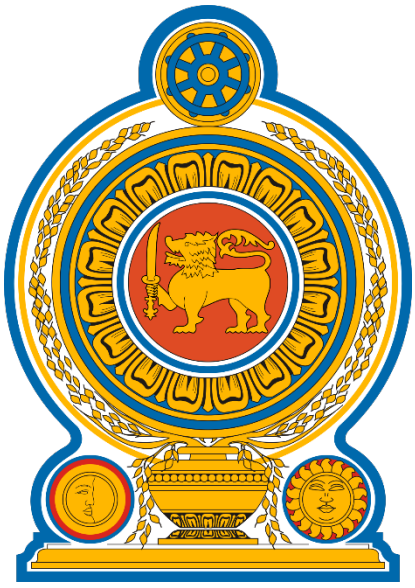

Guideline on Signal Management & Emerging Safety Issues

NATIONAL MEDICINES REGULATORY AUTHORITY
NORRIS CANAL ROAD, COLOMBO 10, SRI LANKA

Content

Signal management 2

1. Definitions 2
2. Sources of data and information for signals 2
3. Signal management process 2

3.1. signal detection 3

3.2. Signal validation and evaluation for further assessment 3

3.3. Signal prioritization 4

3.4. Signal assessment 4

4. Tracking 5
5. Actions/ Regulatory decisions based on signal management process 5
6. Responsibilities of the MAH 6
7. Emerging safety issues 7

7.1. Definition 7

7.2. Reporting requirements 8

7.3. Timeframe for reporting 8

7.4. Reporting channel 8

Signal management
& Emerging safety issues

1. Definitions

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 a medicinal product and an event or set of related events, that is judged to be of sufficient likelihood to justify verificatory action.

New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the adverse reaction.

A signal often relates to all medicinal products containing the same active substance, including combination products. Certain signals may only be relevant for a particular medicinal product or in a specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of medicinal products.

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.

2. Sources of data and information for signals

Signals can arise from a wide variety of data sources. Common sources that can be used for signals detection, validation and assessment include:

- national ADRs database or MAH's ADRs database as applicable
- active surveillance systems
- clinical studies
- scientific literature
- non-clinical studies
- international publicly available ADRs databases, such as EudraVigilance from European Economic Area, VigiBase from the WHO, or FAERS (Adverse Event Reporting System) from the US Food and Drug Administration (FDA)

3. Signal management process

Signal management process is a set of activities performed to determine whether, based on all available information, 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 whole process should be adequately documented.

Signal management activities are often described as a linear process consisting of different steps to be completed in a sequential order, but it is challenging to separate the different steps and not feasible to assign a time sequence or order in which they should be completed. It is acknowledged that flexibility may be required during the whole process.

Both of the NMRA and the MAHs should have its own signal management process and collaborate together. This signal management process includes; signal detection, validation, prioritization and assessment.

For signals detected by the NMRA, the MAHs should collaborate with the NMRA for the assessment of the signals by providing additional information upon request. For signals detected by the MAHs the following signal management process should apply as well as the full responsibilities described under section 6 below.

In general, signal management process includes the following activities:

3.1. signal detection

Signal detection should follow a methodology which takes into account the nature of data and the characteristics (e.g. time on market, patient exposure, target population) as well as the type of medicinal product concerned (e.g. vaccines and biological medicinal products may for example require specific methodological strategies).

Signal detection may involve a review of ICSRs, statistical analyses, or a combination of both, depending on the size of the data set. For small dataset, signal detection will involve mainly review of individual cases. Data from all appropriate sources should be considered. For signals detected from published studies or healthcare record data, assessment of aggregated will be more relevant or feasible rather than assessing each individual case.

3.1.1. Methods of signal detection

For detailed guidance of the Methodology follow EMA Guideline on good pharmacovigilance practices (GVP) Module IX Addendum I – Methodological aspects of signal detection from spontaneous reports of suspected adverse reactions

3.2. Signal validation and evaluation for further assessment

Signal validation is the process of evaluating the detected signal to determine potential causality and justification for further analysis.

During the validation of a signal, the evaluation of the data should be aimed at deciding if further analysis is necessary and the focus should be on determining if the signal reflects new information and if it is at least a reasonable possibility. For signals originating from spontaneous reports, that would include, as a minimum, making sure that the signal is not only based on duplicate reports and that there is a plausible time to onset.

This process takes into account the clinical relevance of the signal (such as its plausible mechanism), the seriousness and severity of the reaction and its outcome, as well as the novelty of the reaction. Other factors such as medicine interactions, occurrence in various populations and previous awareness of a signal should also be considered.

3.3. Signal prioritization

Prioritization should be a continuous process performed during the whole signal management process, rather than in a single step. Signal prioritization is required to focus the resources available on the most important signals. Signals with a potential important public health impact, or which may significantly affect the benefit-risk profile of the medicinal product, require urgent attention and should be prioritized for further management

3.4. Signal assessment

The aim of the signal assessment step is to further evaluate a validated signal so as to decide whether a regulatory action is necessary, and the focus should be on reaching a final decision on the causal relationship and to consider the need for (additional) risk-minimization measures.

The signal assessment should take into account all available data in order to further increase the strength of the evidence to reach a high-quality decision and signal outcome. The data reviewed at this step is usually more extensive.

Different sources of information are available to NMRA for signal assessment, of which the most frequently used are published literature, expert consultation and additional data provided by MAHs.

This assessment step is done mainly by the NMRA however, the MAH should consider the same approach when proposing the regulatory action to be taken.

Summary of the whole signal management process:

Step	Aim	Focus
Detection	Detect potential new signals	Observe: new issues abnormal pattern

validation	Decide if further analysis ins needed	Is it new? Is there at least reasonable possibility?
Prioritization &Assessment	Decide on the regulatory action	Reach conclusion about the causal relationship Options for risk minimization
Action	Official NMRA regulatory decision	

4. Tracking

All validation, prioritization, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps should be recorded and tracked systematically. All records need to be archived.

Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association or the signal which cannot be validated and further monitoring to gather additional information is to be made. These systems should include the reasons why signals were not validated, information that would facilitate further retrieval of ICSRs and validation of signals.

5. Actions/ Regulatory decisions based on signal management process

Following the signal management process, the NMRA decision may include any or a combination of the following conclusions:

- no action is required at this point in time, other than routine pharmacovigilance
- Request for additional data to be submitted:
  - the MAH should provide additional data for assessment within a signal procedure (e.g. cumulative review, collect further information from other data sources;
  - the MAH should provide a review of additional data on the signal in the following PBRER or submit an ad-hoc PBRER;
  - the MAH should sponsor a post-authorization study according to an agreed protocol and submit the final results of that study;
- Need for regulatory action:
  - the MAH should update the product information through an application for a variation;

- the MAH should be requested to submit an RMP or to update the RMP;
- the MAH should implement additional risk minimization measures such as educational materials or the dissemination of a Direct Healthcare Professional Communication (DHPC);
- immediate measures (temporary or otherwise) including suspension, withdrawal of the marketing authorization, removal of an approved indication, or a restriction of use of the medicinal product.

- any other appropriate action that is not listed above;

6. Responsibilities of the MAH

The MAHs and their local representatives should continuously monitor the safety of their medicinal products and inform the NMRA of any new information that might have an impact on the marketing authorization.

Regarding signal management, the MAH shall:

- have in place procedure for signal detection -across all available data sources- and for the whole signal management process
- periodically monitor the data in its own ADRs database and all other sources for signal detection;
- shall validate any signal detected to determine if a further assessment - considering additional sources of information -is warranted or if the signal could be refuted (further assessment is not considered necessary)
- should also assess the validated signal whether any regulatory action is warranted based on the conducted assessment of the risk
- shall report to the NMRA the validated signals together with any proposed regulatory actions to be taken, or justification for no further action
- notify the NMRA about any signal that meets the definition of an emerging safety issue (which could have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health) together with any proposed regulatory actions to be taken, or justification for no further action
- collaborate with the NMRA for the assessment of the signals by providing additional information upon request;
- keep documentation, tracking and an audit trail of its signal management activities.

- based on the signal assessment and the NMRA decision, if the product information and/or the RMP should be updated through a variation, the MAH should submit the variation application as soon as possible and no later than 3 months after completing the assessment of the signal if it corresponds to an important risk, or within 6 months for adverse reactions or risks not considered important
- present comprehensive signal information in PBRERs

7. Emerging safety issues

7.1. Definition

Emerging safety issue: A safety issue considered by a MAH to require urgent attention by the NMRA 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.

Examples include:

- major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contra-indication, modification or removal of an approved indication, a restriction of use of the medicinal product or its withdrawal from the market;
- major safety-related regulatory actions in other countries, e.g. a restriction of the use of the medicinal product, suspension, withdrawal, non-renewal, major changes to warnings, precautions in the product information or distribution of Dear Healthcare Professional (DHCP)
- major safety issues identified by the MAH as a result of its own signal management process once assessment has been completed and actions are proposed
- signal of a possible teratogen effect or of significant hazard to public health;
- major safety issues due to misinformation in the product information
- major safety issues related to use outside the terms of the marketing authorization or directions for use
- major safety issues in relation to any raw materials used in the medicinal product

7.2. Reporting requirements

When the MAH becomes aware of an emerging safety issue from any, they should notify it **in writing** to the NMRA and should include the following:

- description of the safety issue,
- the source(s) of information,
- any planned or taken actions with timelines,
- any relevant documentation available at the time of initial notification,
- any further information relevant to the issue should be provided to NMRA as soon as it becomes available

The MAH should collaborate with the NMRA in the assessment 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 above whose urgency and seriousness cannot permit any delay in handling.

7.3. Timeframe for reporting

The notification of emerging safety issues should be done as soon as possible and no later than **3 working days** after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

This is in addition to the ICSR submission requirements, when the emerging safety issue refers to a single case of suspected adverse reactions.

7.4. Reporting channel

The emerging safety issues should be reported to the NMRA on the following dedicated email

Email: vigilance@nmra.gov.lk

For more guidance on the structure and process of Signal managemnt, refer to the *EMA Guideline on good pharmacovigilance practices (GVP) Module IX*.

The EMA GVP Modules on Product- or Population-Specific Considerations should be consulted as applicable for signal management

Flow chart of signal management by MAH and collaboration with NMRA