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PHARMACY BOARD OF SIERRA LEONE

PMB 322

CENTRAL MEDICAL STORES COMPOUND

NEW ENGLAND VILLE

FREETOWN

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The Pharmacy Board of Sierra Leone extends its sincere appreciation to all individuals and institutions that contributed to the development of this guideline for signal management. Special thanks to the Paul Ehrlich Institut in Germany for their valuable contribution to this guideline. This document is the result of collaborative efforts aimed at strengthening the national pharmacovigilance system and ensuring the continued safety of medicines in Sierra Leone

Executive summary

The safety of medicines and vaccines throughout their lifecycle remains a key regulatory priority of the Pharmacy Board of Sierra Leone. Effective signal management is essential to identify emerging safety issues, evaluate potential risks, and implement timely risk minimisation measures to safeguard patients and the public.

This guideline provides a structured, transparent, and standardised approach to signal detection, validation, prioritisation, assessment, and decision-making within the national pharmacovigilance system. It outlines the roles and responsibilities of key actors, including the Pharmacy Board, Marketing Authorisation Holders (MAHs), healthcare professionals, academic institutions, and national expert committees.

The guideline establishes processes for:

- Identifying potential safety signals from multiple data sources (e.g., VigiFlow reports, clinical studies, published literature, public health programme data)
- Utilizing statistical and clinical methods to validate and prioritise signals
- Conducting structured benefit-risk assessments to determine regulatory actions
- Communicating signal outcomes to stakeholders and the public
- Updating product safety information, including Product Information (PI), Risk Management Plans (RMPs), and Periodic Safety Update Reports (PSURs)

The document aligns with international standards, including ICH Guidelines, WHO Pharmacovigilance Guidance, and best practices from global regulatory authorities, while remaining tailored to Sierra Leone's health system context.

By adopting this guideline, the Pharmacy Board of Sierra Leone aims to:

- Strengthen the national capacity for proactive and responsive pharmacovigilance
- Promote transparency and accountability in safety decision-making
- Support safe and rational medicine use
- Enhance public trust in the regulatory system

1.0 Introduction

In pursuance to Pharmacy and Drugs Act 2001 this guideline is developed by the Pharmacy Board of Sierra Leone (PBSL), to establish a standardized process for signal management of medicines, vaccines, cosmetics, nutritional products, medical devices and related substances authorised for human and veterinary use in Sierra Leone. This guideline is for information, guidance and strict compliance by all stakeholders involved in signal management, i.e. marketing authorisation holders (MAHs) and PBSL. Penalties for non-compliance with these guidelines will be enforced according to the relevant provisions of Pharmacy and Drugs Act 2001 (see section 4.18).

This guideline on signal management in Sierra Leone was developed based on the GVP Module IX Signal Management [1].

Definitions of the technical terms used in the guideline are included in the **Glossary**.

2.0 Objective

The objective of this guideline is to provide general guidance and requirements on scientific and quality aspects of signal management and to describe roles, responsibilities,

and procedural aspects in the signal management process overseen by PBSL. Information on the mandatory reporting of Adverse Drug Reactions (ADRs), Adverse Events Following Immunization (AEFIs), and causality assessment is not the subject of this guideline, and it is described in the national ADR/AEFI guidelines.

3.0 Scope

This guideline applies to all MAHs and other stakeholders involved in the pharmacovigilance activities for medicines, vaccines, cosmetics, nutritional products, medical devices and related substances authorised for human and veterinary use in Sierra Leone. It encompasses the processes of signal detection, validation, prioritization, assessment, and decision-making. This guideline ensures that a consistent and comprehensive approach is taken in managing signals to safeguard public health.

4.0 Requirements (Structures and processes)

4.1 Sources of data and information

Signals can arise from various sources. These include, but are not limited to:

- Scientific information regarding the use of the drug and the outcome of the use, such as quality, non-clinical, and clinical data, Periodic Safety Update Reports/ Periodic Benefit-Risk Evaluation Reports (PSURs/PBRERs), Development Safety Update Reports (DSURs);
- Spontaneous reporting systems (Health Care Professionals (HCPs), patients, consumers, insurance companies, lawyers, etc.), active surveillance systems, studies, and scientific literature reporting safety data, media;
- Periodic database monitoring, such as Sierra Leone national vigiflow database, EUDRAVIGILANCE, UMC VigiBase of the WHO Programme for International Drug Monitoring;
- Safety reports or concerns raised by other NRAs, international organizations.

4.2 Signal detection

Signal detection should follow a methodology that takes into account the nature of data and the characteristics (e.g. time on the market, patient exposure, target population) as well as the type of medicinal product concerned. For further guidance on the methodological strategies for vaccines, refer to Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases [2]. For biologicals, refer to Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products [3]. Data from all appropriate sources should be considered (see 4.1). At all times, clinical judgement should be applied.

Signal detection comprises a review of individual case safety reports (ICSRs), statistical analyses, or a combination of both. In instances when it is not relevant or feasible to assess each individual case (e.g. signals detected from published studies, healthcare record data), assessment of aggregated data should be considered). The signal detection process should be documented (see 4.6.1).

4.2.1 Statistical aspects of signal detection

Summary statistics on data or data subsets should be applied to focus attention on ICSRs containing an adverse reaction. Such statistics look for disproportional reporting, i.e. looking for high proportions of a specific adverse event with a given medicinal product, compared to the reporting of this event for all other medicinal products. Sudden temporal changes in frequency of reporting for a given medicinal product may also indicate a change in quality or use of the product with adverse consequences (which could include a reduction in efficacy). Statistical aspects of signal detection should not be used to replace qualitative aspects of signal detection (the review of individual ICSRs, see 4.2).

4.3 Evaluation during signal validation and further assessment

The following elements should be considered during the signal validation process:

- Previous awareness, e.g.:

  - the extent to which information on the adverse reaction is already included in the product information (Investigators Brochure (IB), summary of product characteristics (SmPC) and package leaflet);
  - whether the signal relates to an adverse reaction already included in the SmPC for other medicinal products containing the active substance of interest, bearing in mind that some signals may only be relevant to a specific medicinal product and/or a specific formulation;
  - whether the association has already been assessed in the initial application for marketing authorisation, DSUR, the risk management plan (RMP), the PSUR/PBRER or any other regulatory procedure, based on information held or known by each organisation.
- Strength of the evidence, taking into account, e.g.:
  - the total number of cases (after exclusion of duplicates), and amongst those, the number of supportive cases, e.g. cases showing a compatible temporal association, positive de- or rechallenge, lack of potential alternative causes, assessed as possibly related by the reporting healthcare professional, with supportive results of relevant investigations;
  - number of cases in the context of patient exposure;
  - additional cases reported with related terms (e.g. other MedDRA terms indicating clinical complications or different stages of the same reaction);
  - consistency of the evidence across cases (e.g. consistent time to onset, pattern with repeated observations of an association);
  - quality of the data and their documentation;
  - cases matching internationally agreed case definitions if applicable (e.g. Brighton collaboration case definitions for vaccines [4])
  - dose-reaction relationship;
  - possible mechanism based on a biological and pharmacological plausibility;
  - disproportionality of reporting, if applicable (see 4.2.1).
- Clinical relevance and context, e.g.:

  - seriousness and severity of the reaction;
  - outcome and reversibility of the reaction;
  - additional insight on a known adverse reaction, e.g. in terms of its severity, duration, outcome, incidence or management;
  - reactions occurring in the context of drug-drug interactions;
  - reactions occurring in vulnerable populations or in patients with pre-existing risk factors;
  - reactions occurring in different patterns of use (e.g. overdose, abuse, misuse, off-label use, medication errors, falsified products).
- Additional sources, including but not limited to:
  - clinical trial data;
  - findings regarding similar cases in the scientific literature, including information on substances of the same class of medicinal products;
  - information on the epidemiology of the adverse reaction or the underlying disease;
  - experimental and/or non-clinical findings;
  - databases with larger datasets (see 4.1), when the signal was detected from national or MAH-specific databases;
  - Healthcare databases that may provide information on characteristics of exposed patients and medicines utilisation patterns;
  - information from other regulatory authorities worldwide.

The signal management process may be iterative, involving several rounds of expert discussions and different levels of decision making.

4.4 Signal prioritisation

Signal prioritisation encompasses the analysis whether signals suggest a risk with an important impact on patients or public health and/or affect the risk-benefit balance of the drug.

The following aspects should be considered for signal prioritisation:

- the severity, seriousness, outcome and reversibility of the adverse reaction and the potential for prevention;
- the patient exposure and the estimated frequency of the adverse reaction;
- the patient exposure in vulnerable populations and/or in populations with different patterns of use, where appropriate;
- the consequences of treatment discontinuation on the disease under treatment and the availability of other therapeutic options;
- the expected extent of the regulatory intervention (e.g. addition of adverse reactions, warnings, contraindications, additional risk minimisation measures, suspension, revocation);
- whether the signal is likely to apply to other substances of the same class of medicinal products.

Signals may also cause media attention and/or public concerns. Such signals may deserve special attention.

The prioritisation determines the timeframe for further management of the signal. If the signal suggests that there could be a risk that requires prevention or minimisation in a timely manner, measures may be required before a formal assessment of the signal is concluded. Clinical judgement and flexibility should be applied throughout the process.

4.5 Quality requirements

Signal management is considered a critical process. All roles, responsibilities and tasks required for the signal management process should be clearly defined. A system of quality management should be applied to all signal management processes (refer to Guideline for Pharmacovigilance Systems in Sierra Leone). Through a tracking system, all organisations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.

Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities.

An audit trail of signal management should be kept to allow traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.

All organisational roles and responsibilities for the activities regarding signal management should be recorded. This includes maintenance of documentation, quality control and review, and corrective and preventive action. Staff members involved in signal management should be specifically trained in accordance with their roles and responsibilities.

The description of the signal management system of MAHs should be described in their pharmacovigilance system master file.

MAHs should implement a record management system for all documents related to signal management. This system should ensure the following:

- Documents are easily retrievable;
- Actions taken to investigate safety concerns are traceable:
- Timelines for safety investigations are documented;
- Decisions regarding safety concerns are recorded, including the date and decision-making process.

Signal management activities should be audited regularly. This includes auditing tasks performed by service providers and contractors. It is essential to ensure the confidentiality, security, and validity of data and documents in accordance with Pharmacy and drugs Act, 2001. This includes maintaining data integrity when transferring information between organizations.

Documentation proving compliance with these requirements should be accessible at all times. This documentation must include justifications and evidence for the actions taken and decisions made.

4.6 Roles and Responsibilities

4.6.1 Responsibilities of the MAH

MAHs in Sierra Leone should continuously monitor the safety of their medicinal products and notify PBSL of any new information that could affect the marketing authorisation, including any information that constitutes an emerging safety issue.

Signals detected from other sources than safety database monitoring should be handled according to the marketing authorisation internal signal management process, adhering to general best practices. These signals should be reported to PBSL as outlined below. The MAH is responsible for ensuring that their product information remains current throughout the product's lifecycle and for including comprehensive signal information in PSURs (PBSL Guideline for PSURs).

Any signals that meet the criteria for emerging safety issues must be promptly reported to PBSL following the prescribed procedures. MAHs should work collaboratively with PBSL in the assessment of signals, providing any additional information requested.

Periodic reporting should be done by MAHs according to defined procedures (PSUR/PBRER, DSUR, clinical trial reports, line listings) in the respective guidelines. MAHs shall ensure their product information is kept up-to-date in accordance with the latest scientific knowledge, including assessments and recommendations made public through official channels.

4.7 Emerging safety issues

Upon becoming aware of an emerging safety issue, whether from internal or external sources, the MAH should promptly notify it in writing to the mailbox to info@pharmacyboard.gov.sl. This notification should be made without delay and no later than three (3) working days after confirming that a validated signal or safety issue qualifies as an emerging safety concern.

This is in addition to the requirements for submission of individual case safety reports as outlined in (PBSL Guideline for Management of Adverse Drug Reaction), when the emerging safety issue refers to a single case of suspected ADRs.

Upon reporting an emerging safety issue, the MAH should provide a detailed description of the safety concern, including its origins, any actions already taken or planned along with associated timelines, and furnish any pertinent documentation available at the time of initial notification. Additionally, any subsequent information pertinent to the issue should be promptly communicated to both PBSL and the relevant national competent authorities as soon as it becomes accessible.

When being informed of an emerging safety issue, PBSL must swiftly assess the urgency and potential impact of the matter. Should it be necessary, this evaluation may involve consulting the Expert Committee on Drug Safety and Clinical Trials (ECODSCT). Moreover, the MAH should collaborate with PBSL in the assessment and management of the emerging safety issue.

In order to ensure its effectiveness, the system should not be saturated by the transmission of less urgent information. MAHs should only communicate as emerging safety issues those safety concerns which meet the definition provided in the **Glossary**., i.e. whose urgency and seriousness cannot permit any delay in handling.

PBSL may also rely on emerging safety issues identified by international organisations, NRAs, or other stakeholders with whom they practice reliance.

If the MAH decides to take any of the following actions in response to the emerging safety issue, PBSL should be notified in parallel:

- Temporary or permanent cessation or suspension of the medicinal product;
- Withdrawal of the medicinal product from the market;
- Request for the withdrawal of a marketing authorisation;
- Non-application for the renewal of the marketing authorisation.

Safety-related data concerning quality defects or suspected falsified medicinal products that could impact the evaluation of a product's benefits and risks, potentially resulting in abnormal supply restrictions, should not be categorized as emerging safety issues and therefore need not be reported as such. This should be notified to PBSL in writing.

4.7.1 Involvement of the Scientific Advisory Committee for CT/PV

PBSL may decide to schedule ad hoc meetings of ECODSCT to assess emerging safety issues. The urgency of the assessment is determined by the severity and potential impact of the safety issue. In case of urgent safety issues, an ad hoc meeting with will be scheduled according with the internal procedures for the Scientific Advisory Committee meetings.

4.8 Monitoring of safety databases

PBSL should continuously monitor the Vigiflow database and UMC VigiBase to ascertain any emerging risks or alterations in existing ones that may influence the risk-benefit assessment of medicinal products. Identification of such risks relies on signal detection and analysis. MAHs are required to monitor data within international databases such as EudraVigilance and the FDA Adverse Event Reporting System (FAERS) to the extent of their access permissions. Consequently, they are obligated to assess and manage any signals related to any of their products marketed in Sierra Leone.

4.8.1 Periodicity of monitoring

Safety databases should be continuously monitored by PBSL and MAHs. The frequency of monitoring should correspond to the assessed risk level, potential risks, and the necessity for further information regarding the drug or active substances.

Factors which influence the appropriate frequency of monitoring are:

- Time since first authorisation;
- Extent of patient exposure;
- Important potential risks and missing information documented in the RMP;
- PSUR submission frequency;
- Number of ICSRs received over a given period;
- Any safety concern of interest in specific situations (e.g. vaccination campaigns).

The databases should be monitored at least every 6 months. The monitoring frequency and any changes thereof as well as the justification should be documented within the respective organisation´s internal procedures.

Literature review on safety signals should be done by MAH at least once per week.

4.8.2 Analysis of safety data

The selection of drug-event combinations for further review should be guided by scientific judgment. Detailed procedures for safety data analysis should be developed, documented and implemented.

4.9 Notifications and procedures for signals detected by the MAH based on the continuous monitoring of safety databases

Where a MAH detects a new signal when monitoring the safety databases, they shall validate it and forthwith inform PBSL.

Signal validation of the MAH shall include a thorough international database analysis complemented by analysis of the MAHs' in-house database and any other accessible database, literature review and review of clinical trial data. The MAH is to check whether a risk may already be addressed in the product information of other medicinal products containing the active substance of interest that are marketed in the EU, USA, other regions/countries. In this case, the product information should be aligned as appropriate through an application for variation of the terms of marketing authorisation.

The MAH may conclude that

- a signal is refuted,
- there is a new or changed risk and/or
- further analysis is required by the competent authorities.

The MAH may seek further analysis by PBSL if validated signals cannot be refuted nor confirmed as new or changed risks. Signals that require further analysis by PBSL may be reported only in PSURs if the conditions outlined in section 4.11 are met. Refuted signals should only be reported in PSURs. All validated signals that require urgent attention should be reported as emerging safety issues (see 4.1.3).

4.10 Variation of the terms of marketing authorisation

If a MAH concludes that the product information and/or the RMP require updating through a variation, a variation application shall be submitted to PBSL. This shall be done as soon as possible and no later than 3 months after completion of signal assessment if the signal corresponds to an important risk or within 6 months for adverse reactions or risks that are not considered important.

In such instances, a separate standalone signal notification is not required, as the proposed changes and supportive evidence will be assessed within the variation procedure by PBSL.

4.11 Inclusion of the signal in the PSUR

If an active substance is included in the List of Union Reference Dates and Frequency of Submission of PSURs (EURD List) and a PSUR is due to be submitted within 6 months of completed signal assessment by the MAH, the submission of a separate standalone signal notification is not required. The signal will be assessed by PBSL within the PSUR procedure. If the data-lock point of the PSUR has elapsed by the time the MAH has completed their assessment of the signal, it should be mentioned in the PSUR section 'Late-breaking Information' together with a proposal for further management of the signal (see PBSL PSUR Guideline). This also applies to the conclusions drawn based on the evaluation of safety signals (see PBSL PSUR Guideline).

All validated signals and emerging safety issues that are concluded during the PSUR reporting interval or that are ongoing at the time of the PSUR data lock point should be reported in that PSUR in sections 15 and 16 (see PBSL PSUR Guideline).

4.12 Other required activities

In addition, the MAH shall evaluate the need for any changes to the IB, SmPC/Patient Information Leaflet (PIL), labelling, educational or reference materials and inform PBSL in a timely manner (see The Safety Variation Guideline, RMP Guideline). PBSL should be informed about any other actions planned to be taken by the MAH (Post-Authorisation Safety Study/ Post-Authorisation Efficacy Study (PASS/PAES), RMM) based on the cumulative safety data and the risk/benefit analysis submitted in the DSUR/PSUR/PBRER, or safety concerns based on literature review, signals confirmed by other NRAs/or WHO/EMA. PBSL shall review and approve or reject the activities proposed by MAH.

4.13 Standalone signal notification

If a validated signal does not meet the conditions as outlined in 4.10 and 4.11 and further signal analysis by PBSL is required, the MAH should complete the standalone signal notification form (see Annex) and send to PBSL. This should be done as soon as possible and no later than 30 days after the completed assessment. Signals refuted by MAHs should not be sent as standalone signal notifications but should be included in PSURs as applicable (see PBSL PSUR Guideline).

4.14 Signal analysis, prioritisation and assessment by PBSL

Signals will be prioritised by PBSL taking into account all the information provided by the MAH. The scope of the signal management may be extended to other active substances of the same class of medicinal products or to other related adverse reactions. Signal assessment will be performed by PBSL using national database, UMC Vigibase, validated statistics analysis tools (e.g. disproportionality method, Proportional Reporting Ratio (PRR), the Reporting Odds Ratio (ROR), the Information Component (IC), the Empirical Bayes Geometric Mean (EBGM) and the Urn model, or any other method (not limited to the mentioned above)). The assessment of causality will be applied for decision-making: expert medical judgement, causality assessment algorithms (Naranjo, UMC WHO method, AEFI causality assessment algorithm, and other methods if necessary) will be used in signal analysis.

RELIANCE mechanism in decision making will be used by PBSL if necessary. The joint review, work-sharing and recognition and reliance on the decision of other NRAs/CAs and international organizations (EMA, WHO, PICs etc.) can be applied.

PERIODICITY OF SIGNAL MANAGEMENT by PBSL

- Conduct signal detection at least every three (3) months for products that have been prioritized for signal detection.
- Conduct signal detection at least every six (6) months for other products

- De-classify products that have been prioritized for signal monitoring after a period of time based on the safety profile (i.e. products no longer considered as high risk)
- Ensure that the threshold for signal detection i.e. a minimum of three (3) cases of the same drug-reaction combination is considered for signal detection
- Perform signal detection using the current MedDRA Preferred Term (PT) level

The signal can be confirmed, refuted or reconsidered by PBSL in case of emerging new information. If additional data is required for the assessment, this should be provided as soon as possible by the MAH, but no later than within two (2) months.

4.15 Signal confirmation by PBSL

Within 30 days following receipt of a validated signal, PBSL should confirm or refute the signal.

PBSL may decide not to confirm a validated signal if, for example:

- it is already adequately handled through a different procedure (e.g. PSUR, variation) at the time confirmation is considered, including procedures for other medicinal products containing the same active substance (e.g. originator product);
- the validated signal involves an adverse reaction that is already adequately reflected in the product information of other products authorised in Sierra Leone with the same active substance;
- the signal has already been subject of review and the data that has arisen since this review does not provide substantial new evidence;
- the available data does not warrant further analysis due to limited evidence or clinical relevance.
- It is already assessed and managed by the MAH, NRAs in other territories or other organisations to which PBSL practices reliance.

PBSL has the option, when needed, of using the external Scientific Advisory Committee in the evaluation of safety issues before and after marketing authorisation. This option is particularly important in the event of PASS imposed due to emerging safety concerns, granting of MA under conditional approval or under exceptional circumstances.

Communicate information to all stakeholders, including patients and the healthcare community, EPIs, other NRAs and international organizations (e.g. WHO UMC), public, Ministry of Health, etc. (as per Safety Communication SOP and Guideline).

SAFETY COMMUNICATION

Feedback from reviews should be disseminated to target audiences as stipulated in the PBSL safety communication guideline within 10 days.

Feedback and further communication should be closely monitored.

4.16 Recommendations on signals to the MAH

The recommendations on signals may include any or a combination of the following:

- the MAH should provide additional data for assessment within a signal procedure;
- the MAH should provide a review of additional data on the signal in the following PSUR or submit an ad-hoc PSUR (see PBSL PSUR Guideline);
- the MAH should discuss all safety signals discovered during the reporting period in the text of the following DSUR (see PBSL DSUR Guideline);
- the MAH should update the product information through an application for a variation to the terms of the marketing authorisation;
- the MAH should be requested to submit an RMP or to update the RMP (see PBSL RMP Guideline);
- the MAH should propose RMMs and implement additional RMM after approval by PBSL (e.g. Direct healthcare professional communication (DHPC), educational materials, training for HCPs and EPI staff);

- the MAH should conduct a PASS/PAES according to an agreed protocol and submit the final results of that study if necessary (see PBSL PASS/PAES Guideline);
- update of the IB or SmPC/PIL accordingly;
- consultation of Data and Safety Monitoring Board (DSMB) and relevant scientific expert groups;
- an inspection may take place (see PBSL PV Inspection Guideline);
- rely on information or decisions made by other competent authorities, international organizations (WHO, UMC, EMA, PICs, etc.) to which PBSL practices reliance as per Reliance Policy.
- any other appropriate action that is not listed above;

4.17 Record management

PBSL will keep records of the following elements pertaining to signal management:

- a description of the validated signal;
- for non-confirmed signals: justification for not confirming;
- for confirmed signals: signal assessment report, timetables, recommendations.

For record keeping, best practices should be employed. Physical records will be stored at PBSL in a manner that ensures their security, accessibility, and longevity. Likewise, electronic documents will be stored on PBSL servers ensuring their security, accessibility, and integrity. Records should be stored for 10 years.

4.18 Penalties

Non-adherence to the requirements of these guidelines by manufacturer representatives and MAH will result in PBSL imposing sanctions.

4.19 Sanctions

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

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

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

4.1.3 Suspension of the Marketing Authorization

4.1.4 Revocation of the Marketing Authorization

5.0 Glossary

Adverse drug reaction (ADR)	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	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.
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.
Important identified risk; 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.
Periodic safety update report (PSUR) used interchangeably with Periodic benefit-risk evaluation report (PBRER)	A regular update of the world-wide safety experience of a medicinal product at defined times during post-registration period.
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 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 precautions section of the product information should be considered important.
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 PBSL and the general population.
Safety concern	An important identified risk, important potential risk, or important missing information.
Signal*	Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
Signal management process*	A Set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking. The signal management process includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action.
Signal prioritisation*	The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay.
Signal detection*	The process of looking for and/or identifying signals using

	data from any source
Signal validation*	The process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.
Validated signal*	A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.
Non-validated signal*	A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted.
Signal assessment*	The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or medicinal product or whether known risks have changed. This review may include non-clinical and clinical data and should be as comprehensive as possible regarding the sources of information.
Refuted signal*	validated signal which, following further assessment has been determined to be "false" i.e. a causal association cannot be established at that point in time.

Emerging safety issue*	A safety issue considered by a MAH to require urgent attention by PBSL because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Definitions marked with an (*) are adopted from GVP Module IX [1].

Abbreviations

ADR – Adverse Drug Reaction
AEFI – Adverse Event Following Immunization
CIOMS – Council for International Organizations of Medical Sciences
DHPC – Direct healthcare professional communications
DSUR – Development Safety Update Report
DSMB – Data and Safety Monitoring Board
EBMG – Empirical Bayes Geometric Mean
EMA – European Medicines Agency
EPI – Expanded Programme on Immunisation
EU – European Union
EURD List – List of Union Reference Dates and Frequency of Submission of PSURs
FDA – Food and Drug Administration
GVP – Good pharmacovigilance practices
HCP – Health Care Professional
IB – Investigators Brochure
IC – Information Component
ICSR – Individual Case Safety Report
ICH – International Conference on Harmonization

MAH – Marketing Authorisation Holder

MedDRA – Medical Dictionary for Drug Regulatory Activities

NRA – National Regulatory Authority

PASS/PAES – Post-Authorisation Safety Study/ Post-Authorisation Efficacy Study

PBSL – Pharmacy Board of Sierra Leone

PIL – Patient Information Leaflet

RMP – Risk Management Plan

RMM – Risk Minimisation Measure

ROR – Reporting Odds Ratio

PSUR/PBRER – Periodic Safety Update Reports/ Periodic Benefit-Risk Evaluation Report

PT – Preferred Term

SmPC – Summary of Product Characteristics

UMC – Uppsala Monitoring Centre

USA – United States of America

WHO – World Health Organisation

6.0 References and Information Sources

[1] Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1)

[2] Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases.

[3] Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products.

[4] Brighton collaboration case definitions, accessible via https://brightoncollaboration.org/case-definitions/

Legislations and guidelines used to develop this guideline

E2A: Guideline Clinical Safety Data Management Definitions and standards for expedited reporting.

E2C: R2_Step4 Periodic Benefit -Risk Evaluation Report (PBRER)

E2D: Guideline Post approval safety data management- Definitions and standards for expedited reporting

E2E: Guideline Pharmacovigilance Planning

E2F: Step_4 Development Safety Update Report

E2: Clinical Safety Data Management

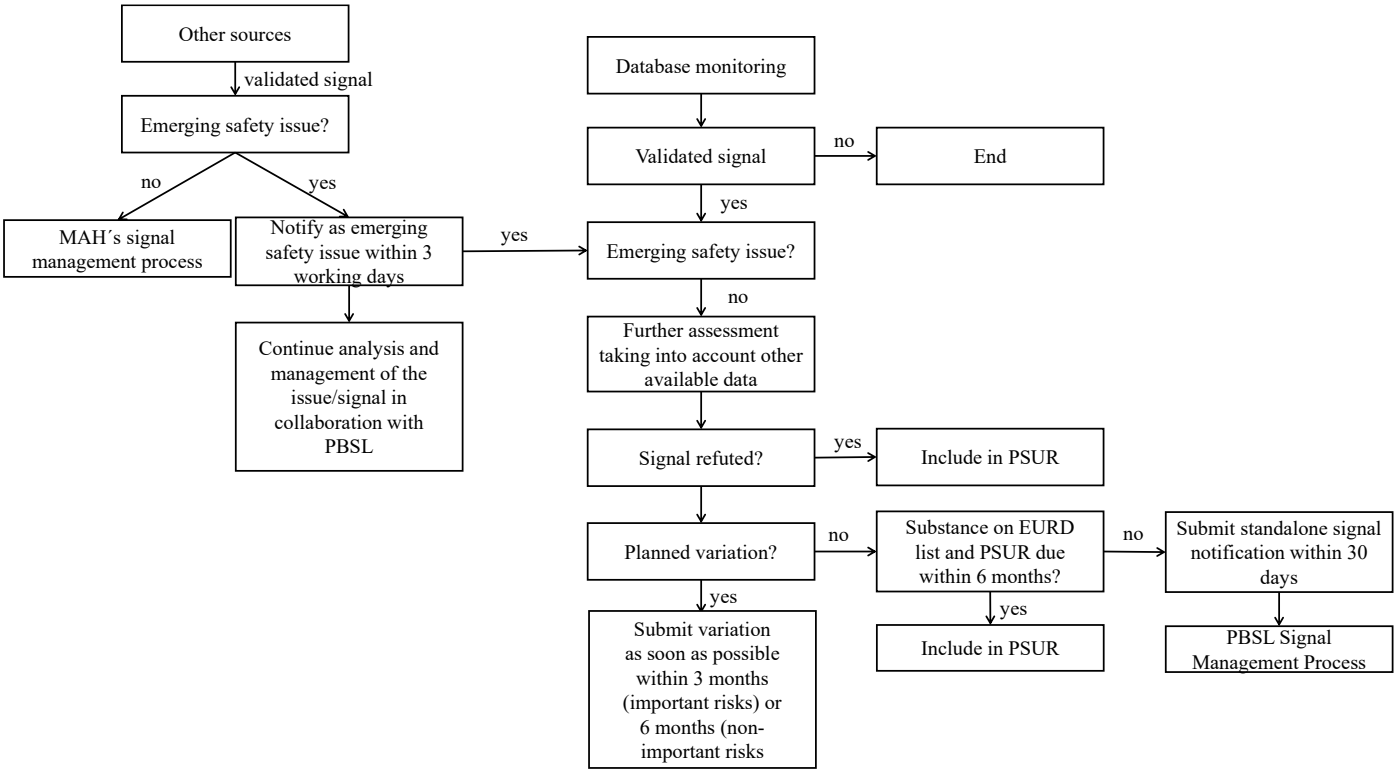
GVP Module IX – Signal management

GVP Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

SCOPE Work Package 5 Signal Management – Best Practice Guide

Annex 7.0

7.1 Flowchart MAH Signal Management Process



7.2 Standalone signal notification form (if applicable)

Standalone Signal Notification for <Active substance/INN – BRANDNAME (therapeutic class) and adverse reaction (MedDRA term)>

General guidance

This form should be used by marketing authorisation holders to notify the PBSL of any signals detected for which they conclude after validation and assessment, that further analysis by the Sierra leone regulatory authority is required.

The requirements outlined in the Good Pharmacovigilance Practices (GVP) Module IX on Signal Management (Revision 1) must be followed when completing the form.

Standalone signal notifications should not be used for:

- non-validated or refuted signals,

- signals to be included within PSURs or variation applications provided that the conditions outlined in section IX.C.4. of the module are met,

- signals meeting the definition of an emerging safety issue (unless a standalone signal notification is requested by the regulatory authorities).

Once completed, please send the form (in Microsoft Word format) and any attachments in a single e-mail to the PBSL (info@pharmacyboard.gov.sl) Please use as e-mail message subject the following format: Signal from <MAH> on <active substance> and <adverse reaction>.

All the sections should be completed with the information requested or a justification should be provided. Sections should not be left blank.

1. ADMINISTRATIVE INFORMATION

Date of this notification	DD month YYYY
Active substance(s) (invented name(s))	<Text>
Pharmaceutical form(s)/Route(s) of administration / Strength(s)	<Text>
Marketing authorisation holder(s)	<Name(s)>
QPPV	<Name(s) and contact details>
MAH contact person for the signal	<Name(s) and contact details>

Authorisation procedure and number	
☐	National: <marketing authorisation number(s)>
Has any other NRA been notified of the signal? *[Tick the appropriate box below.]*	
☐	Yes
☐	No
☐	Not applicable

Next PSUR submission date *[if PSURs are required for the medicinal product]*	<DD month YYYY> ☐ PSUR not required.

2. SIGNAL DESCRIPTION

2.1. Highlights

Clinical relevance: <Text>

<Please briefly summarise how seriousness criteria were met in the cases, e.g. fatal, life-threatening, hospitalisation etc. See GVP Module VI.A.1.6.>

Relevant statistical measures: <Text>

<Please provide any relevant statistical measures if applicable.>

Patient exposure: <Text>

<Please provide the most recent estimate of the population cumulatively exposed to the medicinal product in the post-authorisation setting and in clinical trials if applicable. Methods used to calculate the exposure do not need to be included>.

Previous awareness: <Text>

<Please provide information on any regulatory actions or previous assessments, performed at national, EU or non-EU level in relation to the signal.>

2.2. Background

<Text here.>

<This section should include a concise summary of the relevant information on the product(s)/ active substance (including therapeutic indication(s)), and on the adverse reaction(s) (e.g. morbidity, epidemiology, case definition, etc.)>

2.3. Signal validation and further assessment

2.3.1. Evidence from

Data sources

☐ Literature ☐ MAH database

☐ Clinical trials ☐ Other *[please specify below]*

☐ EudraVigilance ☐ VIGIBASE

Date of the query: <DD month YYYY> Monitoring periodicity: <Text here.>

<Text here.>

<This section should include a summary of evidence from your MAH database, highlighting the strength of evidence, clinical relevance and a summary of the supportive cases. MedDRA terms used, number of cases, positive de-challenge or re-challenge, seriousness, dose-reaction relationship, biological and temporal plausibility, causality assessment, clinical context (e.g. drug interactions, specific population, risk factors) and quality of documentation should be provided.

It should also include a summary of all additional evidence, e.g. from the scientific literature, clinical trials etc. >

3. CONCLUSION

<Text here.>

<This section should include a brief statement highlighting why further analysis by PBSL is warranted and proposed actions>.

4. ANNEXES

<Text here.>

<List of literature references, if applicable>

<List of attachments, if applicable>

7.3 Signal assessment report template

<insert date DD Month 20YY>

< insert Doc ref ID>

Expert committee on drug safety and clinical trials(ECODSCT)

Signal assessment report on <adverse event/reaction> with <INN(s)>[1]

General guidance

Send this report to infopharm@pbsl.gov.sl using as e-mail message subject the following format: Signal AR on <adverse event/reaction> with INN(s)[1] . Copy the PBSL signal management team (berylonome@gmail.com).

All validated signals (confirmed or not) should continue to be entered into the European Pharmacovigilance Issues Tracking Tool (EPITT). This AR should only be used for confirmed signals. Signals concerning safety topics that are being addressed within another ongoing parallel procedure, e.g. PSURs or variation, should in principle not be confirmed; this should be investigated before a decision on confirmation is made. For non-confirmed signals, a justification should be provided

This template should be used throughout all stages from signal confirmation until adoption of recommendation(s). It will therefore be completed by different stakeholders, as specified below:

[1] In case there are several products authorised for the same active substance and the signal applies only to a specific product, please add the product name in brackets. For product classes, please only state the class and list the relevant active substances in the administrative information table.

- *Timetable and administrative information: whoever drafts the AR as relevant information becomes available.*

- *Background and initial evidence: whoever confirms the signal*

- *Additional evidence:*

- *Adopted recommendation(s): PBSL*

If the ECODSCT recommends that the signal follow-up is to be handled within another procedure such as periodic safety update report (PSUR), referral, etc., the relevant template for these procedures should be used at that point.

In case data have been requested from a marketing authorisation holder (MAH), the assessment report will be shared with them after appropriate redaction by the PBSL.

Confirmation assessment report	DD Month YYYY
Adoption of <first> ECODSCT recommendation	DD Month YYYY
<Preliminary assessment report on additional data>[2]	<DD Month YYYY>
<Deadline for comments>[4]	<DD Month YYYY>
<Updated rapporteur assessment report>[4]	<DD Month YYYY>
<Adoption of <second> ECODSCT recommendation>[4]	<DD Month YYYY>

[2] Please delete or repeat as applicable

Administrative information

Active substance(s) (invented name)[1]	<Text>
Strength(s)	<Text> *[Only if relevant to the signal]*
Pharmaceutical form(s)	<Text> *[Only if relevant to the signal]*
Route(s) of administration	<Text> *[Only if relevant to the signal]*
Indication(s)	<Text> *[Only if relevant to the signal]*
Marketing authorisation holder(s)	<Name(s)>

Authorisation procedure *[Tick the appropriate box(es) below.]*	
☐	Centralised
☐	Mutual recognition or decentralised
☐	National

Adverse event/reaction:[3]	

Signal validated by:	<Member State>PBSL
Date of circulation of signal validation report:	DD Month YYYY
Signal confirmed by:	<Member State>PBSL
Date of confirmation:	DD Month YYYY
ECODSCT Rapporteur appointed for the assessment of the signal:	<Name>ECODSCT Members name <E-mail address>
Assessor(s):	<Name> <E-mail address>

[3] Please use MedDRA terminology whenever possible

Rapporteur's contact person:	<Name> <E-mail address>
PBSL signal management team member:	<Name> <E-mail address>

Declarations

☐ The assessor confirms that this assessment does not include any commercially confidential information (e.g. ASMF, reference to on-going assessments or development plans etc), non-public information shared by other competent authorities or organisations, irrespective from which entity was received*, or reference to pharmacovigilance inspections.

**If the entity from which commercial confidential information and/or non-public information originates has consented to its further disclosure, the box should be ticked and there would be no need to add details below.*

Whenever the above box is un-ticked please indicate the section and page where the confidential information is located here:

Confidential information:

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4. References

<Annex>

1. Background

<Text here.>

[This section should be copied from EPITT by whoever confirms the signal.]

2. Initial evidence

2.1. Signal validation

<Text here.>

[This section should be completed at the time of confirmation by whoever confirms the signal. The signal validation section from EPITT should be copied into this section. Case narratives may be included here in full, summarised (e.g. in a table) or provided in an Annex, as appropriate.]

2.2. Signal confirmation

<Text here.>

[This section should be completed by whoever confirms the signal. It should provide a critical discussion of the strengths and limitations of the available evidence supporting the signal validation. Any additional information available at the time of confirmation and not considered during validation may be presented.]

2.3. Proposed recommendation

<Text here.>

[This section should be completed by whoever confirms the signal. It should include details of the proposed actions, e.g. request for supplementary information, changes to the summary of product characteristics (SmPC) and/or package leaflet (PL), additional communication (e.g. direct healthcare professional communication -DHPC), etc. A brief rationale should be included. Timelines for e.g. submission and assessment of additional data, submission of variation, etc., should be specified. If changes to the SmPC and/or PL are proposed, please provide the exact wording (new text underlined, text to be removed ~~struck-through~~).]

2.4. Adopted ECODSCT recommendation

<Text here.>

[This section should be completed by the PBSL signal management team member. The exact text of the adopted ECODSCT recommendation should be included.]

3. Additional evidence

[This section only applies when the ECODSCT recommends gathering additional evidence after initial discussion on the signal for assessment within the signal procedure. The following sub sections may be repeated if there is more than one round of assessment. If the ECODSCT recommends that the signal follow-up is to be handled within another procedure such as periodic safety update report (PSUR), referral, etc., the relevant template for these procedures should be used at that point.]

3.1. Assessment of additional data

<Text here.>

[This section should be completed by the ECODSCT Rapporteur appointed for the assessment of the signal. It should provide an appraisal of all the evidence gathered e.g. MAH responses, results of non-urgent information (NUI), additional analyses carried out by regulators or other stakeholders (e.g. VIGIBASE, studies in The Health Improvement Network - THIN, Clinical practice Research Datalink – CPRD - or EudraVigilance).]

3.2. Rapporteur's proposed recommendation

<Text here.>

[This section should be completed by the PECODSCT Rapporteur appointed for the assessment of the signal. It should specify whether further actions are warranted and the rationale behind them. Details of any proposed actions, e.g. (follow-on) request for supplementary information, changes to the SmPC and/or PL, additional communication (e.g. DHPC), etc., should be presented. Timelines for e.g. submission and assessment of additional data, submission of variation, etc., should be specified. If changes to the SmPC and/or PL are proposed, please provide the exact wording (new text underlined, text to be removed ~~struck-through~~).]

3.3. Comments from other ECODSCT members and MAH(s)

<Text here (if applicable).>

[This section should discuss comments received. If no comment was received, please write "No comment received".]

3.4. Updated rapporteur's proposed recommendation

<Text here (if applicable).>

[This section should provide an updated proposed recommendation, following comments received from ECODSCT members and MAH(s), when applicable, including rationale, details of proposed actions and timelines.]

3.5. Adopted ECODSCT recommendation

<Text here.>

[This section should be completed by the PBSL signal management team member. The exact text of the adopted ECODSCT recommendation should be included.]

4. References

<Text here.>

[A consistent style for references and citations should be used throughout the report. When referencing electronic publications, the date on which the publication was accessed should be shown after the web address. The Agency's standard style for citing (in the body of the report) and referencing (the full source in a list) is illustrated below:

The effect of magnesium in myocardial infarctions has been reviewed (Woods, 1991 [1]). Ten years later, a number of recommendations were made to prevent the injection of vinca alkaloids by the intrathecal route (Woods, 2001 [2]).

1. Woods, K.L., 'Possible pharmacological actions of magnesium in acute myocardial infarction', Br J Clin Pharmac, 32, 1991, pp. 3–10.

2. Woods, K, 'The prevention of intrathecal medication errors: a report to the Chief Medical Officer', London, Department of Health, 2001 [cited 11 May 2009]. Available from:

http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4065044 [Accessed 11 May 2009]. Specific referencing software may be used, if available.]

<Annex>

Prepared by	**Reviewed by**	**Approved by**
Signature	**Signature**	**Signature**
Head, Pharmacovigilance & Clinical trials	**Head, Quality Assurance**	**Registrar**
Name: Dr. Onome Abiri	**Name**	**Name**