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Guideline for Signal Management

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Guideline for Signal Management

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Acknowledgements

We duly thank the European Medicines Agency (EMA) for publishing their guidelines that contributed in several aspects relevantly to the development of this guideline.

1 Introduction (background)

1.1. This guideline is developed by MCA to define a standard process of signal management on medicines for human use.

1.2. This guideline is for information, guidance and strict compliance by all stakeholders involved in signal management, i.e. marketing authorisation holders (MAHs), MCA and other stakeholders.

1.3. Penalties for non-compliance with this guideline might be enforced according to the relevant legal provisions.

2 Legal basis

2.1. The regulation of medicines in The Gambia is governed by the provisions and requirements of the Medicines and Related Products Act, 2014 ("Act"), by which the Medicines Control Agency (MCA) was established as the regulatory body for medicines and related products.

2.2. Part II Sections 4 (c) requires the Agency to ensure that evidence of existing and new adverse events, interactions and information about pharmacovigilance of medicines being monitored globally, are analysed and acted upon.

2.3. The Medicines and Related Products Regulations, 2020 ("Regulations") details the legal requirements.

2.4. MCA functions as the National Pharmacovigilance Centre. Safety monitoring of medicines by the Agency ensures that they continue to be safe for patients and the general public. Healthcare professionals, marketing authorisation holders (MAHs) or their local representatives and manufacturers are key stakeholders in the continuous safety monitoring of medicines marketed in The Gambia.

3 Purpose and Scope

3.1. 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 MCA.

3.2. Information on the mandatory reporting of Adverse Drug Reactions (ADRs), Adverse Events Following Immunization (AEFIs), and causality assessment is not subject of this guideline and it is described in the MCA *Guideline for Reporting of Adverse Reactions to Medicines including Vaccines*.

3.3. This guideline applies to all MAHs and other stakeholders involved in the pharmacovigilance activities for medicines for human use authorised in The Gambia for marketing.

3.4. It encompasses the processes of signal detection, validation, prioritisation, assessment, and decision-making. This guideline ensures that a consistent and comprehensive approach is taken in managing signals to safeguard public health.

4 Structures and Processes

4.1 Sources of data and information

4.1.1. The following are sources for data and information:

- Scientific information regarding the use of the medicine 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 (healthcare professionals, patients, consumers, insurance companies, lawyers, etc.), active surveillance systems, studies and scientific literature reporting safety data, media;
- Periodic database monitoring, such as the MCA database, EudraVigilance, UMC VigiBase of the WHO Programme for International Drug Monitoring;
- Safety reports or concerns raised by other national regulatory authorities (NRAs), international organisations.

4.2 Signal detection

4.2.1. 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 medicine concerned. For further guidance on the methodological strategies for vaccines, refer to EMA Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases (see references). For biologicals, refer to EMA Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products.

4.2.2. Data from all appropriate sources should be considered (see **Error! Reference source not found.**). At all times, clinical judgement should be applied.

4.2.3. 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.

Statistical aspects of signal detection

4.2.4. 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).

4.2.5. Statistical aspects of signal detection should not be used to replace qualitative aspects of signal detection (the review of individual ICSRs, see 4.2.3).

4.3 Evaluation during signal validation and further assessment

4.3.1. 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 patient information leaflet patient information leaflet (PIL));
  - whether the signal relates to an adverse reaction already included in the SmPC for other medicines containing the active substance of interest, bearing in mind that some signals may only be relevant to a specific medicine 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 (see references);
  - dose-reaction relationship;
  - possible mechanism based on a biological and pharmacological plausibility;
  - disproportionality of reporting, if applicable (see 0).
- 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 medicine;
- 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 local 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.

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

4.4 Signal prioritisation

4.4.1. 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 medicine.

4.4.2. 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.

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

4.4.4. 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.

4.4.5. Clinical judgement and flexibility should be applied throughout the process.

4.5 Quality requirements

4.5.1. 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 MCA *Guideline for the National*

Pharmacovigilance System).

4.5.2. 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.

4.5.3. 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.

4.5.4. 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.

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

4.5.6. 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.

4.5.7. 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. This includes maintaining data integrity when transferring information between organisations.

4.5.8. 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.

5 Roles and Responsibilities

5.1 Responsibilities of the MAH

5.1.1. MAHs in The Gambia should continuously monitor the safety of their medicines and notify MCA of any new information that could affect the marketing authorisation, including any information that constitutes an emerging safety issue.

5.1.2. 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 MCA as outlined below.

5.1.3. 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/PBRER (see MCA *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*).

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

5.1.5. 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.

5.2 Emerging safety issues

5.2.1. 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@mca.gm or via phone to: 3363068, short code 1233. This notification should be made without delay and no later than three (3) calendar days after confirming that a validated signal or safety issue qualifies as an emerging safety concern.

5.2.2. This is in addition to the requirements for submission of individual case safety reports as outlined in the MCA *Guideline for Reporting of Adverse Reactions to Medicines including Vaccines*, when the emerging safety issue refers to a single case of suspected ADRs.

5.2.3. 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 MCA and the relevant national competent authorities as soon as it becomes accessible.

5.2.4. When being informed of an emerging safety issue, MCA must swiftly assess the urgency and potential impact of the matter. Should it be necessary, this evaluation may involve consulting the Medicines Safety Experts Committee (MSEC). Moreover, the MAH should collaborate with MCA in the assessment and management of the emerging safety issue.

5.2.5. 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, i.e. whose urgency and seriousness cannot permit any delay in handling.

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

5.2.7. If the MAH decides to take any of the following actions in response to the emerging safety issue, MCA 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.

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

5.2.9. MCA may decide to schedule ad hoc meetings of the MSEC 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 will be scheduled accordingly.

5.3 Monitoring of safety databases

5.3.1. MCA should continuously monitor the local 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.

5.3.2. 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 The Gambia.

Periodicity of monitoring

5.3.3. Safety databases should be continuously monitored by MCA 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).

5.3.4. 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.

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

5.3.6. 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.

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

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

5.4.2. 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.

5.4.3. The MAH is to check whether a risk may already be addressed in the product information of other medicines containing the active substance of interest that are marketed in the EU, USA, Asia and Africa. In this case, the product information should be aligned as appropriate through an application for variation of the terms of marketing authorisation.

5.4.4. 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.

5.4.5. The MAH may seek further analysis by MCA if validated signals cannot be refuted nor confirmed as new or changed risks. Signals that require further analysis by MCA may be reported only in PSURs/PBRERs if the conditions outlined in section 5.6 are met. Refuted signals should only be reported in PSURs//BRERs. All validated signals that require urgent attention should be reported as emerging safety issues (see 5.7).

5.5 Variation of the terms of marketing authorisation

5.5.1. If a MAH concludes that the product information and/or the RMP require updating through a variation, a variation application shall be submitted to MCA. 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.

5.5.2. 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 MCA.

5.6 Inclusion of the signal in the PSUR/PBRER

5.6.1. If an active substance is included in the List of Union Reference Dates and Frequency of Submission of PSURs (see references) and a PSUR/PBRERs 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.

5.6.2. The signal will be assessed by MCA within the PSUR/PBRERs procedure. If the data-lock point of the PSUR/PBRERs has elapsed by the time the MAH has completed their assessment of the signal, it should be mentioned in the PSUR/PBRERs section 'Late-breaking Information' together with a proposal for further management of the signal. This also applies to the conclusions drawn based on the evaluation of safety signals.

5.6.3. 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/PBRERs.

Other required activities

5.6.4. In addition, the MAH shall evaluate the need for any changes to the IB, SmPC/PIL, labelling, educational or reference materials and inform MCA in a timely manner (see MCA *Guideline for Variations* and MCA *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*).

5.6.5. MCA should be informed about any other actions planned to be taken by the MAH (Post-Authorisation Safety Study/ Post-Authorisation Efficacy Study (PASS/PAES), Risk Minimization Measures (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, WHO, EMA. MCA shall review and approve or reject the activities proposed by MAH.

5.7 Signal notification

5.7.1. If a validated signal does not meet the conditions as outlined in 5.5 and 5.6 and further signal analysis by MCA is required, the MAH should complete the signal notification form (see MCA-T-309/01, Annex 1) available from the MCA website and send to MCA.

5.7.2. 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 MCA *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*).

5.8 Signal analysis, prioritisation and assessment by MCA

5.8.1. Signals will be prioritised by MCA 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 medicines or to other related adverse reactions.

5.8.2. Signal assessment will be performed by MCA using local database, and 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)).

5.8.3. 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.

5.8.4. Reliance mechanism in decision making will be used by MCA if necessary. The joint review, work-sharing and recognition and reliance on the decision of other NRAs and international organisations (EMA, WHO, PICs, etc.) can be applied.

5.8.5. The MCA shall conduct signal management periodically as follows:

- Conduct signal detection at least every three (3) months for products that have been prioritised for signal detection.

- Conduct signal detection at least every six (6) months for other products.
- De-classify products that have been prioritised 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.

5.8.6. The signal can be confirmed, refuted or reconsidered by MCA 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.

5.9 Signal confirmation by MCA

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

5.9.2. MCA may decide not to confirm a validated signal if, for example:

- it is already adequately handled through a different procedure (e.g. PSUR/PBRER, 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 The Gambia 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 MCA practices reliance.

5.9.3. MCA has the option, when needed, of using the MSEC 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.

Safety communication and feedback

5.9.4. MCA communicates information to all stakeholders, including patients and the healthcare community, Expanded Programme on Immunisation (EPI), other NRAs and international organisations (e.g. WHO UMC), public, Ministry of Health, etc. (as per MCA *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*).

5.9.5. Feedback from reviews should be disseminated to target audiences as soon as possible but in no case later than within 10 days.

5.9.6. Feedback should be shared with the sender of the report for possible

regulatory action taken within 5 working days in the form of:

- Letter to healthcare professionals;
- Product recall;
- PIL and/or SmPC update;
- Newsletter;
- Publishing of the recommendations on MCA website.

5.9.7. Feedback and further communication should be closely monitored.

5.10 Recommendations on signals to the MAH

5.10.1. 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/PBRER (see MCA *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*);
- the MAH should discuss all safety signals discovered during the reporting period in the text of the following DSUR (see MCA *Guideline for Clinical Trials in Humans*);
- 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 *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*);
- the MAH should propose RMMs and implement additional RMM after approval by MCA (e.g. Direct healthcare professional communication, educational materials, training for healthcare professionals 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 *Guideline for Safety Monitoring of Medicines (Pharmacovigilance) including Vaccines*);
- update of the IB or SmPC/PIL accordingly;
- consultation of Data and Safety Monitoring Boar (DSMB) and relevant scientific expert groups;
- an inspection may take place (see MCA *Guideline for the National Pharmacovigilance System*);
- rely on information or decisions made by other competent authorities, international organizations (WHO, UMC, EMA, PICs, etc.) to which MCA practices reliance as per MCA Reliance Policy;
- any other appropriate action that is not listed above.

5.11 Record management

5.11.1. MCA 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.

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

Definitions

Interpretations and abbreviations contained in the MCA Glossary can be found on the MCA Website: **www.mca.gm.**

The definitions provided below apply to the terms used in this guideline. They may have different meanings in other contexts and documents.

The interpretation of terms provided in the Act and Regulations apply, unless further defined in this guideline.

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

Adverse Drug Reaction (ADR) Case Report
A case report in pharmacovigilance is a notification related to a patient who has experienced an adverse medical event or laboratory test abnormality suspected to be induced by a medicine. It is important to stress that healthcare professionals should send reports of ADRs even if they do not have all the information required.

Adverse Event/Experience
Any unwanted medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. The basic point here is that an unwanted event occurs during or after the use of a medicine; the time of occurrence may be related to the use of the medicine but the event is not necessarily caused by it.

Adverse Event Following Immunisation (AEFI)
Any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse Reaction (AR)/Adverse Drug Reaction (ADR)
A response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

Drug (see Medicine/Medicinal Product)

Healthcare professional (Health professional, Health practitioner)
A person who is a medically qualified person such as a physician, dentist, pharmacist, or nurse.

Individual Case Safety Report (ICSR); synonym: Adverse (Drug) Reaction Report

Format and content for the reporting of one or several suspected adverse reactions to a medicine that occur in a single patient at a specific point of time.

ICSRs shall be used for collection, processing, quality control, coding, classification, medical review and reporting suspected adverse reactions to a medicine that occur in a single patient at a specific point in time. The source for an ICSR could also be the literature, clinical study or post-authorisation safety study.

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.

Marketing Authorisation Holder (MAH)
An organisation that has been issued a licence by the competent authority to market a medicine, medical equipment, or cosmetics within The Gambia or any other country and may or may not be the manufacturer of the particular product.

Medicine/Medicinal Product
Any substance or combination of substances prepared, sold or presented for use in the diagnosis, treatment, mitigation or prevention of disease, disorder of abnormal physical state or the symptoms of it or restoring, correcting or modifying organic functions in human beings and animals.

Medicines in the context of this guideline includes finished pharmaceutical products, biologicals (biotherapeutics), vaccines and herbal medicinal products for human use. Not included are related products, if not indicated otherwise.

Periodic Benefit Risk Evaluation Report (PBRER)
An update of the world-wide marketing experience of a product at defined times with focus on formal evaluation of benefit in special population at defined times during post-registration period.

Periodic Safety Update Report (PSUR)
A regular update of the world-wide safety experience of a product at defined times during post registration period.

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 MCA and the general population.

Safety concern
An important identified risk, important potential risk, or important missing information.

Signal
Refers to "Reported information on a possible causal relationship between an adverse event and a medicine; the relationship being known or incompletely documented previously" Usually more than a single report is required to generate a signal depending upon the seriousness of the event and the quality of the information.

Signal 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 MCA 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.

References

- Medicines and Related Products Act, 2014
- Medicines and Related Products Regulations, 2020
- Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1)

- EMA: Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases.
- EMA: Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products.
- Brighton collaboration case definitions, accessible via https://brightoncollaboration.org/case-definitions/
- EMA, List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), (EURD List)

Annexes

Annex 1: Signal Notification (MCA-T-309/01)

Appendix: Flowchart MAH signal management process