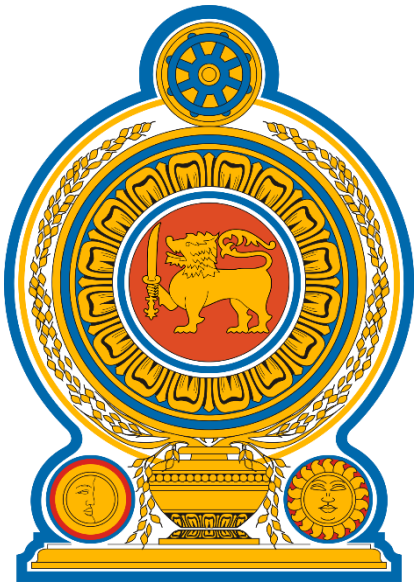

Guideline for Preparation of the GMP inspection

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NATIONAL MEDICINE REGULATORY AUTHORITY
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GUIDELINE FOR PREPARATION OF THE GMP INSPECTION

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1 . Introduction

A company applying with the National Medicines Regulatory Authority (NMRA) for registration of a medicinal product in Sri Lanka must provide acceptable evidence to show that the manufacturer of the product follows an internationally accepted standard of Good Manufacturing Practice (GMP) and recognized by the authority in Sri Lanka.

GMP inspections are conducted as one of the requirements for registration of medicinal products in the NMRA Sri Lanka. Such inspections are also conducted for operating as well as new pharmaceutical sites so as to verify compliance with GMP standards. Inspection involves review of documents, records, facilities. Consistency in conducting GMP inspection activities are very important in ensuring quality assurance of pharmaceuticals by the NMRA. This results into common decision making by GMP inspectors at the end of inspections and thus avoiding complaints from manufacturer.

The guideline defines procedures to be followed when preparing and planning for inspection, reporting requirements including format and classification system adopted for non-compliances observed during GMP inspection. Various working documents are also referred to in this guidelines to help inspectors to comprehend matters related to GMP. It is also expected that the guideline shall help inspectors to conduct GMP inspection with integrity and diligence.

2. PURPOSE

The objective of the GMP inspection is to assess the conformance of manufacturers to GMP requirements and ensure quality of products that are registered or in the process of registration / re-registration /change of manufacturing site.

The purpose of this guidance is**:**

To provide information on the types of GMP evidence acceptable to the NMRA Sri Lanka.

To provide the requirements for an on-site inspection of manufacturing facility where GMP evidence of the premise is not available or acceptable to the NMRA Sri Lanka.

3. Scope

The guideline is applicable for all types of GMP inspections for pharmaceutical manufacturing plants of API and finished Pharmaceutical Product.

4. Definitions

4.1 Critical Observation

Critical observation means an observation describing a situation that will most likely result in a non-compliant product or a situation that may result in an immediate or latent health risk and any observation that involves fraud, misrepresentation or falsification of products or data.

4.2 Major Observation

Major observation means an observation describing a situation that may have an impact on the product but is not as significant as a critical observation. It may have an indirect impact in the strength, identity, purity or safety of the product. There is reduced usability of the product without a probability of causing harm to the consumer. Observation of a major deficiency puts a question mark on the reliability of the firm's quality assurance system.

4.3 Minor Observation

Minor observation means an observation describing a situation that is a departure from GMP but has no significant impact on the product quality. It has low probability of affecting the quality or usability of the product.

4.4 GMP inspector

GMP Inspector means a GMP Inspector is an officer appointed by the NMRA . The role of the inspector is to evaluate the compliance of site inspected in Sri Lanka and abroad, with the requirements of national regulations (in Sri Lanka).

These sites may be

- Manufacturers and distributor of medicinal products
- Manufacturers of investigational medicinal product
- Site involved in the storage of medicinal product
- Manufacturers of the active pharmaceutical ingredients and certain excipients

The role involves inspecting, reporting and forming conclusions in respect of the suitability of a site for the activities which it has sought or for which it is already authorized.

The inspector provides technical information and advice to relevant individuals and organizations both internal and external to the NMRA.

The inspector provides support to the enforcement and execution of national regulations in relation to medicinal products.

4.5 Lead inspector

Lead GMP Inspector is a Senior GMP Inspector who is charged with the responsibility for leading a GMP inspection team to undertake inspection of a specified pharmaceutical manufacturing site(s)

Key responsibilities

- Preparing ,organizing and carry out inspections in accordance with NMRA procedures
- Write inspection reports when acting as lead inspector and contributing to preparation of reports for joint or accompanied inspections.
- Assisting in the compilation of data and preparation of management report as required
- Applying risk management principle
- Submitting reports as required and maintain appropriate records of meetings and activities

4.6 Senior GMP inspector

Senior GMP Inspector is an officer who by virtue of experience and competence is appointed as such to conduct GMP inspections and train junior officers in inspections after evaluation by the NMRA as by the criteria outlined in the assessment form.

Report to lead inspector, the inspector will be primarily responsible for assessing the compliance of manufacturers with NMRA guidelines

4.7 Specialized GMP inspector.

Specialized GMP Inspector is a GMP inspector who possesses specialized knowledge and experience in conducting GMP inspections for specialized areas e.g., Biological, Blood products

5. TYPES OF INSPECTIONS

There are four types of inspection as indicated below;

a) Routine inspection

b) Concise inspection

c) Follow-up inspection

d) Special inspection

5.1 ROUTINE INSPECTION

Routine inspection is a full review of all aspects and components of GMP within a facility. Routine inspection is conducted under the following circumstances:

a) To a newly established manufacturing facility or a manufacturer who has expressed interest of expanding manufacturing activities e.g. introduction of new products.

b) When there is modification to manufacturing methods or processes; or changes in key personnel, premises and/or equipment.

c) When GMP certification has expired. This type of inspection should be announced

5.2 CONCISE INSPECTION

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Concise inspection is the evaluation of limited aspects relating to GMP compliance within a facility. A limited number of GMP requirements are selected by the inspector to serve as indicators of the overall GMP compliance by the manufacturer. The inspector also has to identify and evaluate any significant changes that could have been introduced by the manufacturer since the last inspection. Collectively, the selected indicators and the changes identified indicate the manufacturer's attitude toward GMP. A concise inspection is conducted under the following circumstances:

a) Where a manufacturer has a consistent record of compliance with GMP through routine inspections in the past.

b) Where a sample of aspects can be taken as a good indication of the overall level of compliance with GMP. However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, a more comprehensive or full GMP inspection should be performed soon after the concise inspection. These inspections can be announced or unannounced.

5.3 FOLLOW-UP INSPECTION

A follow up inspection is also referred to as a re-inspection or a reassessment of the manufacturing facilities. It is performed specifically to monitor the result of corrective actions of the manufacturer following a previous inspection. Depending on the nature of the defects and the work required, the follow-up inspection could be carried out within the agreed timeframe after the previous inspection. The follow-up inspection is limited to specified GMP non compliances that have been observed. A follow up inspection shall be unannounced.

5.4 SPECIAL INSPECTION

A special inspection is undertaken to do spot checks which could focus on one product, a group of related products, or specific operations e.g. mixing, or labeling. Special inspection is conducted under the following circumstances:

a) When there are complaints about a specific product that suggest there may be defects.

b) When there is a product recall due to events such as adverse drug reactions.

c) To gather specific information, or to investigate specific operations of the manufacturing processes. The inspection shall be unannounced.

6. FREQUENCY OF INSPECTIONS

The frequency of inspection of local and foreign manufacturers shall be as follows:

6.1 LOCAL PHARMACEUTICAL MANUFACTURERS

Local manufacturers shall be inspected every 2 years for routine inspection.

6.2 FOREIGN PHARMACEUTICAL MANUFACTURERS

Foreign manufacturers shall be inspected once after 5 years. A manufacturer may be inspected more than once within 5 years, depending on the type of inspection to be performed if required.

7. PLANNING FOR GMP INSPECTIONS

The planning for GMP inspection shall be as per NMRA Procedure for Planning for GMP Inspections (SOP-MFR-003). While planning for GMP inspection, the following categories of manufacturers should be considered;

a) The new domestic manufacturer Facilities and contracted manufacturing sites shall be inspected in time to time with the NMRA's recommendation – after that at least once in two years for routine GMP inspection.
b) All new manufacturing Facilities intended to market medicines in Sri Lanka located within the SAARC Region with their own and contracted manufacturing sites shall be inspected at regular intervals in accordance with the NMRA's recommendation - at least once in five years for routine GMP inspection or as decided by NMRA.

c) Facilities located in reference countries of the NMRA shall be inspected when critical issues reported.

8. PREPARATION FOR GMP INSPECTION

The preparation for GMP inspection shall be as per the NMRA Procedure for Preparation for GMP Inspection (SOP-MFR-003)

9. INSPECTION REPORT

Inspection report should be written immediately after completing the inspection. The compiled report shall be shared within the members of the pier review committee for GMP inspection within fourteen (14) calendar days upon completion of inspection.

GMP inspection report is sent to the inspected facility within thirty (30) calendar days after completing the inspection. GMP inspection report shall be written according to the WHO TRS 996 Annex 4 Model Procedure for Preparing GMP Inspection Report (SOP-MFR-003) sufficient details should be provided to allow for an independent assessment, comprehension and easy decision making.

Where observations are included in the report, clear distinction should be made between "compliances" and "non-compliances". Noncompliance observations should be classified as "critical", "major" and "minor". These classes are detailed below.

10. CLASSIFICATION OF GMP INSPECTION OBSERVATIONS

Overall, the evaluation should commensurate with the nature and extent of the deviations (i.e. severity).

Non-compliances should be noted by Inspectors and classified as critical, major and minor according to the WHO guidelines on quality risk management (WHO Technical Report Series, No. 986, Annex 6, 2014), Procedure for Risk Classification of GMP deficiencies

11. RECOMMENDED REGULATORY ACTION(S)

Category of noncompliance's	Regulatory action(s)
11. 1. Minor Critical	• Recommend corrective action within a given timeframe • Request for compliance report
11.2 Major	• Issue warning letter • Recommend corrective action within a given timeframe • Recommend temporary withdrawal or suspension of market authorization • Follow-up inspection to verify implementation if necessary
11.3 Critical	• Recommend corrective action within a given timeframe • Request for compliance report • Recommend permanent withdrawal of marketing authorization in case • Recommend suspension of marketing authorization in case of registered products • Recommend not to grant marketing authorization for new application

12. APPEAL

Any manufacturer may appeal against any decision of the NMRA. When a manufacturer appeals against a decision of NMRA, the written submission by the manufacturer will be evaluated by the NMRA. The NMRA will then decide whether to accede to the appeal of the manufacturer after evaluating the submitted reason (s) appeal. The NMRA may consider the reason (s) and motivation for appeal and accept or reject the appeal according to the national regulations.

13. REFERENCES

a) WHO Prequalification Program documents: http://apps.who.int/prequal/

b) The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) guidance documents on inspection: www.picscheme.org

c) EAC Partner State guidelines and SOPs on GMP inspection

14.FEEDBACK

14.1 Staff and customers may provide feedback about this document by emailing info@nmra.gov.lk.

1. APPROVAL AND REVIEW DETAILS

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