



National Agency for Food & Drug Administration &Control (NAFDAC)

Pharmacovigilance Directorate

NAFDAC Good Pharmacovigilance Practice Guideline

Chapter 9 Signal Management

CHAPTER 9: SIGNAL MANAGEMENT	3
9.1. Purpose	3
9.2. Scope and Applicability	3
9.3. Definitions	3
9.4. Governance of Signal Management	5
9.4.1. Signal Management Structure and Coordination	5
9.4.2. Roles and Responsibilities.....	6
9.5. Structure and processes	7
9.5.1. Sources of Signals	7
9.4.2. Signal Detection	8
9.4.3. Signal Validation	9
9.4.3.1. Previous Knowledge of the Association.....	9
9.4.3.2. Strength of the Initial Evidence	9
9.4.3.3. Clinical Relevance.....	10
9.4.3.4. Decision	10
9.4.4. Signal Prioritisation and Public Health Impact	10
9.4.5. Signal Assessment	11
9.4.6. Signal Detection and Notification by Marketing Authorisation Holders	12
9.4.7. Review by the NAFDAC National Drug Safety Advisory Committee.....	13
9.4.8. Communication	15
9.4.9. Signal Closure	16
9.5. Timelines for signal management activities	16
9.5.3. Frequency of Safety Data Monitoring.....	16
9.5.4. Timelines for Signal Management Steps.....	17
9.6. Urgent Safety Signals	18
9.7. Documentation and Quality Requirements for Signal Management.....	18
9.7.11. Minimum Documentation Requirements for Signals	19

CHAPTER 9: SIGNAL MANAGEMENT

9.1. Purpose

Chapter 9 of the NAFDAC Good Pharmacovigilance Practice (GVP) Guideline provides the framework for the implementation of signal management activities in accordance with the legal requirements outlined in the Good Pharmacovigilance Practice Regulation, Section 15, as applicable to Marketing Authorization Holders (MAHs) and the Agency. It establishes the expectations for the systematic and proactive management of safety signals throughout the lifecycle of medicinal products authorized for human use in Nigeria.

This chapter defines the roles and responsibilities and procedural aspects of the signal management process in Nigeria. The guidance is consistent with internationally recognised standards for signal management, including relevant ICH pharmacovigilance principles outlined in ICH E2E, and aligns with established best practices as described in EMA GVP Module IX. It is adapted to support effective implementation within the Nigerian regulatory framework.

9.2. Scope and Applicability

This chapter applies to:

- All medicinal products authorised for human use in Nigeria, including prescription medicines, over-the-counter medicines, biological products, vaccines, and other regulated therapeutic products, unless otherwise specified by the agency
- Marketing Authorization Holders (MAHs) and their local representatives, where applicable, with respect to their obligations for continuous signal detection, evaluation, documentation, and communication to the Agency.
- The Agency, in its role as the National Regulatory Authority, includes activities related to independent signal detection, validation, assessment, regulatory decision-making, and communication of safety information.
- The requirements outlined in this chapter are applicable throughout the lifecycle of a medicinal product, from the time of marketing authorisation and continuing for as long as the product remains on the market, unless otherwise determined by the Agency.

This chapter should be implemented in conjunction with other relevant chapters of this GVP Guideline, particularly those relating to ICSR management, risk management systems, and safety communication.

9.3. Definitions

- **Signal:** A signal is information arising from one or multiple sources, including observations and scientific investigations, that suggests a new potential causal association, or a new aspect of a known association, between a medicinal product and an event or set of related events, either adverse or beneficial. Signals may relate to:
 - All medicinal products containing the same active substance
 - Combination products
 - A specific product formulation

- A particular strength, indication, route of administration, or patient population.
In some circumstances, a signal may apply to an entire therapeutic class, while in other situations it may be limited to a specific medicinal product.
- **Signal Management Process:** The signal management process refers to the structured set of pharmacovigilance activities undertaken to determine whether new risks are associated with a medicinal product or whether known risks have changed.
- **Signal Detection:** Signal detection is the process of systematically reviewing safety data from one or more sources to identify potential signals. Signal detection activities may be conducted by Marketing Authorisation Holders (MAHs) through their global pharmacovigilance systems and the Agency through national pharmacovigilance surveillance activities.
- **Signal Validation:** Signal validation is the process of evaluating the evidence supporting a detected signal to determine whether sufficient data exist to justify further investigation.
- **Validated Signal:** A validated signal is a signal for which the available documentation has been evaluated and determined to contain sufficient evidence suggesting a potential association that justifies further investigation and assessment. Validated signals may be subjected to structured regulatory review and further evaluation.
- **Non-validated Signal:** A non-validated signal is a signal for which the available evidence is considered insufficient at the time of evaluation to support further investigation. Non-validated signals may still be monitored over time as additional data become available.
- **Confirmed Signal:** A confirmed signal is a validated signal that has been formally accepted for structured regulatory assessment. Confirmed signals may be referred to expert bodies such as the NAFDAC National Drug Safety Advisory Committee (NNDsAC) for scientific review and recommendations on appropriate regulatory action.
- **Signal Prioritisation:** Signal prioritisation is the process of determining which signals require the most urgent attention and regulatory evaluation. Signals may be prioritised based on factors such as: Seriousness and clinical severity of the event; Impact on patients or public health; Strength and consistency of evidence; Preventability or potential for risk minimisation; Extent of population exposure to the product.
Signals suggesting significant public health impact or major changes in the benefit-risk balance of a medicinal product should be prioritised for expedited evaluation.

- **Signal Assessment:** Signal assessment is the process of conducting a comprehensive scientific evaluation of a validated signal using all available evidence. The objective is to determine whether a causal relationship is likely and whether regulatory action is required.
- **Refuted Signal:** A refuted signal is a previously validated signal that, after comprehensive assessment, is determined not to represent a causal association between the medicinal product and the event based on available evidence. Refuted signals should continue to be monitored as new information becomes available.
- **Emerging Safety Issue:** An emerging safety issue is a safety concern that may require urgent regulatory attention because of its potential major impact on the benefit-risk balance of a medicinal product or on public health.

Examples may include:

- Unexpectedly high rates of serious or fatal adverse events identified in studies
- New serious adverse reactions identified through spontaneous reports or literature
- Safety concerns that may require restrictions of use, contraindications, or product withdrawal
- Significant safety-related regulatory actions taken by other regulatory authorities.

Emerging safety issues should be promptly communicated to the Agency, and may require immediate regulatory evaluation and risk management actions.

- **Closed Signal:** A signal for which evaluation has been completed and regulatory conclusions reached.

9.4. Governance of Signal Management

9.4.1. Signal Management Structure and Coordination

9.4.1.1. Signal management in Nigeria is conducted through a coordinated framework involving the Agency, Marketing Authorisation Holders (MAH), and the NAFDAC National Drug Safety Advisory Committee (NNDAC). MAHs are responsible for the continuous monitoring of the safety of their authorised medicinal products and for identifying and evaluating potential safety signals arising from all available data sources throughout the product lifecycle. The Agency serves as the national regulatory authority responsible for the detection, validation, prioritisation, and regulatory assessment of safety signals using data from the national pharmacovigilance system and other relevant sources.

9.4.1.2. Where appropriate, the Agency may refer validated and assessed signals to the NNDAC for independent scientific review and expert recommendations. Based on the available evidence and expert advice, the Agency determines the appropriate regulatory actions required to protect public health.

9.4.2. Roles and Responsibilities

Signal management in Nigeria involves coordinated responsibilities between the Agency, Marketing Authorisation Holders, and the National Drug Safety Advisory Committee

MAHs are responsible for ongoing safety monitoring and the detection, validation, and assessment of safety signals. NAFDAC provides regulatory oversight, including signal evaluation and decision-making to protect public health. Where required, NAFDAC may seek independent scientific advice from NDSAC for prioritised or high-impact signals.

The table below summarises the roles and responsibilities of each stakeholder.

ACTIVITY	NAFDAC	MAHs	NNDSAC
Continuous Safety Monitoring	Monitor safety data from the national pharmacovigilance system and other relevant sources to identify potential signals.	Continuously monitor the safety of authorised products using all available safety data sources.	—
Signal Detection	Implement signal detection methods and review national and international safety data.	Apply appropriate signal detection methodologies within their pharmacovigilance systems.	—
Signal Validation	Validate potential signals to determine if further evaluation is required.	Perform internal validation of detected signals prior to detailed assessment and report to the Agency	—
Signal Prioritisation and Assessment	Prioritise validated signals and conduct or coordinate scientific evaluation.	Conduct scientific assessment of validated signals to determine potential impact on the benefit–risk balance and report to the Agency.	Provide an independent scientific review of validated and assessed signals when referred by NAFDAC.
Information Requests and Collaboration	Request additional data or analyses from MAHs to support signal evaluation.	Provide requested data, analyses, and supporting documentation within required timelines.	Provide expert advice to support regulatory assessment when requested.
Communication of Safety Signals	Communicate validated safety concerns and	Notify the Agency of significant or emerging	Advise on appropriate risk communication

	regulatory decisions to relevant stakeholders.	safety issues in line with specified timelines.	strategies and public health considerations.
Regulatory Action and Risk Management	Determine, Approve and implement appropriate regulatory actions, including safety updates or risk minimisation measures.	Implement regulatory decisions and required risk minimisation measures.	Provide recommendations on regulatory actions and risk minimisation measures.
Safety-Related Variations	Review and approve safety-related variation applications affecting product information.	Submit variation applications when signal evaluation requires updates to safety information.	—
Maintenance of Product Information	Issue recommendations or requirements for updates to product safety information.	Ensure product information remains up to date in light of emerging scientific evidence and regulatory recommendations.	—
Urgent Safety Assessments	Coordinate regulatory review of high-priority or emerging safety issues.	Provide urgent safety data and analyses.	Conduct urgent independent assessments for high-risk signals and provide recommendations, where feasible within 30 days.
Documentation and Record Keeping	Maintain records of signal detection, evaluation, and regulatory decisions.	Maintain documentation of signal management activities within the pharmacovigilance system.	Maintain records of committee deliberations and recommendations provided to the Agency.

Table 1 Roles and Responsibilities

9.5. Structure and processes

9.5.1. Sources of Signals

Signals may arise from a wide range of data sources including any scientific or clinical information concerning the use of a medicinal product and its associated outcomes. Signal detection activities shall therefore not be limited to spontaneous reports of suspected adverse reactions. MAHs and the Agency

shall ensure that signal detection activities systematically consider all relevant sources of safety information, as outlined in **Chapter 5.4.2 Sources of Report**

Signal detection is frequently based on the periodic monitoring of databases containing reports of suspected adverse reactions. These databases may vary in scope and size and may include marketing authorisation holder global safety databases, national pharmacovigilance databases, and international pharmacovigilance databases such as those maintained under the WHO Programme for International Drug Monitoring (VigiBase).

9.4.2. Signal Detection

- 9.4.2.1. Signal detection involves the systematic review of safety data to identify new potential associations or new aspects of known associations between a medicinal product and adverse events. Signal detection activities may include: Clinical review of individual case safety reports; Statistical or disproportionality analyses where sufficient data exist; Trend analysis over time; Review of case series or clusters of similar events; Monitoring of scientific literature and emerging evidence
- 9.4.2.2. Detection activities shall be conducted in a structured and documented manner. Criteria for prioritisation should consider factors such as: seriousness and severity of the adverse event; potential impact on patients or public health; preventability of the event; and strength and consistency of the available evidence.
- 9.4.2.3. Signal detection from Individual Case Safety Reports (ICSRs) may involve both qualitative clinical review and, where applicable, quantitative data screening methodologies. Clinical review should consider factors such as seriousness, clinical pattern, temporal relationship between the medicinal product and the event, biological plausibility, and recurrence of similar reports.
- 9.4.2.4. MAHs shall conduct routine signal detection using their global safety databases and all relevant safety data available to them worldwide. Where an emerging signal is identified that may affect products authorised in Nigeria, or that may have implications for the Nigerian population, the MAH shall promptly notify the Agency and provide a summary of the available evidence, including any proposed risk evaluation or risk minimisation measures.
- 9.4.2.5. Where the volume of available data permits, statistical or disproportionality analyses may be applied to support the identification of potential safety signals
- 9.4.2.6. While signal detection frequently originates from spontaneous reporting systems, both the Agency and Marketing Authorisation Holders shall ensure that signal management activities consider all relevant safety information. Reliance on a single data source shall not be considered sufficient where additional data are reasonably available

9.4.3. Signal Validation

Signal validation is the process of evaluating the available information supporting a detected signal in order to determine whether the available evidence supports a new potentially causal association or a new aspect of a known association between a medicinal product and an adverse event, and therefore requires further in-depth assessment. Validation should be conducted promptly after signal detection and documented as part of the pharmacovigilance system.

Signal validation should be based on a structured review of the available evidence. When validating a detected signal, the Agency and MAHs should consider the following elements.

9.4.3.1. Previous Knowledge of the Association

Evaluation should determine whether the suspected association is already known or previously assessed. The Agency or MAH should assess the extent to which the suspected association is already known. This may include consideration of:

- Whether the suspected adverse reaction is already described in the product information (e.g., Summary of Product Characteristics or equivalent approved Nigerian product information).
- Whether the reaction has been identified for other medicinal products containing the same active substance or belonging to the same pharmacological class.
- Whether the association has previously been evaluated in regulatory procedures such as:
 - the Risk Management Plan (RMP),
 - Periodic Safety Update Reports (PSURs), or
 - any other regulatory assessment procedure.
- Whether the signal provides new information regarding a known adverse reaction, such as changes in:
 - severity,
 - duration,
 - incidence,
 - clinical management.

9.4.3.2. Strength of the Initial Evidence

The available case reports or data should be reviewed to determine whether they provide sufficient support for the signal. This may include:

- The number of reported cases, after removal of duplicates.
- The presence of supportive clinical features, such as:
 - plausible temporal relationship between drug exposure and event
 - positive dechallenge or rechallenge
 - absence of strong alternative explanations.

- Consistency of clinical patterns across cases (e.g., similar time-to-onset or clinical presentation).
- Quality and completeness of the available case information.
- Presence of supporting signals from other sources, including other regulatory authorities.

9.4.3.3. **Clinical Relevance**

Initial validation should also consider the potential clinical importance of the suspected reaction, including:

- seriousness or severity of the reaction
- outcome of the event
- potential impact on patient safety.

9.4.3.4. **Decision**

Following the review of available information, the signal should be classified as:

- Validated signal where sufficient evidence exists to support further assessment through signal assessment; or
- Non-validated signal when available evidence does not support a causal association at the current time.

9.4.3.5. Where validation supports further assessment, the signal shall be formally confirmed and entered in the signal tracking system. Confirmation shall ensure structured assessment, allocation of responsibilities, and defined timelines.

9.4.3.6. Validated signals should proceed to signal assessment where all available evidence is assessed to determine whether the association represents a new risk or a change in a known risk.

9.4.3.7. Both validated and non-validated signals, including the justification for the decision, shall be documented as part of the signal management process.

9.4.4. **Signal Prioritisation and Public Health Impact**

9.4.4.1. Throughout the signal management process, the Agency and MAHs shall consider whether a detected or validated signal may represent a risk with significant implications for patient safety, public health, or the overall benefit–risk balance of the medicinal product.

9.4.4.2. Validated signals should therefore be prioritised for further assessment based on their potential impact and urgency. In determining the level of priority for further signal evaluation, the following factors should be considered.

Factor	Considerations
Seriousness / Severity	Life-threatening, fatal, or disabling events
Public Health Impact	Number of patients affected, population vulnerability
Evidence Strength	Consistency, plausibility, quality of data
Preventability	Availability of mitigation measures
Population Exposure	Extent and distribution of product use. Exposure in vulnerable or special populations, such as children, pregnant women, older adults, or patients with underlying medical conditions
Urgency	Emerging safety concerns requiring immediate action
Public concern	potential public concern or media attention
Class Effects:	Applicability of risk to other products containing the same active substance, or other medicinal products within the same pharmacological class

Table 2 Signal Prioritization Considerations

9.4.4.3. The timeframe for further signal assessment should be determined based on the assigned priority. Where available information suggests the presence of a potential risk requiring prompt action, the Agency may implement interim risk minimisation or communication measures before completion of the full signal assessment process.

9.4.4.4. Clinical judgement and scientific expertise should be applied throughout the signal management process to ensure timely protection of public health.

9.4.5. Signal Assessment

9.4.5.1. Signal assessment is the process of performing a comprehensive scientific evaluation of a validated signal to determine whether a causal association between the medicinal product and the event is likely, and whether regulatory or risk minimisation actions are required. Signal assessment should consider all available sources of evidence, including clinical, epidemiological, pharmacological, and regulatory information.

9.4.5.2. During signal assessment, the Agency and MAHs should conduct a structured evaluation of the available evidence including:

9.4.5.2.1. **Clinical Evidence from Case Reports:** A detailed review of relevant Individual Case Safety Reports (ICSRs) should be undertaken, considering:

- clinical description and pattern of the reaction
- time to onset after drug exposure
- outcomes and reversibility
- evidence of dechallenge or rechallenge
- presence of alternative causes such as underlying disease or concomitant medications
- recurrence of similar cases across different populations.

9.4.5.2.2. **Biological and Pharmacological Plausibility:** Assessment should examine whether a credible biological mechanism may explain the association, including:

- pharmacological properties of the medicinal product
- known class effects
- experimental or non-clinical evidence.

9.4.5.2.3. **Epidemiological Evidence:** Where available, additional analyses may be undertaken to strengthen or refute the signal, including:

- review of exposure data
- epidemiological studies or pharmacoepidemiological analyses
- data from clinical trials.

9.4.5.2.4. **Evidence from External Sources:** Additional information that may support or refute the signal includes findings from the scientific literature; safety information from other regulatory authorities; data from ongoing or completed clinical studies; information from healthcare utilisation or observational databases.

9.4.5.2.5. **Regulatory Considerations:** In determining the regulatory significance of a validated signal, consideration should be given to the seriousness and severity of the reaction; frequency of occurrence relative to patient exposure; potential for prevention or risk minimisation; impact on the overall benefit–risk balance of the medicinal product; availability of alternative therapeutic options. Signals affecting vulnerable populations, including children, pregnant women, older persons, or patients with comorbidities, may warrant particular attention.

9.4.5.3. The outcome of signal assessment may include confirmation of a new or changed safety risk; conclusion that the signal is refuted or unsupported; recommendation for additional data collection or monitoring.

9.4.5.4. Where a new or changed risk is confirmed, the Agency may consider regulatory actions such as updates to product information; additional risk minimisation measures; post-authorisation safety studies; safety communications to healthcare professionals and the public.

9.4.5.5. Validated signals requiring regulatory decision-making may be referred to the NNDSAC for expert review and recommendations to the Agency

9.4.6. Signal Detection and Notification by Marketing Authorisation Holders

9.4.6.1. Marketing Authorisation Holders are responsible for the continuous monitoring of safety data related to their authorised medicinal products to identify potential safety signals. This monitoring should include review and analysis of data from all relevant sources available to the MAH.

- 9.4.6.2. Where an MAH detects a potential signal during routine pharmacovigilance activities, the MAH shall conduct signal validation to determine whether the information suggests a new or changed risk associated with the medicinal product.
- 9.4.6.3. Signal validation should include a comprehensive review of available data sources, which may include Individual Case Safety Reports available to the MAH; Data from the MAH's internal safety database; Scientific and medical literature; Clinical trial data; Post-authorisation studies; Relevant information from international pharmacovigilance databases or regulatory communications.
- 9.4.6.4. Where a signal is validated, the MAH should evaluate whether the safety issue represents a refuted signal; a new or changed risk associated with the product; or a potential safety issue that requires further evaluation by the regulatory authority.
- 9.4.6.5. Where the MAH concludes that a validated signal represents a new or changed risk, or where the available data are insufficient to confirm or refute the signal, the MAH shall promptly inform the Agency and provide the relevant supporting information for regulatory assessment.
- 9.4.6.6. If the signal suggests that the safety profile of the medicinal product may require modification, the MAH may be required to submit an application to update the product information or implement additional pharmacovigilance or risk minimisation measures as determined by the Agency.
- 9.4.6.7. Signals that are refuted following the MAH's internal evaluation should be documented and may be reported within the relevant periodic safety reports submitted to the Agency.
- 9.4.6.8. All signal evaluations conducted by the MAH should be adequately documented and made available to the Agency upon request.

9.4.7. Review by the NAFDAC National Drug Safety Advisory Committee

- 9.4.7.1. Where a signal has undergone validation and/or assessment and is considered to have potential for regulatory action, the Agency may present the signal to the NNDSAC for independent scientific review and expert recommendations.
- 9.4.7.2. The Committee shall evaluate the available evidence, consider the public health implications, and provide recommendations to the Agency regarding appropriate regulatory actions or risk minimisation measures.
- 9.4.7.3. Consultation with the Committee may occur during or after signal Validation/assessment, depending on the urgency and complexity of the safety concern. For urgent signals, an extraordinary NNDSAC session may be convened within 30 calendar days.
- 9.4.7.4. The Agency shall document signal summaries submitted to NNDSAC; Committee deliberations, recommendations made and final regulatory decisions.

9.4.7.5. Recommendations of the NNDSAC may include one or a combination of the following actions, depending on the nature, strength, and public health relevance of the signal:

- 9.4.7.5.1. Request for additional data: the MAH may be requested to provide additional data or analyses to support further assessment of the signal within a defined timeline.
- 9.4.7.5.2. Submission or review of data through periodic safety reporting: The MAH may be requested to provide a comprehensive review of the signal in the next Periodic Safety Update Report (PSUR) or to submit an ad-hoc PSUR where necessary.
- 9.4.7.5.3. Update of product information: The MAH may be required to update the product information (including the Summary of Product Characteristics, Patient Information Leaflet, or labeling) through an appropriate regulatory variation to reflect new safety information.
- 9.4.7.5.4. Submission or update of a Risk Management Plan (RMP): The MAH may be requested to submit a Risk Management Plan or update an existing RMP to include additional pharmacovigilance activities or risk minimisation measures related to the identified signal.
- 9.4.7.5.5. Implementation of additional risk minimisation measures: The MAH may be required to implement risk minimisation measures, such as educational materials for healthcare professionals and patients, or the dissemination of a Direct Healthcare Professional Communication (DHPC), where necessary to mitigate identified risks.
- 9.4.7.5.6. Post-authorisation safety studies: The MAH may be required to conduct a post-authorisation safety study (PASS) or other pharmacoepidemiological study in accordance with an agreed protocol and submit the results within a defined timeline.
- 9.4.7.5.7. Regulatory review or referral procedures: Where the signal raises significant safety concerns, the Agency may initiate further regulatory review procedures or refer the matter to appropriate national regulatory mechanisms for comprehensive evaluation.
- 9.4.7.5.8. Collection of additional information: NAFDAC may undertake further data collection activities, including targeted follow-up of individual case safety reports (ICSRs), analysis of national or international pharmacovigilance databases, or engagement with healthcare institutions to obtain additional information relevant to the signal.
- 9.4.7.5.9. Consultation with experts: The agency may seek advice from external experts, technical working groups, or relevant national committees where specialised expertise is required.
- 9.4.7.5.10. Pharmacovigilance inspections: Where concerns relate to compliance with pharmacovigilance obligations, the agency may conduct inspections of the MAH to verify adherence to pharmacovigilance requirements.

- 9.4.7.5.11. Other regulatory actions: Any other regulatory or risk management measures considered appropriate by the agency in the interest of public health may be recommended.
- 9.4.7.5.12. No immediate regulatory action: Where the available evidence is insufficient to confirm or refute the signal, the NNDSAC may recommend continued routine pharmacovigilance and ongoing monitoring of the issue.
- 9.4.7.5.13. Where applicable, the Agency shall communicate required actions to the relevant MAHs and monitor compliance within specified timelines.

9.4.8. Communication

- 9.4.8.1. Following the assessment of a validated signal and the issuance of recommendations by the NNDSAC, the Agency shall determine the appropriate communication strategy based on the level of risk identified, the urgency of the safety concern, and the population potentially affected. The level and urgency of communication shall be proportionate to the potential impact of the safety issue. Communication will generally follow the principles outlined in Good Pharmacovigilance Practice guidelines chapter 4: Safety Communication
- 9.4.8.2. Depending on the nature of the signal and the recommended regulatory action, the agency may communicate signal outcomes through one or more of the following mechanisms. In certain cases, the MAH may be required to support or implement specific communication activities under the oversight and approval of the Agency
 - 9.4.8.2.1. Direct Healthcare Professional Communications (DHPCs): Where urgent communication to healthcare professionals is necessary to mitigate risks associated with a medicinal product.
 - 9.4.8.2.2. Public Alerts: These communications may be issued directly by the Agency where immediate regulatory notification is required. The Agency may issue public alerts to inform healthcare professionals, public health programmes, and the general public of emerging safety concerns.
 - 9.4.8.2.3. Updates to Product Information: Where signal assessment results in changes to the safety profile of a medicinal product, the MAH may be required to submit an application to update the product information, including the Summary of Product Characteristics, Patient Information Leaflet, and product labelling. Following approval by the Agency, the MAH shall ensure that the updated product information is implemented and distributed appropriately.
 - 9.4.8.2.4. Educational and Risk Minimisation Materials: Where additional risk minimisation measures are required, the MAH may be required to develop and disseminate educational materials or other communication tools aimed at healthcare professionals and patients. Such materials shall be subject to prior review and approval by the Agency.

- 9.4.8.2.5. Publication through Regulatory Platforms: The Agency may communicate signal outcomes through official channels such as the Agency's website, Pharmacovigilance newsletters, or other regulatory publications in order to promote transparency and awareness among stakeholders.
- 9.4.8.2.6. Targeted Communication to Public Health Programmes: Where signals relate to medicinal products used within national public health programmes, the Agency may communicate the safety information directly to programme managers, healthcare institutions, and implementing partners to ensure appropriate risk management actions are taken.
- 9.4.8.2.7. Stakeholder Engagement: The Agency may also communicate signal outcomes through meetings, workshops, or official correspondence with relevant stakeholders, including MAHs, professional associations, healthcare institutions, and public health authorities. MAHs may be required to participate in such engagements where the communication relates to their authorised products.

9.4.9. Signal Closure

- 9.4.9.1. A signal may be considered closed once the evaluation process has been completed and an appropriate regulatory conclusion has been reached. Signal closure occurs when the available evidence does not support a causal association between the medicinal product and the reported adverse event, or when the signal has resulted in appropriate regulatory action and the necessary risk management measures have been implemented.
- 9.4.9.2. Closure of a signal should be formally documented to ensure transparency and traceability of the decision-making process. The documentation should include a summary of the scientific assessment conducted, any recommendations provided by the NNDSAC, the final regulatory decision taken by the Agency and details of any communication or risk minimisation measures implemented. The rationale for closing the signal should also be recorded in the signal tracking system to allow future reference and regulatory review where necessary.

9.5. Timelines for signal management activities

The Agency and Marketing Authorisation Holders (MAHs) shall ensure that signal management activities are conducted within appropriate timelines that are proportionate to the level of potential public health risk.

9.5.2. Frequency of Safety Data Monitoring

- 9.5.2.1. The Agency and MAHs shall ensure the continuous monitoring of safety data sources, including spontaneous reports and other pharmacovigilance data.
- 9.5.2.2. The frequency of monitoring should be proportionate to the known or potential risk profile of the medicinal product and should take into account factors such as:
- Time since first marketing authorisation

- Extent of patient exposure
- Important identified or potential risks
- Missing safety information
- Frequency of periodic safety reporting
- Volume of ICSRs received
- Safety concerns identified during special programmes (e.g. vaccination campaigns)

9.5.2.3. As a general principle, Safety data monitoring should be conducted at least every (6) months for authorised products.

9.5.2.4. More frequent monitoring, including monthly or quarterly is required for:

- Newly authorised medicinal products
- Products under additional safety monitoring
- Products associated with emerging safety concerns
- Products used in large public health programmes
- the seriousness of potential adverse reactions

9.5.2.5. MAHs and the Agency should determine the appropriate monitoring frequency for each medicinal product or active substance based on a risk-based approach, taking into account the factors listed above

9.5.2.6. The selected monitoring frequency, including any subsequent modifications and the justification for such changes, should be clearly documented within the organisation's pharmacovigilance procedures and maintained as part of the signal management documentation.

9.5.3. Timelines for Signal Management Steps

The following indicative timelines should guide the management of identified signals, however, where signals indicate potential serious risks to public health, accelerated evaluation and regulatory action should be undertaken

Signal Management Step	Recommended Timeline
Signal detection review	Continuous monitoring
Initial signal validation by NAFDAC	Within 30 calendar days of signal detection
Signal validation by Marketing Authorisation Holder (MAH)	Within 30 calendar days of signal detection through routine pharmacovigilance activities

Notification of validated signals by MAH to the Agency	Promptly following validation and not later than 15 calendar days after confirmation of a signal that may represent a new or changed risk
Signal prioritisation	Within 15 calendar days following validation
Signal assessment	Within 60–90 calendar days, depending on complexity and availability of data
Escalation to the NNDSAC for expert review	At the earliest available committee meeting, or through urgent consultation where necessary
Regulatory decision and implementation of risk minimisation measures	As soon as practicable following completion of signal assessment
Communication of signal outcome	Within 15 calendar days of regulatory decision

Table 3: Timelines for Signal Management activities

9.6. Urgent Safety Signals

Where available information suggests an emerging safety issue that may significantly affect the benefit–risk balance of a medicinal product, the MAH shall notify the Agency without delay.

Urgent signals may arise from:

- Unexpected fatal or life-threatening adverse reactions
- Rapidly increasing reporting trends
- Safety findings from ongoing studies
- Major regulatory actions taken by other regulatory authorities.

In such cases, the Agency may initiate immediate risk evaluation and regulatory measures, including safety communications to healthcare professionals and the public.

9.7. Documentation and Quality Requirements for Signal Management

9.7.2. Signal management is a critical pharmacovigilance process and should be conducted within a structured quality management system to ensure that activities are performed consistently, transparently, and effectively.

9.7.3. All organisations involved in signal management, including the Agency and MAHs, should ensure that signal management processes are clearly documented. Documentation should describe the procedures, roles, responsibilities, and tasks associated with signal detection, validation, prioritisation, assessment, and regulatory decision-making.

9.7.4. Appropriate standard operating procedures (SOPs) should be developed, implemented, and maintained to support signal management activities. These procedures should include the methodology used for signal detection, the frequency of signal review activities, and the criteria used for validation, prioritisation, and escalation of signals.

- 9.7.5. Organisations should maintain a tracking system that provides a clear audit trail of signal management activities. This system should ensure traceability of all steps in the signal management process, including signal detection, validation, assessment, decision-making, and regulatory actions taken. Records should include relevant dates, documentation of analyses conducted, decisions made, and the rationale for those decisions in order to demonstrate compliance with established timelines and procedures.
- 9.7.6. Roles and responsibilities for signal management activities, including documentation, quality control, and review processes, should be clearly defined and assigned within the organisation. Mechanisms should also be in place to ensure the implementation of corrective and preventive actions where deficiencies in the signal management process are identified.
- 9.7.7. Staff involved in signal management activities should possess the necessary qualifications and expertise and should receive appropriate training relevant to their roles and responsibilities. Training records should be maintained and periodically reviewed to ensure that personnel remain competent to perform signal management tasks.
- 9.7.8. MAHs should document their signal management processes as part of their pharmacovigilance system documentation and ensure that records relating to signal detection, validation, evaluation, and regulatory communication are maintained and readily retrievable. MAHs should implement a record management system that ensures traceability of actions taken to investigate safety concerns, including documentation of the timelines, analyses performed, and decisions reached.
- 9.7.9. Signal management systems should be subject to periodic review and audit to ensure that they are functioning effectively and in compliance with applicable pharmacovigilance requirements. This may include internal audits conducted by MAHs as well as inspections conducted by the Agency.
- 9.7.10. Appropriate measures should also be implemented to ensure the confidentiality, security, and integrity of data and documents used in signal management activities. This includes ensuring that safety data are protected from unauthorized access and that data integrity is maintained when information is transferred or shared between organisations.

9.7.11. Minimum Documentation Requirements for Signals

To ensure transparency, traceability, and effective oversight of signal management activities, the Agency shall maintain documentation for each signal assessed within the pharmacovigilance system. Documentation should allow the entire signal management process to be reconstructed and reviewed where necessary. At a minimum, the following information should be recorded for each signal:

Signal Documentation Element	Description
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Signal identifier/reference number	Unique identifier assigned to the signal for tracking purposes
Date of signal detection	Date the potential signal was first identified
Source of signal	Source of detection (e.g., ICSRs, literature, international regulatory communication, clinical studies, MAH notification)
Product(s) and active substance(s) involved	Medicinal product(s) associated with the signal
Suspected adverse reaction(s)	Description of the safety concern or adverse event
Date of signal validation	Date the signal was confirmed as requiring further evaluation
Signal prioritisation category	Priority level assigned based on public health impact
Summary of assessment	Summary of the scientific evaluation conducted
NNDSAC review and recommendation (if applicable)	Advice provided by the NNDSAC
Regulatory decision	Final decision taken by NAFDAC
Risk minimisation or regulatory actions implemented	Any actions taken, such as product information updates or safety communications
Communication measures	Details of communications issued to healthcare professionals, MAHs, or the public
Signal closure date	Date the signal was formally closed
Rationale for closure	Justification for closure based on assessment outcome

Table 4: Minimum Documentation requirement for Detected Signals

Annexure: Signal Detection Process Flow

