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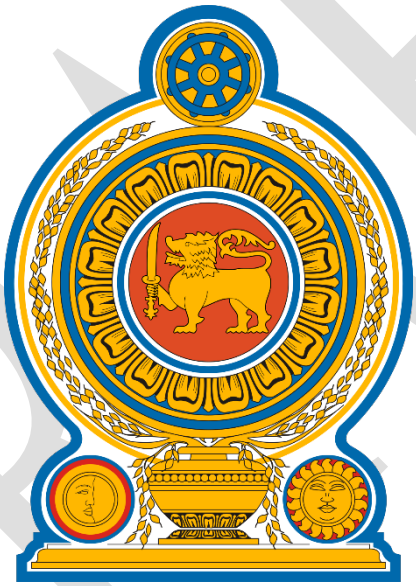

GUIDELINE ON PHARMACOVIGILANCE INSPECTION

NATIONAL MEDICINE REGULATORY AUTHORITY
NORRIS CANAL RD, COLOMBO 10, SRI LANKA

GUIDELINE ON PHARMACOVIGILANCE INSPECTION

CONTENT

DRAFT

1. INTRODUCTION

This guideline contains guidance on the planning, conducting, reporting and follow-up of pharmacovigilance inspections carried out by the National Medicines Regulatory Authority (NMRA).

All local manufactures, marketing authorization holders (MAHs) and their local representative (registered importers) are subjected to the pharmacovigilance inspection and they are responsible for meeting pharmacovigilance reporting requirements for their products.

This guideline describes how to schedule pharmacovigilance inspections, pharmacovigilance inspection types and responsibility of MAH to facilitate PV inspection.

Throughout this chapter the terms for marketing authorization holders applies also for their local representatives in Sri Lanka.

2. OBJECTIVES OF PHARMACOVIGILANCE INSPECTION

- To ensure compliance of the pharmacovigilance system with the legislation and guidelines provided by the NMRA.
- To ensure that the MAH and local representative has personal, system and facilities in place to meet their pharmacovigilance obligations
- To identify, record and address non-compliance which may pose a risk to public health
- To use the inspection results as a basis for enforcement action, where considered necessary

3. INSPECTION TYPES

3.1. Routine pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes developed by the NMRA.

These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

There is no specific trigger to initiate these inspections, although the Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to enable the frequency, scope and breadth of inspections to be determined accordingly.

3.2. For-cause pharmacovigilance inspections

For cause pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified

DRAFT

compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger.

3.3. Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritize re-inspections.

The scope of re-inspection will depend on the inspection history. It includes, but is **not limited to** the following:

- A review of the corrective and preventive action(s) resulting from previous pharmacovigilance inspection;
- A review of significant changes that have been made to the pharmacovigilance system since the last pharmacovigilance inspection;
- A review of the process and/or issues not covered in the previous inspection;
- Reviewing the complete pharmacovigilance system especially if a long time has elapsed since the previous inspection.

Early re-inspection may take place where significant non-compliance has been identified or when the NMRA have concerns regarding one or more of the stated above points

3.4. System and product related inspections

Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.

Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g. the system used for that product).

4. NATIONAL PHARMACOVIGILANCE INSPECTION PROGRAM

A national routine pharmacovigilance inspection program for authorized products in Sri Lanka will be determined by the NMRA. These inspections will be prioritized based on the potential risk to public health, triggers and other risk factors described below.

As a general approach, a MAH should be inspected on the basis of risk-based considerations, but it is recommended to routinely inspect MAH at least once every 4 years.

This routine inspection program will be separate from any “for cause” inspections, but if a “for cause” inspection takes place it may replace the need for one under this programme, dependent on its scope.

4.1. Inspection Planning and prioritization

4.1.1. Factors for risk-based approach planning

There is no specific trigger to initiate routine inspections, although the Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to enable the frequency, scope and breadth of inspections to be determined accordingly.

Factors which may be taken into consideration, as appropriate, include, but are not limited to:

inspection related:

- compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP);
- re-inspection date recommended by the inspectors or assessors as a result of a previous inspection;

product related:

- product with additional pharmacovigilance activities or risk-minimisation activities;
- authorization with conditions associated with safety, e.g. requirement for post-authorization safety studies (PASS);
- product(s) with large sales volume, i.e. products associated with large patient exposure in Sri Lanka;
- product(s) with limited alternative in the market place;

MAH or local representative related:

- MAH that has never been subject to a pharmacovigilance inspection;
- MAH with many products on the market in Sri Lanka;
- resources available to the MAH for the pharmacovigilance activities they undertake;
- MAH with no previous marketing authorizations in the Sri Lanka;
- negative information and/or safety concerns raised by NMRA (i.e. GCP, GMP, GLP and GDP);
- changes in the MAH organization, such as mergers and acquisitions;

pharmacovigilance system related:

- MAH with sub-contracted pharmacovigilance activities (function of the qualified person responsible for pharmacovigilance in Sri Lanka (QPPV), reporting of safety data etc.) and/or multiple firms employed to perform pharmacovigilance activities
- change of QPPV/ LSR since the last inspection;

DRAFT

- changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;
- changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted;
- delegation or transfer of pharmacovigilance system master file management.

4.1.2. Triggers of "For-cause inspections"

Unlike the routine inspection; the For-cause inspections may arise when, for example, one or more of the triggers listed below are identified:

risk-benefit balance of the product:

- change in the risk-benefit balance where further examination through an inspection is considered appropriate;
- delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
- communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the NMRA, as applicable;
- non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the NMRA;
- suspension or product withdrawal with no advance notice to the NMRA;

Reporting obligations (expedited and periodic):

- delays or omissions in reporting;
- poor quality or incomplete reports;
- inconsistencies between reports and other information sources;
- failure to provide the requested information or data within the deadline specified by the NMRA;
- poor quality or inadequate provision of data to fulfil requests for information from the NMRA;

Fulfilment of commitments:

- concerns about the status or fulfilment of risk management plan (RMP) commitments;
- delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorisation;
- poor quality of reports requested as specific obligations;
- delays in the implementation or inappropriate implementation of corrective and preventive actions;

DRAFT

- information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP);
- inspection information received from other authorities, which may highlight issues of non-compliance;

Others:

- concerns following review of the pharmacovigilance system master file;
- non-inspection related information received from other authorities, which may highlight issues of non-compliance;
- other sources of information or complaints.

4.2. Announcement of inspections

It is anticipated that the majority of inspections will be announced i.e. notified in advance to the inspected party, to ensure the availability of relevant individuals for the inspection. However, on occasion, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice (e.g. when the announcement could compromise the objectives of the inspection or when the inspection is conducted in a short timeframe due to urgent safety reasons).

4.3. Sites to be inspected

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the MAH and its local representative may be inspected, in order to confirm their capability to support the MAH's compliance with pharmacovigilance obligations.

The sites to be inspected may be located in or outside Sri Lanka. The later might be appropriate where the main pharmacovigilance functions, databases and/or activities are located outside Sri Lanka.

The type and number of sites to be inspected should be selected appropriately to ensure that the key objectives within the scope of the inspection are met.

4.4. Inspection scope

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections

The following elements should be considered when preparing the scope of the inspection, as applicable:

- information supplied in the pharmacovigilance system master file;
- information concerning the functioning of the pharmacovigilance system, e.g. compliance data available at the NMRA;

DRAFT

- specific triggers;
- It may be appropriate for additional data to be requested in advance of an inspection in order to select appropriate sites or clarify aspects of the pharmacovigilance system.

The pharmacovigilance inspections should include the following elements as appropriate:

Individual Case Safety Reports (ICSRs):

- collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including from those firms employed to fulfil MAH's pharmacovigilance obligations and departments other than drug safety;
- assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of ICSRs from within the EU, examples of ICSRs reported from outside the EU should be examined as part of this review (if applicable);
- follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
- reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
- record keeping and archiving for ICSRs;

Periodic Benefit Risk Evaluation Reports (PBRERs), (as applicable): −

- completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
- addressing safety topics, providing relevant analyses and actions;
- formatting according to requirements;
- timeliness of submissions;
- ongoing safety evaluation
- use of all relevant sources of information for signal detection;
- appropriately applied methodology concerning analysis;
- appropriateness of investigations and follow-up actions, e.g. the implementation of
- recommendations following data review;
- implementation of the RMP, or other commitments, e.g. conditions of marketing authorisation;
- timely identification and provision of complete and accurate data to the competent authority(ies), in particular in response to specific requests for data;
- implementation of approved changes to safety communications and product information, including internal distribution and external publication;

DRAFT

interventional (where appropriate) and non-interventional clinical trials:

- reporting suspected unexpected serious adverse reactions (SUSARs);
- receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);
- submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PBRER), where applicable, PASS or post authorization efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
- appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
- the inclusion of study data in ongoing safety evaluation;

pharmacovigilance system:

- QPPV roles and responsibilities, e.g. access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
- the roles and responsibilities of the MAH in relation to the pharmacovigilance system;
- accuracy, completeness and maintenance of the pharmacovigilance system master file;
- quality and adequacy of training, qualifications and experience of staff;
- coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
- fitness for purpose of computerised systems;
- contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.
- The inspection may include the system for the fulfilment of conditions of a marketing authorization and the implementation of risk–minimization activities, as they relate to any of the above safety topics.

For cause inspections

The scope of the inspection will depend on the specific trigger(s). and below, may be relevant:

- QPPV involvement and awareness of product-specific issues;
- In-depth examination of processes, decision-making, communications and actions relating to a specific trigger and/or product.

If a “for cause” inspection has been or will be conducted in a similar timeframe as a routine one, it may replace the need for the planned routine inspection and the program shall be revised to reflect

this.

4.5. Classification of inspection findings

Finding is a deviation or deficiency noted by an inspector during an inspection. The findings can be classified according to the severity as follow:

Critical is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.

Deficiencies classified as critical may include a pattern of deviations classified as major.

A critical deficiency also occurs when a MAH or local representative is observed to have engaged in fraud, misrepresentation or falsification of data.

Major is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.

Deficiencies classified as major may include a pattern of deviations classified as minor.

Minor is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.

A deficiency may be minor either because it is judged as minor or because there is insufficient information to classify it as major or critical.

4.6. Inspection follow-up

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, as appropriate:

- requests for a meeting with the MAH to discuss the deficiencies, the impact of the deficiencies and action plans;
- review of the MAH's corrective and preventive action plan;
- review of the periodic progress reports, when deemed necessary;
- re-inspection to assess appropriate implementation of the corrective and preventive action plan;

- requests for submission of previously un-submitted data; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities;

4.7. Regulatory Action

In the event of non-compliance, the NMRA shall take the necessary measures to ensure that a MAH is subject to effective, proportionate and dissuasive penalties. Possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- education and facilitation: the NMRA may communicate with MAH representatives (e.g. in a meeting) to summarize the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the MAH's proposals for corrective and preventive actions;
- inspection: non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- warning letter, non-compliance statement or infringement notice: these are non-statutory or statutory instruments in accordance with national legislation which NMRA may issue stating the legislation and guideline that has been breached, reminding MAHs of their pharmacovigilance obligations or specifying the steps that the MAH must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- provision of information to medicines authorities in other countries, under the framework of confidentiality arrangements;
- the NMRA may consider making public a list of MAHs found to be seriously or persistently non-compliant;
- product-related actions depending on the impact of the deficiencies on the benefit-risk profile of the concerned medicinal products and the outcome of follow-up actions including as appropriate:
  - urgent safety restriction;
  - variation of the marketing authorization;
  - suspension or revocation of the marketing authorization;
  - delays in approvals of new marketing authorization applications until CAPAs have been implemented or the addition of safety conditions to new authorizations;
  - requests for pre-authorization inspections;
  - amendments or suspension of clinical trials due to product-specific safety issues;
  - product recalls e.g. where important safety warnings have been omitted from product information;

DRAFT

- requests for issuing safety communications, including amendments of marketing and/or advertising information;

- administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;
- Referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

4.8. Pharmacovigilance inspection process

Based on the national pharmacovigilance inspection program described above, as a general overview, each pharmacovigilance inspection is consisting of the following phases:

- **preparation of a pharmacovigilance inspection**;

Preparation encompasses those activities undertaken after the selection of an MAH, for a pharmacovigilance inspection and prior to inspection conduct. These activities include but are not limited to:

- allocating resource to conduct the inspection;
- announcing the inspection to the inspected MAH;
- making the necessary logistical arrangements;
- review the pharmacovigilance system & collecting information about the history performance of the MAH to be inspected
- defining the inspection scope and agenda.

- **conduct of pharmacovigilance inspections; consist mainly of the following:**
  - **Opening meeting**; held between the inspection team and representatives of the MAH being inspected
  - **Collecting and verifying information**; depending on the type and scope of the inspection, this include:
    - review of relevant documents;
    - review of processes
    - examination of computer systems;
    - conduct of interviews;
    - review of internal and external communication
  - **Closing meeting;** held at the end of the inspection, between the inspection team and representatives of the inspected MAH
- **reporting of pharmacovigilance inspections findings**
- **inspection follow-up for corrective and preventive actions (CAPA)**;

When findings or non-compliance is identified during an inspection, the MAH will be requested to

design and implement corrective and preventive actions plan (CAPA), follow-up by the NMRA will be required until a CAPA plan is completed.

- **taking appropriate regulatory action and sanctions in case of serious non-compliance**;

5. ROLE OF MAHS AND APPLICANTS

MAHs with authorized products may be subject to pharmacovigilance inspections.

Their responsibilities in relation to inspections, including but not limited to the following:

- always to be inspection-ready as inspections may be unannounced;
- to maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request, the pharmacovigilance system master file;
- to ensure that the sites selected for inspection, which may include firms employed by the MAH to perform pharmacovigilance activities, agree to be inspected before the inspection is performed;
- to make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;
- to ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;
- to ensure that relevant pharmacovigilance data is accessible;
- to ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritisation of critical and/or major findings.

6. INSPECTION FEES

An inspection fee(s) will be charged in accordance with the national regulations on fees payable to the NMRA.

References:

EMA Guideline on good pharmacovigilance practices (GVP) Module III, Pharmacovigilance inspections

7. APPROVAL AND REVIEW DETAILS

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