra Leone in pursuant to the Board's PV requirements and obligations shall have a written study protocol and conducted in accordance with the protocol. The study protocol should be developed by individuals with appropriate scientific background and experience and submitted to the Board for scientific and regulatory approval and to the Sierra Leone Ethics and Scientific Review Committee for ethical authorization

10.4.2.1 Format and content of the PASS

The study protocol shall follow the format described in this section.

1. **Title:** informative title including a commonly used term indicating the study design and the medicinal product, substance or medicinal product class concerned, and a sub-title with a version identifier and the date of the last version.
2. **Marketing authorisation holder:** name and address of the marketing authorisation holder.
3. **Responsible parties:** names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, and coordinating investigator A list of all collaborating institutions and investigators should be made available to the Board.
4. **Abstract:** stand-alone summary of the study protocol including the following sub-sections: – Title with subtitles including version and date of the protocol and name and affiliation of main author – Rationale and background – Research question and objectives – Study design – Population – Variables – Data sources – Study size – Data analysis – Milestones.
5. **Amendments and updates:** any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.
6. **Milestones:** table with planned dates for the following milestones: – Start of data collection – End of data collection – Study progress report(s) – Interim report(s) of study results, where applicable, in line with phases of data analyses – Final report of study results.

   Any other important timelines in the conduct of the study should be presented.

7. **Rationale and background:** short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of relevant published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.
8. **Research question and objectives:** research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.
9. **Research methods:** description of the research methods, including:

   9.1. **Study design:** overall research design and rationale for this choice.

   9.2. **Setting:** study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained. The study should be conducted in a Sierra Leonean population resident in Sierra Leone or in a study population to be determined in consultation with the Board.

   9.3. **Variables:** outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.

9.4. **Data sources:** strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported. Involvement of any expert committees to validate diagnoses should be stated.

9.5. **Study size:** any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a prespecified statistical precision.

9.6. **Data management:** data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.

9.7. **Data analysis:** the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses. The primary analyses should be clearly identified from sub-group analyses and secondary analyses.

9.8. **Quality control:** description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

9.9. **Limitations of the research methods:** any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalisability, and random error. The likely success of efforts taken to reduce errors should be discussed.

10. **Protection of human subjects:** safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in postauthorisation safety studies.
11. **Management and reporting of adverse events/adverse reactions:** procedures for the collection, management and reporting of individual cases of suspected adverse reactions and of other medically important events that might influence the evaluation of the risk-benefit balance of the product while the study is being conducted.
12. **Plans for disseminating and communicating study results,** including any plans for submission of progress reports and final reports.
13. **References.** All references cited in the study must be provided in a list. Also n annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

10.4.2.2 Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes and submitted to the Sierra Leone Ethics and Scientific Committee for ethics clearance and to the Board for regulatory authorisation.

If such amendments are necessary to protect the life of subjects, an urgent amendment may be carried out but the investigator shall inform the Sierra Leone Ethics and Scientific Review Committee and the Board of such amendments with an immediate phone call, followed by a written report within forty-eight (48) hours.

Reports of all amendments shall include but not be limited to the following:

- ✓ Reasons for the amendments.
- ✓ Possible consequences for subjects already included in the study.
- ✓ Possible consequences for the evaluation of the report.
- ✓ All amendment shall attract a fee which shall be determined by the Board as stipulated in the Board's fee schedule

10.4.3 Reporting of pharmacovigilance data to the Board

10.4.3.1. Data relevant to the risk-benefit balance of the product

The marketing authorisation holder and local representaive shall monitor the data generated while the study is being conducted and consider their implications for the risk-

benefit balance of the medicinal product concerned. Any new information that may affect the risk-benefit balance of the medicinal product shall be communicated immediately via email and in writing within 7 days to the Board. Information affecting the risk-benefit balance of the medicinal product may include an analysis of adverse reactions and aggregated data. This communication is without prejudice of the information on the findings of studies which should be provided by means of periodic safety update reports (PSURs and in the RMP updates where applicable.

10.4.3.2. Reporting of adverse reactions/adverse events

Individual cases of suspected adverse reactions should be reported to the Board. Adverse events/adverse reactions collected in studies with primary data collection should be recorded and summarised in the interim safety analysis and in the final study report. Adverse events/adverse reactions collected in studies with secondary data collection should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification.

Procedures for the collection, management (including a review by the marketing authorisation holder if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol Reporting can be done using the adverse reaction reporting form which can be obtained from the Board's office or applicants may use their in-house reporting forms, provided all the necessary data elements included on the forms are in a readable format and the form also complies with the CIOMS 1 format.

10.4.4. Study reports

10.4.4.1. Progress report and interim report of study results

The progress report is meant to include relevant information to document the progress of the study, for example, the number of patients who have entered the study, the number of exposed patients or the number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report should be submitted in the Format approved by the Board (please refer to appendix I). Progress report should be submitted within 21 days after the end of the preceding quarter. The quarter starts from the study start date.

The progress report may include an interim report of study results. The interim report of study results is meant to include results of any planned interim analysis of study data before or after the end of data collection and shall be submitted upon request by the Board

10.4.4.2. Final study report

The final study report should be submitted to the Board no later than 12 months after the end of data collection. If a study is discontinued, the MAH should inform the Board with reasons for the termination within 10 days and a final report should be submitted no later than 90 days. The final study report should contain information in the format prescribed in the Guideline on Good Vigilance Practices (GVP), Module VIII – Post-Authorization Safety Studies- VIII.B.4.3.2. Final study report (Rev 3).

Where the result of the PASS affects the risk management system or the marketing authorization status of the medicinal product, this shall be communicated to the Board and steps to incorporate these changes in the RMP and variation to the marketing authorization described.

The Board may also request variation to the risk management system or the marketing authorization after review of the PASS study report. If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

10.4.5 Publication of study results

For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

10.4.5.1. Submission of manuscripts accepted for publication

In order to allow the Board to review in advance the results and interpretations to be published, the marketing authorisation holder initiating, managing or financing a PASS should communicate to the Board the final manuscript of the article within two weeks after first acceptance for publication.

10.4.6. Data protection

Marketing authorisation holders and investigators shall follow relevant national legislation and guidance of Sierra Leone.

All study information shall be handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

10.4.7. Quality systems, audits and inspections

The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the marketing authorisation holder shall ensure that the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. For PASS required in the risk management plan or conducted voluntarily in Sierra Leone, record management and data retention shall follow the Board's requirements.

SECTION

11

POST AUTHORIZATION EFFICACY STUDIES

Background

11.1 Post-authorization efficacy studies take place after marketing authorization is granted and the medicine is in general use. The granting and maintenance of a marketing authorisation (MA) is dependent on data generated to that point in time supporting a positive benefit-risk within the therapeutic indication and terms of the MA as laid out in the Summary of Product Characteristics (SmPC). In general, to

support a positive benefit-risk in an indication at the time of the initial MA, demonstration of benefit is required from pivotal, almost invariably randomised, trials that are appropriately designed and conducted in accordance with applicable guidance.

PAES of medicinal products are studies subsequently conducted within the authorised therapeutic indication to address well-reasoned scientific uncertainties identified on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation.

A PAES may, therefore, be needed at the time of the initial MA or the extension of an existing MA where there is a well-reasoned scientific uncertainty on an aspect of the established therapeutic efficacy and the resolution of this uncertainty is important for further understanding this aspect of benefit-risk. The uncertainty should also be such that it may be addressed post-authorisation by a study that can be designed and conducted to give interpretable results with the potential to impact on the MA status or product labelling.

There may be circumstances where important uncertainties concerning a product's benefits become relevant in the context of such a post-marketing benefit-risk evaluation particularly where knowledge of the safety or benefit-risk profile has changed significantly since first MA. In such circumstances a PAES may be considered.

A PAES may also be needed if an improved understanding of the disease or the pharmacology of a medicinal product has brought into question the criteria used to establish the efficacy of the medicinal product at the time of the initial MA.

The need for a PAES may therefore be seen as in keeping with the concept of life-cycle product benefit-risk profiling and monitoring through targeted research that translates into better labelling and better use of medicines.

The Board requests such studies when there are important questions about the efficacy of the medicine that can only be answered once the product is in general use, or when questions arise in the post-authorisation period.

OBJECTIVE

11.2 To address well-reasoned scientific uncertainties identified on aspects of the evidence of benefits that should be, or can only be, addressed post-authorisation.

SCOPE

11.3 The intention is to provide scientific guidance for MAHs on PAES in the context of decision-making with regard to the general need for such studies and general methodological considerations.

11.4 REQUIREMENTS

11.4.1 When a PAES may be conducted

PAES may be initiated by the MAH or requested by the Board. Conditions under which PAES are conducted by Local Representatives or MAHs under the conditions listed below:

1. An initial efficacy assessment based on surrogate endpoints requires verification.
2. In the case of medicinal products used in combination with other medicinal products, there may be a need for further efficacy data to clarify uncertainties
3. Uncertainties with respect to the efficacy of a medicinal product in certain subpopulations that could not be resolved prior to marketing authorisation.
4. A change in the understanding of the standard of care for a disease or the pharmacology of a medicinal product.
5. The potential lack of efficacy in the long term that raises concerns with respect to the maintenance of a positive benefit-risk balance of the medicinal product.
6. New concrete and objective scientific factors that may constitute a basis for finding that previous efficacy evaluations may need to be significantly revised.

11.4.2 Study protocol

PAES conducted in Sierra Leone in pursuant to the Board's PV requirements and obligations shall have a written study protocol and conducted in accordance with the protocol. The study protocol should be developed by individuals with appropriate scientific background and experience and submitted to the Board for scientific and regulatory approval and to the Sierra Leone Ethics and Scientific Review Committee for ethical authorization

11.4.2.1 Format and content of the PAES

The study protocol shall follow the format described in this section.

14. **Title:** informative title including a commonly used term indicating the study design and the medicinal product, substance or medicinal product class concerned, and a sub-title with a version identifier and the date of the last version.
15. **Marketing authorisation holder:** name and address of the marketing authorisation holder.
16. **Responsible parties:** names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, and coordinating investigator A list of all collaborating institutions and investigators should be made available to the Board.
17. **Abstract:** stand-alone summary of the study protocol including the following sub-sections: – Title with subtitles including version and date of the protocol and name and affiliation of main author – Rationale and background – Research question and objectives – Study design – Population – Variables – Data sources – Study size – Data analysis – Milestones.
18. **Amendments and updates:** any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.
19. **Milestones:** table with planned dates for the following milestones: – Start of data collection – End of data collection – Study progress report(s) – Interim report(s) of study results, where applicable, in line with phases of data analyses – Final report of study results.

    Any other important timelines in the conduct of the study should be presented.

20. **Rationale and background:** short description of the need at the time of the initial MA or the extension of an existing MA where there is a well-reasoned scientific uncertainty on an aspect of the established therapeutic efficacy and the resolution of this uncertainty is important for further understanding this aspect of benefit-risk and short critical review of relevant published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.
21. **Research question and objectives:** research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.
22. **Research methods:** description of the research methods, including:

    9.1. **Study design:** overall research design and rationale for this choice.

    9.2. **Setting:** study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained. The study should be conducted in a Sierra Leonean population resident in Sierra Leone or in a study population to be determined in consultation with the Board.

9.3. **Variables:** outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.

9.4. **Data sources:** strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers.

9.5. **Study size:** any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a prespecified statistical precision.

9.6. **Data management:** data management and statistical programmes to be used in the study, including procedures for data collection, retrieval and preparation.

9.7. **Data analysis:** the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorise, analyse and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses. The primary analyses should be clearly identified from sub-group analyses and secondary analyses.

9.8. **Quality control:** description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programmes. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

9.9. **Limitations of the research methods:** any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalisability, and random error. The likely success of efforts taken to reduce errors should be discussed.

23. **Protection of human subjects:** safeguards in order to comply with national requirements for ensuring the well-being and rights of participants in postauthorisation safety studies.
24. **Management and reporting of adverse events/adverse reactions:** procedures for the collection, management and reporting of individual cases of suspected adverse reactions and of other medically important events that might influence the evaluation of the risk-benefit balance of the product while the study is being conducted.
25. **Plans for disseminating and communicating study results,** including any plans for submission of progress reports and final reports.
26. **References.** All references cited in the study must be provided in a list. Also, n annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

11.4.2.2 Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the

changes and submitted to the Sierra Leone Ethics and Scientific Committee for ethics clearance and to the Board for regulatory authorisation.

If such amendments are necessary to protect the life of subjects, an urgent amendment may be carried out but the investigator shall inform the Sierra Leone Ethics and Scientific Review Committee and the Board of such amendments with an immediate phone call, followed by a written report within forty-eight (48) hours.

Reports of all amendments shall include but not be limited to the following:

- ✓ Reasons for the amendments.
- ✓ Possible consequences for subjects already included in the study.
- ✓ Possible consequences for the evaluation of the report.
- ✓ All amendment shall attract a fee which shall be determined by the Board as stipulated in the Board's fee schedule

11.4.3 Reporting of pharmacovigilance data to the Board

11.4.3.1. Data relevant to the risk-benefit balance of the product

The marketing authorisation holder and local representaive shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned. Any new information that may affect the risk-benefit balance of the medicinal product shall be communicated immediately via email and in writing within 7 days to the Board. Information affecting the risk-benefit balance of the medicinal product may include an analysis of adverse reactions and aggregated data.

11.4.3.2. Reporting of adverse reactions/adverse events

Individual cases of suspected adverse reactions should be reported to the Board. Adverse events/adverse reactions collected in studies with primary data collection should be recorded and summarised in the interim safety analysis and in the final study report. Adverse events/adverse reactions collected in studies with secondary data collection should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification.

Procedures for the collection, management (including a review by the marketing authorisation holder if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol Reporting can be done using the adverse reaction reporting form which can be obtained from the Board's office or applicants may use their in-house reporting forms, provided all the necessary data elements included on the forms are in a readable format and the form also complies with the CIOMS 1 format.

11.4.3.3. Study reports

11.4. 3.3.1. Progress report and interim report of study results

The progress report is meant to include relevant information to document the progress of the study, for example, the number of patients who have entered the study, the number of exposed patients or the number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report should be submitted in the Format approved by the Board (please refer to appendix 11). Progress report should be

submitted within 21 days after the end of the preceding quarter. The quarter starts from the study start date.

The progress report may include an interim report of study results. The interim report of study results is meant to include results of any planned interim analysis of study data before or after the end of data collection and shall be submitted upon request by the Board

11.4.3.3.2. Final study report

The final study report should be submitted to the Board no later than 12 months after the end of data collection. If a study is discontinued, the MAH should inform the Board with reasons for the termination within 10 days and a final report should be submitted no later than 90 days. The final study report should contain information in the format prescribed in the Guideline on Good Vigilance Practices (GVP), Module VIII – Post-Authorization Safety Studies- VIII.B.4.3.2. Final study report (Rev 3).

Where the result of the PAES affects the risk management system or the marketing authorization status of the medicinal product, this shall be communicated to the Board and steps to incorporate these changes in the RMP and variation to the marketing authorization described.

11.4.4. Publication of study results

For studies that are fully or partially conducted by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder and the investigator

should agree in advance on a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The marketing authorisation holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

11.4.4.1. Submission of manuscripts accepted for publication

In order to allow the Board to review in advance the results and interpretations to be published, the marketing authorisation holder initiating, managing or financing a PAES should communicate to the Board the final manuscript of the article within two weeks after first acceptance for publication.

11.4.5. Data protection

Marketing authorisation holders and investigators shall follow relevant national legislation and guidance of Sierra Leone.

All study information shall be handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

11.4.6. Quality systems, audits and inspections

The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified.

	Title: A GUIDE FOR SAFETY MONITORING OF MEDICINES IN SIERRA LEONE	
Rev No: 01	**Doc No: PBSL/GL/004**	Version no. 02
Issue date: 15 Feb 2021	**Effective date: 17 Feb 2021**	Approved by: Registrar

SECTION

12

DEVELOPMENT SAFETY UPDATE REPORT (DSUR)

Background

12.1 The Development Safety Update Report (DSUR) is a standard for periodic reporting on drugs under development (including marketed drugs that are under further study) in Sierra Leone and it should be submitted annually.

During the clinical development of an investigational drug, periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subjects. It is also important to inform regulators (the Board) and other interested parties (e.g., Sierra Leone Ethics and Scientific Review Committee) at regular intervals about the results of such analyses and the evolving safety profile of an investigational drug, and apprise them of actions proposed or being taken to address safety concerns. However, significant differences in the content, format and timing of these reports highlight the importance of a common standard report in promoting consistency and enhancing efficiency.

A DSUR should be concise and provide information to assure regulators that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug. All safety issues discovered during the reporting period should be discussed in the text of the DSUR; however, it should not be used to provide the initial notification of significant new safety information or provide the means by which new safety issues are detected.

12.2 OBJECTIVE

The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by:

(1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug's safety;

(2) describing new safety issues that could have an impact on the protection of clinical trial subjects;

(3) summarising the current understanding and management of identified and potential risks; and

(4) providing an update on the status of the clinical investigation/development programme and study results.

12.3 SCOPE

The main focus of the DSUR is data and findings from interventional clinical trials (hereafter referred to as "clinical trials") of drugs and biologicals that are under investigation, whether or not they have a marketing approval. Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies should also be included in the DSUR.

The DSUR should concentrate primarily on the investigational drug, providing information on comparators only where relevant to the safety of trial subjects. The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:

- Clinical trials using an investigational drug (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials [Phase I – III]);
- Clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase IV));
- Therapeutic use of an investigational drug (e.g., expanded access programmes, compassionate and monitored compassionate use programmes, particular patient use, single patient INDs, and treatment INDs); and
- Clinical trials conducted to support changes in the manufacturing process of medicinal products.

The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from:

- Observational or epidemiological studies;
- Non-clinical studies (toxicological and in vitro studies);
- Related DSURs, if applicable to the investigational drug;
- Manufacturing or microbiological changes;
- Studies recently published in the literature;
- Clinical trials with results indicating lack of efficacy that could have a direct impact on subject safety (e.g., worsening of the underlying condition if the indication is serious or life-threatening);
- Any other source of relevant safety findings for products in the same therapeutic class;
- Clinical trials conducted by a co-development partner, if permitted by the contractual agreement.

12.4 REQUIREMENTS

12.4.1 Format and Presentation of DSUR

12.4.1.1 Format

The recommended format and content of the DSUR, including table of contents, section numbering, and content of each section, is outlined below. The full ICH Guideline E2F format should be used for all DSUR. For each heading where information is available, the information should be presented concisely; when no information is available or a DSUR section is not applicable, this should be stated. If a sponsor intends to submit a DSUR in

eCTD format, the sponsor should consult with the Board regarding the appropriate placement of the DSUR in the eCTD structure.

12.4.1.2 Presentation

The recommended table of contents, including section numbering, for the DSUR is provided below:

Title Page

Executive Summary

Table of Contents

1. Introduction

2. Worldwide Marketing Approval Status

3. Actions Taken in the Reporting Period for Safety Reasons

4. Changes to Reference Safety Information

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

6. Estimated Cumulative Exposure

    6.1 Cumulative Subject Exposure in the Development Programme

    6.2 Patient Exposure from Marketing Experience

7. Data in Line Listings and Summary Tabulations

    7.1 Reference Information

SEE APPENDIX 12 FOR TIMELINE FOR SUBMISSION OF DSUR

SECTION

13

RECOGNITION OR RELIANCE ON PHARMACOVIGILANCE DECISIONS OR SCIENTIFIC OPINION FROM OTHER NRAS, REGIONAL AND INTERNATIONAL BODIES

13.1 BACKGROUND

To ensure safety of regulated medical products, PBSL will implement alternative /non-routine pharmacovigilance pathways - to the standard approval pathways - especially for

products whose safety has been evaluated by well-resourced regulatory authorities. The instituted alternative pathways are designed to facilitate conducting pharmacovigilance reviews and evaluations in a timely manner and at the same time, accelerate the evaluation process without compromising the safety and effectiveness of the medical products. Further, it focuses on risk-based evaluations, concentrating on what is locally critical (i.e., value-added in terms of resource/time investment) versus what can be leveraged/relied upon from decisions made by a well-resourced NRA that operates within the ICH region and other reference bodies. The activity is achieved in a variety of ways, including information and/or work-sharing and reliance (partly or fully) on dossier assessment reports, and particularly the risk management plan (RMP)/Pharmacovigilance plans. Other scientific decisions that PBSL can relies on may include but not limited to assessment reports on PBRER/PSUR, DSUR etc. Furthermore, PBSL may also relies on signal information from well-resources NRA and also from scientific bodies such as the Uppsala Monitoring Centre (UMC). The PBSL perception of reliance implies that the work done is submitted by an applicant or MAH in the case of marketing authorization or product registration or shared by the well-resourced NRA (e.g., through assessment reports, pharmacovigilance inspection reports, etc...), while PBSL uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities

Note: PBSL shall activate the reliance pathway to facilitate regulatory decisions either on a case-by-case basis.

13.2 OBJECTIVE

To facilitate and expedite the evaluation of safety and effectiveness of medical products such as medicines and vaccines that has been evaluated by a well-resourced NRA while retaining the PBSL regulatory responsibilities and decision making

13.3 SCOPE

The policy guideline shall be applicable to all medical products for human use, veterinary drugs, biological products and medical devices.

13.4 REQUIREMENTS

This will be permitted and considered by the Agency, when a product has been registered by the underlisted countries and together with their pharmacovigilance decision or scientific opinions:

(i) ICH founding regulatory members
(ii) ICH standing regulatory members
(iii) ICH regulatory members
(iv) ICH legislative and administrative authorities
(v) the African Vaccine Regulatory Forum (AVAREF) at a joint review meeting facilitated by the World Health Organization with the provision of a favourable scientific opinion.
(vi) WHO collaborative registration pathways (CRP) such as EUAL or PQ.
(vii) Any other regulatory decision deemed appropriate by the Board

13.5 Reliance Procedure

13.5.1 Verification

The PBSL shall 'verify' that the product intended to be imported and distributed in Sierra Leone or has been duly registered or authorised respectively by a well-resourced NRA. The application (product dossier including the RMP and other relevant documents) should be identical to that submitted, evaluated and approved by the well-resourced or reference NRA. Notwithstanding, the FDA reserves the right to subject all submissions for approval to an 'abridged' evaluation of a certain part of the application (e.g., relevant to use under local condition) such as product quality data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.

REFERENCES

1. Lazarou J.et al., 198. Incidence of ADR in hospitalization patients: A meta-analysis of prospective studied. JMA, 1998, 279 (15) 1000-5.
2. Moore N. et al., 1998, Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol. 1998, 45 (3) 301 308.
3. Imbs J.L et al., Iatrogenic medication: estimation of its prevalence in French public hospital, therapie, 1999, 54 (1)21-27
4. Griffins G.P., Th evaluation of human medicines control from a national to an international perspective AD Drug React Toxico rev., 1998, 17 (1), 19-50
5. White T et al., Counting the cost of drug-related adverse events Pharmacovigilance, 1999, 15 (5), 455-458

6. European Medicine Agency 2012. Guidelines on Good Pharmacovigilance Practices (GVP)-Module I-Pharmacovigilance Systems (Rev1).

7. European Medicine Agency 2016. Scientific Guidance on Post authorisation efficacy studies.

8. European Medicine Agency 2017. Guidelines on Good Pharmacovigilance Practices (GVP)-Module XV-Safety Communication (Rev1).

9. European Medicine Agency 2017. Guidelines on Good Pharmacovigilance Practices (GVP)-Module III- Post authorisation safety studies (Rev3).

5. Food and Drug Authority Ghana 2013. Guidelines for conducting Pharmacovigilance inspections.

6. Food and Drug Authority Ghana 2019 Guidelines for safety monitoring of medicinal products

7. International Conference on Harmonisation (ICH) Guideline. ICH E2F. Development Safety Update Report

8. International Conference on Harmonisation (ICH) Guideline. ICH E2C and E2C (R2).

9. Medicines Control Council of South African 2014. Reporting of post-marketing adverse drug reactions to human medicinal products in South Africa

10. United States Food and Drug Administration 2013. Guidance for Industry. Safety Labelling Changes.

11. *Reporting of post-marketing adverse drug reactions to human medicinal products in South Africa*. Medicines Control council, South Africa, 2014.

12. *Guidelines for Reporting Adverse Reaction*. Food and Drug Administration, Sierra Leone,2016.

13. Safety of Medicines in Sierra Leone A Guide for detecting and reporting adverse drug reactions Why Health professionals need to Act. Pharmacy Board of Sierra Leone, 2005.

ANNEXES

APPENDIX 1: ADR form for Health Care Professional

Ministry of Health and Sanitation

☐ **Adverse Drug Reaction Initial Report**

☐ **Products Quality Defect Follow –up Report**

☐ **Medication Error**

Suspected Adverse Drug Reaction/Medication Error Reporting Form

	Title: A GUIDE FOR SAFETY MONITORING OF MEDICINES IN SIERRA LEONE	
Rev No: 01	**Doc No: PBSL/GL/004**	Version no. 02
Issue date: 15 Feb 2021	**Effective date: 17 Feb 2021**	Approved by: Registrar

1.PATIENT DETAILS		
*Patient's initials		Address:
*Sex:	*Age(months/years):	Weight: (kg)
Height:(cm)		
Health		Facility:
Inpatient/Outpatient No:		
Pregnancy Status: ☐	1st Trim☐ster ☐	2nd Trimester 3rd
Trimester		
2. DETAILS OF DRUGS		
*Brand Name of Drug	*Generic Name:	Batch No.
Man. Date: Expiry date		
*Strength:	*Dose:	*Start date:
End date:		
Therapeutic indication:		Route of
administration:		
Name and Address of Manufacturer:		
Drugs taken concomitantly /in the last 3 months prior to the reaction (include OTCs and herbals). ***use rear side of this form/separate sheet for additional drugs***		

Brand or Generic Name	**Daily dose**	**Route of Administration**	**Date started**	**Date Stopped**	**Therapeutic indication**

3. DETAILS OF ADVERSE EVENTS/MEDICATION ERROR (use separate sheet if necessary)

*Description of reaction/ medication error:

*Date/time reaction/incident started	Date/time reaction/incident stopped	**Treatment of Reaction**:…… …….. ……
If patient was hospitalized what is the duration of admission (hours/days):…… ……	**ACTION TAKEN** ☐ Drug withdrawn ☐ Dose Increased ☐ Dose Reduced ☐ Dose not changed ☐ Unknown	**OUTCOME OF REACTION If reaction/error is serious, What was the outcome:** ☐ ☐ ☐ Recovering/Resolving. Death Other (specfiy) ☐ Recovered/resolved

		Disability ☐ Recovered with sequelae Life – threatening ☐ Not ☐ recovered Hospitalization ☐ Congenital abnormality

4. REPORTER DETAILS

☐ Doctor ☐ Pharmacist ☐ Nurse ☐ Pharm. Tech CHO (specify):.....

Name: Telephone/Mobile:

Address: Signature:

Email:

Date:

Note: fields marked (*) are mandatory

ADDITIONAL IF REQUIRED

Details of medication error (Fill if applicable)

Stage of Medication Error in the Medication use System (tick all that apply)

☐ Prescribing ☐ Transcription ☐ Dispensing ☐ Administration Monitoring

Other (specify)

Type of Medication Error (tick all that apply)

☐ Wrong patient ☐ ☐ Wrong medicine

Contraindication including known allergy

☐ Wrong dose or strength ☐ ☐ Wrong quantity

Wrong duration

☐ Wrong rate (too fast/too slow) ☐ Wrong dosage form/formulation

Expired medicine

☐ Wrong route of administration ☐ Wrong preparation method

Dose omitted or delayed

☐ Wrong method of administration ☐ Wrong time of dose administration

Wrong frequency

☐ Poor quality or counterfeit medicine Monitoring error clinical or laboratory

Other (specify)

Staff or health care professional who made the error

☐ Physician ☐ Pharmacist Nurse ☐ Dentist CHO

Patient/caregiver Unknown

☐ Other (please specify).....

PRODUCT QUALITY DEFECT/ THERAPEUTIC INEFFECTIVENESS (Fill if applicable)

Brand or Generic Name	**Batch No**	**Dosage Form & Strength**	**Mfg. Date**	**Expiry Date**	**Type of Container**

Note: Fields marked (*.) are mandatory

APPENDIX 2: ADR form for patients/consumer reporting

Ministry of Health and Sanitation

☐ **Adverse Drug Reaction** ☐

☐ **Products** **Quality** ☐ **Defect**

Follow –up report

☐ **Medication Error**

Suspected Adverse Drug Reaction/Medication Error Reporting Form

1. PATIENT DETAILS		
*Patient's name:		Address:
*Sex:	*Age(months/years):	Height:(cm)
Weight:(kg)		
Health Facility		
2. DETAILS OF DRUGS		
*Name:		*Strength:
*Daily Dose:	*Start date:	End date:
Therapeutic indication:		Route of administration:
Name and Address of Manufacturer:		
3. DETAILS OF ADVERSE EVENTS		
*Description of reaction experienced by patient:		

*Date/time reaction started	Date/time reaction stopped	Was patient admitted ☐ Yes ☐ No	Duration of admission (hours/days)

4. DRUGS TAKEN CONCOMITANTLY /IN THE LAST 3 MONTHS PRIOR TO THE REACTION.

All concomitant drugs including self- medication and herbal preparations

Brand or Generic Name:	Daily dose	Route of Administration	Date started	Date Stopped	Reasons for Use

Action taken of reaction	**Outcome**	**Treatment**
☐ *Drug withdrawn* ☐ *Recovering/resolving* ☐ *Dose increased* ☐ *Recovered/resolved* ☐ *Dose reduced* ☐		

☐ *Dose not changed* ☐ *Unknown* ☐ *Not recovered* *Recovered with sequelae*	

5. *REPORTER DETAILS	
Name:	
Designation:	
Date:	Telephone No:

Note: Fields marked (*.) are mandatory

APPENDIX 3: CONTACT INFORMATION OF PBSL OFFICES

PBSL HEAD OFFICE

Postal address

The Registrar

Pharmacy Board of Sierra Leone

Central Medical Stores

New England Ville

Freetown

PMB 322

Tel :(0023222) 025-282826

Email: registrar@pharmacyboard gov.sl

Website:pharmacyboard.gov.sl

Kono Regional Office

57, Masinqbi road

Koidu city

Email: konooffice@pharmacyboard.gov.sl

Tel: 025-388748

Lungi 0ffice

Freetown International Airport

Lungi

Email: pbsllungi@gmail.com

Tel: 077-527220

Bo Regional Office

Bo-Kenema Highway

Nyagolihun junction

Email**:** booffice@pharmacyboard.gov.sl

Tel: +232-76466786

Kenema Regional office

10 Humonya Avenue

Tel: 025582886

Email: registrar@pharmacyboard.gov.sl

Makeni Regional Office

87 Aluzin highway

Makeni

Tel: +23278855471

APPENDIX 4

APPLICATION FORM FOR QUALIFIED PERSON RESPONSIBLE FOR PHARMACOVIGILANCE

NAME

GENDER

MOBILE

WORK PHONE

EMAIL

MARKETTING AUTHORIZATION HOLDERS DETAILS

NAME:

ADDRESS:

TELEPHONE NUMBER:

EMAIL:

QUALIFICATION

SIGNATURE

DATE.....

APPENDIX 5: APPLICATION FORM FOR RE-DESIGNATION AS A QPPV

Addressed to: THE REGISTRAR

PHARMACY BOARD OF SIERRA LEONE

CENTRAL MEDICAL STORE
NEW ENGLAND VILLE ,
FREETOWN

A. Particulars of the QPPV:

1. Name
……...

2. Postal Address
……...

3. Tel
……...

4. Fax ……...

5. Educational Qualification / Profession ……...

6. Qualified Person for Pharmacovigilance …….... (QPPV) Certificate Number

7. Date of Formal Designation as a QPPV ……...

8. Date of Expiration of designation as a QPPV ……..

B. Employment History as a Qualified Person for Pharmacovigilance

No.	Name of Local Representative	Name of Marketing Authorization Holder	Period (dd/mm/yyyy-dd/mm/yyy

C. Continuing Professional Development Undertaken within the last three years

No.	Name of Training Programme	Institution	Certificate Awarded (attach copie
Period (dd/mm/yyyy-dd/mm/yyyy)			

Declaration

I/We, the undersigned, hereby declare that all information contained herein is correct and true. Name of QPPV:……

Signature :……..

Date :…….

If QPPV is designated to a company

Name of Director of LR/MAH Representative ……..

Signature

:…….

Date

:…….

Official Stamp:

APPENDIX 6: QPPV DECLARATION FOR PHARMACOVIGILANCE SITE MASTER FILE(PSMF)

DECLARATION

1. I, the undersigned certify that all the information in PSMF and accompanying documentation is correct, complete and true to the best of my knowledge.
2. I further confirm that the information on all PSMF activities will be available for verification during Good Pharmacovigilance Practice (GVP) inspection.
3. I also agree that, I the Qualified Person for Pharmacovigilance in collaboration with the Marketing Authorization Holder (MAH) will implement all activities contained in the PSMF for this product in accordance with the PBSL requirements.

4. I also agree that I am obliged to follow all the requirements of the PHARMACY and DRUGS ACT 2001 and all applicable guidelines in ensuring the safety of marketed products.

……..

Name

Date: …….

APPENDIX 7: QPPV DECLARATION FOR RISK MANAGEMENT PLAN

DECLARATION

1. I, the undersigned certify that all the information in Risk Management Plan and accompanying documentation is correct, complete and true to the best of my knowledge.

2. I further confirm that the information on all Risk Management activities will be available for verification during Good Pharmacovigilance Practice (GVP) inspection.

3. I also agree that, I the Qualified Person for Pharmacovigilance in collaboration with the Marketing Authorization Holder (MAH) will implement all activities contained in the Risk Management and Pharmacovigilance plans for this product in accordance with the PBSL requirements.

4. I also agree that I am obliged to follow all the requirements of the PHARMACY and DRUGS ACT 2001 and all applicable guidelines in ensuring the safety of marketed products.

……..

Name

Date: …….

APPENDIX 8 : TABULATED SUMMARY OF REPORTING REQUIREMENTS

Post-Registration ADR Reports (registered medicinal products)

Type of ADR report	Time frame for reporting	Format for report
Local Serious (Expected and Unexpected)	7 days	PBSL ADR form#
Local non-serious (Expected and Unexpected)	28days	PBSL Summary report format#
Foreign Serious (Spontaneous/Published/Study)	On request or relating to specific safety issue	As appropriate
Notification of change in nature, severity, frequency or risk factor	28 days	Detailed report (including publications)
New information impacting benefit-risk profile of product including international regulatory decisions	7 days	Detailed report (including publications)

Applicant"s in-house ADR report form or PBSL ADR report form or format.

APPENDIX 9: SUMMARY REPORT

Every applicant shall submit to the PBSL all ADR reports which occurred in Sierra Leone received during the specified reporting period on an annual basis as a summary report (SR). The Board may also request a SR for any other time period if deemed necessary.

Format of the SR: Each applicant should submit a single report which covers all medicines for which it received ADR reports. The format used should include for each medicine (Appendix 3):

(i) the local usage of each formulation for the review period (e.g. sales data or patient exposure).

(ii) a concise critical analysis of the reported ADRs for each medicine. The critical analysis should - identify any new ADRs and risk factors associated with the

medicine - indicate any changes in the reporting rates of ADRs in a comparable period using estimated exposure (local) of the medicine, and with reference to international and cumulative data - address any new safety issue related to drug interactions, overdose, drug abuse or misuse, use in pregnancy, use in special patient groups or effects of long-term treatment

(iii) any actions taken or to be taken, including actions taken by any other regulatory authority or marketing authorisation holder

(iv) in a conclusion a simple risk-benefit statement for ongoing use and monitoring of the medicine.

(v) a line listing which includes the source, patient gender and age, formulation (including strength), daily dose, treatment dates and duration or time to onset, adverse reaction(s), seriousness, outcome and comment (including medical history and concomitant medicines). Reports received from a consumer should be clearly identified.

Depending on the medicine or circumstances, it may be useful or practical to have more than one line listing, such as dosage forms or indications, if such differentiation facilitates presentation and interpretation of data. It may also be useful to have separate tabulations for serious reactions and for non-serious reactions, for expected and unexpected reactions, or any other breakdown as may be useful for interpretation of the data. When the number of cases is very small, or the information is inadequate for any of the tabulations, a narrative description rather than a formal table would be considered suitable.

Time frame for submission of SR: Each applicant will specify the 12-month period which it will use for the SR. The 12-month period and the data lock-point selected by an applicant should be communicated to the PBSL.

ADR reports to be included: All domestic (Sierra Leone) spontaneous reports (serious and nonserious) received by the applicant during the specified 12-month period, all published reports of suspected ADRs, all domestic lack of efficacy reports, and all reports from post-marketing studies (published and unpublished).

If an applicant has received no reports during the time period, it must communicate this to the PBSL.

APPENDIX 10: TEMPLATE FOR SUMMARY REPORT

Each applicant should submit a single summary report (SR) which covers all medicines for which it received ADR reports. If an applicant has received no reports during the time period, it must communicate this to the PBSL.

The format of the SR used should include for each medicine:

1. Review period

Specify the dates for the 12-month period applicable to the data presented. If periods differ for different medicines, this needs to be specified. It should be kept in mind that the data must be presented annually.

2. Local usage of each formulation for the review period

This may be sales data or patient exposure.

3. Critical (concise) analysis of the reported ADRs for each medicine

3.1 New ADRs identified Indicate whether any new ADRs have been identified and whether such are serious or nonserious

3.2 New risk factors identified

3.3 Changes in reporting rate Any changes in reporting rate(s) of ADRs reported in a comparable period, using estimated exposure (local) of the medicine, and with reference to international and cumulative data

3.4 Other new safety issues This includes any new safety issue related to drug interactions, overdose, drug abuse or misuse, use in pregnancy, use in special patient groups or effects of long-term treatment, if not included in any of the above points

3.5 Actions taken or to be taken This includes actions taken or to be taken by any other regulatory authority or marketing authorisation holder (includes the local applicant)

4. Conclusion

A simple risk-benefit statement for ongoing use and monitoring of the medicine is required.

5. Line-listing

The line listing should include the source, patient gender and age, formulation (including strength), daily dose, treatment dates and duration or time to onset, adverse reaction(s), seriousness, outcome and comment (including medical history and concomitant medicines). Reports received from a consumer should be clearly identified.

Depending on the medicine or circumstances, it may be useful or practical to have more than one line-listing, such as dosage forms or indications, if such differentiation facilitates presentation and interpretation of data. It may also be useful to have separate tabulations for serious reactions and for non-serious reactions, for expected and unexpected reactions, or any other breakdown as may be useful for interpretation of the data. When the number of cases is very small, or the information is inadequate for any of the tabulations, a narrative description rather than a formal table would be considered suitable.

The line-listing should include all domestic (Sierra Leone) spontaneous reports (serious and nonserious) received by the applicant during the specified 12-month period, all published reports of suspected ADRs, all domestic lack of efficacy reports, and all reports from post-marketing studies (published and unpublished).

APPENDIX 11: Progress Report Form

SECTION A: ADMINISTRATIVE INFORMATION

Clinical Trial Certificate Number: …… ……	Expected Date of Commencement (as indicated on the certificate):……./…… ./… …….	Actual Date(s) of Commencement (at the Study Centre(s): ……./……./…….	Protocol Number: …… …… …… ……

Study Title:

Reporting Period From…….
to……

…….

Principal Investigator: Name:

Address: Phone:

Mobile:

E-mail:

Co-Investigators:

Name(s): Phone:

Mobile:

E-mail:

Other Study Contact (if applicable): Name: Phone:

Address: Mobile:

E-mail:

SECTION B: STUDY STATUS (Check one category only)

□Enrollment has not begun

□Actively enrolling subjects

□Enrollment closed on: ..... (insert date): subjects are receiving treatment/intervention

□Enrollment closed on: ..... (insert date): subjects are in follow-up only.

□Analyzing data

SECTION C: INFORMATION ON SUBJECTS & STUDY ACTIVITIES

a. Number of subjects consented and screened.....

b. Total number of subjects consented and screened who are eligible for the study.....

c. Number of subjects to which the investigational product(s) has been administered.....

d. Number of subjects left to be enrolled in the coming months (years).....

e. Number of participants who have discontinued the study:

- by Investigator:
- voluntarily:
- due to SAE:

f. Have there been any Serious Adverse Events (SAEs)? □Yes □ No

g. Total number of SAEs:
.....
(attach line list of SAEs documented for the quarter) □Yes □ No

h. Have these SAEs been reported to PBSL

i.If No, explain..... □Yes □ No

.....

.....

□Yes □ No

j. Have there been any changes to the protocol since PBSL approved?

k. Was this amendment submitted to the PBSL?

I. If No,

explain……

……..…….

.....

m. Date for the end of the study.....

n. Date for the final study report.....

SECTION D: COMMENTS (if any)

.....

.....

.....

.....

.....

.....

.....

.....

.....

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

APPENDIX 12 – DSUR Timelines for submission to the Board

The DSUR should be submitted to the Board by the sponsor no later than 60 days after the DSUR data lock point. The data lock point of the DSUR should be the last day of the one-year reporting period.

The "Development International Birth Date" (DIBD) is used to determine the start of the annual period for

the DSUR. This date is the sponsor's first authorisation to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD. Where clinical trials are ongoing in one country and are later initiated in another country, the original DIBD should be maintained and used for all countries in preparing the DSUR.

When submission of an annual report is no longer required in Sierra Leone, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug. The sponsor should also indicate whether or not clinical trials are continuing elsewhere.

Appendix 13- Timelines for submission of PSUR/PBRER to the Board

For New Chemical Entities (NCEs) PSURs/PBRERs should be submitted as stated below unless otherwise requested by the Board

1. 6 monthly for the first two years
2. At the time of renewal of the registration of the drug.
3. Immediately upon request by the Board.

For all other products, the most recent PSUR/PBRER should be submitted at the time of renewal of the registration of the drug. PSURs and PBRERs should be harmonized with the International Birth Date of the Product. Generally, each PSUR and PBRER should cover the period of time since the last PSUR/PBRER and should be submitted within 60 days after the Data Lock Point. For medicinal products with marketing authorization in different countries, the MAH may synchronize the Local Birth Date (LBD) with the International Birth Date (IBD). The Board will accept a single harmonized IBD and Data Lock Point (DLP) for each product in order to reduce the burden of work in preparing PSURs/PBRERs for different regulatory authorities. In situations where an MAH is preparing PSURs/PBRERs on annual basis or longer period for different regulatory authorities based on the IBD and the Board requires a six-month cycle based on the LBD, the most recent PSUR/PBRER with a longer time frame will be acceptable to the Board. The Board may also request for Ad hoc PSUR/ PBRERs i.e., reports outside the specified reporting requirements when there are new risks, when risks have changed, when efficacy/effectiveness has changed, or when there are changes to the benefit-risk profile of a medicinal product.

	Title: A GUIDE FOR SAFETY MONITORING OF MEDICINES IN SIERRA LEONE	
Rev No: 01	**Doc No: PBSL/GL/004**	Version no. 02
Issue date: 15 Feb 2021	**Effective date: 17 Feb 2021**	Approved by: Registrar

Prepared by	***Reviewed by***	***Approved by***
Head of PVG-CT	Head, Quality Assurance	Registrar
Dr Onome T Abiri	Dr Michael Lahai	Dr James P.Komeh