# Guidelines for Medical device manufacturer's Good Manufacturing Practices site inspection management

**First Edition**

**May2022**

**Addis Ababa, Ethiopia**

## Contents

# 1 Introduction

EFDA is mandated by Food and Medicine Administration proclamation 1112/2019 to regulate medical products including medical devices among others. Medical device is one of the crucial medical products used in the healthcare system. Failure of these products leads to failure in healthcare delivery service and loss of life. To regulate medical devices, the authority requires all the five conformity assessment elementsalso being employed internationally one of which is the manufacturer's compliance of the mandatory Quality management System. In this document, these two terms (Quality management system and Good manufacturing practice) are used interchangeably. Article 20 sub-article 4 of the FMA proclamation 1112/2019 requires medical device manufacturers to comply with the Good manufacturing practiceto register their products with the Authority. Following this requirement set by the proclamation; the Authority has developed and approved the Guideline for Medical device Good manufacturing practice to carry out the manufacturing site inspection as part of its premarket as well as on-market conformity assessment.

As the inspection of medical device manufacturers for its compliance with the GMP/QMS for the regulatory decision requires commitment, appropriate/relevantpre-requisite education, competence (foundational, functional and technical), training, and experience, it is important to set requirements which will help in assigning experts as auditor/inspector, lead auditor/lead inspector.

Therefore, this guideline is prepared to specify the required minimum competencies of the inspectors and requirements for of ethical integrity, complaint handling and the quality assurance mechanism of the inspection of medical device manufacturer's GMP.

In addition, theresponsibilities of inspectors, lead inspectors as well as the need for the inspection planningand their findings reporting procedures are provided in this guideline.

## 2 Definitions

***Quality Management System***- means a structured system of procedures and processes covering all aspects of design, manufacturing, supplier management, risk management, complaint handling, clinical data, packaging, labeling, storage, distribution Recall procedures, Good Practices in Quality Control Laboratory and servicing. It ensures that medical devices or medical device services produced by a company consistently meet their predetermined intended use and specification. It is interchangeably used with Good manufacturing practice in this document.

***Inspection or audit***- meansa systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

***Inspector or auditor***- means a person with relevant qualifications and competence to perform audits or specified partsof such audits and who belongs to, or is authorized by the Authority.

***Lead Inspector/Auditor***- means an auditor or inspector designated to manage an audit (also known as an audit team leader).

***Non-conformity***- means the non-fulfillment of specified requirements within the planned arrangements.Other terms may be used to mean the same as nonconformity (e.g. 'non-compliance','deficiency').

## 3 Scopes

This guideline is applicable to medical devicesto be registered with the Authority that are subject to GMP inspection. It is applicable to both foreign and local manufacturers of such devices.

## 4 Objectives

The main objective of this guideline is to set procedures for medical device manufacturers GMP inspection.

It is specifically to-

- Set requirements for inspectors and lead inspector's code of conduct.
- Set requirements (including pre-requisite education, experience, training and technical competence) for selecting relevant experts to conduct medical device manufacturer GMP inspection.
- List the responsibilities of GMP inspectors and lead inspectors while conducting the regulatory inspection.
- Describe how the medical device GMP inspection programs are managed.
- Put up administrative measures and complaint handling procedures.

# 5 Requirements for Auditors and Lead Auditors

## 5.1 General

The primary selection criteria of an expert to conduct auditing of medical device manufacturers quality management system is the product regulation sector where that expert is working (i.e. any of the regulatory functions of medical device).

An expert who has recentlyconductedor is currently conducting or is proceeding to conduct the medicine GMP inspection shall not be designated as a medical device GMP/QMS auditor/Inspector.

## 5.2 Commitment to Impartiality and Confidentiality

Each person involved in auditing or inspection activities shall sign a conflict of interestand confidentiality and disclose any potential conflicts of interest, including prior association with a manufacturer or its personnel. The Authority is expected to implement appropriate arrangements to manage perceived or actual conflicts of interest.

The auditors/inspectorsshould understand the importance of a conflict of interest and confidentialityin maintaining integrity.

The Authority keeps signed statements of adherence to a code of conduct for personnel involved in regulatory inspection/audit. The signed statement shall attest to at least the following elements:

1. To act in a professional and ethical manner at all times.
2. To faithfully represent the interests of the Authority.
3. The selected inspector shall declare and sign the conflict of interest and confidentiality agreement before participating the GMP inspection and shall follow respective MIFD SOPs and directives.
4. The inspector shall properly maintain confidentiality information of the manufacturer unless it is disclosed by the manufacturer.
5. The inspectors shall properly maintain confidential information unless it is required by judiciary body.

6. To disclose any relationship, or financial interest, past or present, that may create a conflict of interest, or the appearance of a conflict of interest, and to notify the Authorityof any new conflicts of interest or potential conflicts of interest as soon as the case may arise.
7. To record and report truthfully and accurately inspection/audit evidence in an impartial and unbiased way.

## 5.3 Education Requirements

Lead Auditors and Auditors shall hold a minimum of Bachelor degree from a university or technical college in medicine, science, or engineering (educational requirement). Disciplines of interest shall include;

- Biomedical Engineering
- Microbiology
- Clinical Engineering
- Medical laboratory Technology
- Bioengineering
- Pharmacy
- Public health

The field of study related to the degree shall be the primary basis for the classification of Technical Knowledge.

## 5.4 Experience requirements

Potential Lead Auditors and Auditors shall be able to demonstrate sufficient experience to have acquired the requisite knowledge and skills to successfully perform assigned tasks.

A potential lead auditor shall:

a. Have a minimum of specialization or Master'sDegree in any of the disciplines listed under 5.3 having at least four years work experience and one roundGMP inspection experience as inspector (this includes both local and foreign GMP inspections). OR

b. Havea minimum of Bachelor Degree for any of the disciplines listed under 5.3 and a minimum work experience of five years with at least twoGMP inspectionrounds (this includes both local and foreign GMP inspections).AND
c. Priority should be given to experts who have experience in medical device facilities inspection and/ormedical device dossier assessment and/ormedical device quality control.

A potential auditor with appropriate education certificate listed under 5.3 shall have a minimum of three years of work experience in any of medical device regulatory functions in the authority and/or in medical device manufacturing facility. The audit team should have at least one technical auditor who is knowledgeable about the technology of the medical device being audited including- how it is made, how it works and how it is to be used.

The experience for auditorcan be in one or more of the following medical device regulatory functions:

- Medical device registration dossiers assessment;
- Medical device facilities inspection;
- Medical device inspection at port of entry;
- Medical device quality or performance testing;
- Medical device safety assessment and
- Other medical device related experts working in the authority

However, as the competence qualification of auditors specially to become a lead auditor needs foundational and functional competencies in addition to the technical competency, the lead auditors of an audit program may be selected by the director of Medicine facility Inspection directorate.

## 5.5 Technical Competencies requirements

a) **Regulatory requirements**: Knowledge of the regulatory requirements provided in the proclamation, regulation, relevant directives, medical device guidelines and other related documents used in medical device regulation by EFDA. This knowledge shall

include the principles and applications of medical device quality management system requirements for the purpose of:

- achieving conformity with regulatory requirements
- implementing and maintaining risk management system requirements
- Ensuring the relevant requirements for products and services have been determined by the manufacturer.
- Ensuring that the interfaces of the manufacturer with its suppliers are effectively documented and controlled.

b) **Medical devices and the manufacturing environment**: Knowledge of medical devices and the related manufacturing activities, including:

- the types of medical devices including their complexities, technologies, and risk classifications
- Their intended use, terminology and technology specific to the technical area.
- safety and risks of medical devices
- the processes and technologies used by medical device manufacturers
- The infrastructure and environment for operation of processes affecting product and service.
- The provision of processes, products and services from external suppliers.

c) **Inspection or Auditing Standards and Techniques**: Knowledge of internationally recognized standards and techniques for auditing quality management systems or good manufacturing practice of medical device manufacturers to ensure that each QMS auditor has knowledge of:

- fundamental concepts and quality management principles and their application
- terms and definitions related to quality management
- the process approach including related monitoring and measurement
- the role of leadership in the organization (manufacturer) and its impact on the QMS
- application of risk based thinking including the determination of risks and opportunities
- application of the PDCA (plan, do, check, act) cycle

- structures and interrelationships of documented information specific to quality management
- quality management related tools, methods, techniques and their application.

d) **Statistical Analysis**: Knowledge of the basic concepts of probability and statistics including mean, median, confidence level and standard deviation as it relates to representative sampling and trend analysis.

e) **Others**: Knowledge of medical deviceQuality Control Testing, performance check, safety evaluation and understanding instrumentation of medical devices.

## 5.6 Training requirements

Lead Auditors and Auditors shall have successfully completed the following training prior to performing medical device GMP inspection work:

- Medical device basic GMP Inspection training (which is currently similar to Medicine basic GMP Inspection training).
- Medical device advanced GMP Inspection training.

# 6 Roles and Responsibilities

## 6.1 Auditor/Inspector

The responsibilities of GMP auditors include:

a) Fulfilling the ethics, education, experience, competence and training requirements set in section one.
b) Helping the manufacturer understand the regulatory requirements;
c) Planning and carrying out assigned responsibilities objectively, effectivelyand efficiently within the audit scope and in accordance with a code ofethics;
d) Co-operating with and supporting the lead auditor;
e) Collecting, analyzing and, where appropriate, documenting objectiveevidence that is relevant and sufficient to permit the establishment ofconclusions regarding compliance of the quality management system with regulatoryrequirements and the effectiveness of its implementation in meeting qualityobjectives;
f) Remaining alert to any indications or evidence that can influence the auditresults and possibly require more extensive auditing;
g) Informing the lead auditor of quality audit observations in a timely manner;
h) Assisting the lead auditor in preparing the report of the audit;
i) Informing the lead auditor of any major obstacles encountered inperforming the audit;
j) Safeguarding the confidentiality of all documents and information obtained in association with the audit;
k) Verifying that corrective actions have been taken and have been effective as a result of a previous audit;
l) Complying with any health and safety or other applicable requirements of the manufacturer.

## 6.2 Lead Auditor

The responsibilities of the lead auditor include, in addition to those of the auditors:

a) Identifying the requirements of each audit assigned to the lead auditor by the Authority;
b) Previewing the manufacturer's quality system description (where appropriate) for adequacy in meeting applicable regulatory requirements, prior to the on-site audit;
c) Preparing the audit plan and working documents and briefing the audit team;
d) Representing the audit team with the auditee's management;
e) Communicating any nonconformities to the manufacturer as soon as possible after they are identified and indicating whether such nonconformities may affect compliance with the regulatory requirements;
f) Reporting to the manufacturer and to the Authority any major obstacles encountered in performing the audit as planned;
g) Preparing and presenting the audit results clearly and conclusively to the manufacturer at the closing meeting;
h) Preparing and submitting the audit report to the Authority (MFID) in a timely manner.

# 7 Program Administration

## 7.1 Program Administration and Management

Both the local and foreign inspection program shall be managed and directed by MFID and the inspection directorate shall schedule the inspection trips and provide all the documentations necessary for the program activities.Inspectors and Lead Inspectors shall be nominated by MFID director and appointed by respective Deputy Director General or Director General of the Authority. The MFID of the Authority shall ensure in advance the presence of any conflict of interest among the assigned inspectors.

All local facilities inspection Management, including but not limited to assignment and approval of inspectors, evaluation of the inspection report will be handled by MFID. If necessary, the MFID may also assign appropriate experts from other directorates of the Authority.

A maximum of five facilities oversees and not more than three countries shall be assigned for inspection on a single trip. The inspection time schedule shall be decided based on manufacturing complexity and manufactured product properties and risk class. The allocated number of inspection days is attached to this guideline (see Annex-1).

## 7.2 Exceptional conditions for local Medical device manufacturers

The inspection shall be conducted by MFID experts. If necessary, thedirectorate may assign experts from different directorate of the Authority for the inspection.

Validity of the GMP certificate shall be for five years; however, the inspection shall be conducted at any times within the validity period.The incompliance for GMP requirements by existing local medical device industries may be acceptable for a defined period of time. In such cases, an investigation of the quality through laboratory testing shall be required.

## 7.3 Inspection planning

There shall be a site inspection/audit plan to be developed by the assigned lead auditor and presented to the remaining team members.Based on the type of inspection, itshould be communicated with the manufacturer, in advance of the site visit (one month before the site audit).

The audit plan should at least include:

i) the audit scope and purpose;
ii) Identification of the manufacturer's management team havingsignificant direct responsibilities regarding the audit scope andpurpose, if available;
iii) Identification of reference documents (such as the applicableequality system standard and, if available, the manufacturer's qualitymanual);
iv) Identification of audit team members;
v) the language of the audit;
vi) the date and place where the site visit is to be conducted;
vii) identification, where possible, of the manufacturer’s relevant organizational units and, where appropriate, other auditeesto be auditedwho are operating the critical phases of the subsystem;
viii) the expected time and duration for each major audit activity;
ix) the schedule of meetings, including any necessary daily briefings, to be held with the manufacturer’s management;
x) the audit report distribution and the expected date of issue.

Earliest inspection application shall be given priority during inspection planning or scheduling. In addition, sites whose inspection would be crucial in making an ongoing regulatory decision or meeting an emergency or a public health issue shall be given priority during inspection planning.

## 7.4 Classification and Recommendation of Observation

Situations involving fraud, misrepresentation or falsification of source data or records linked with medical device manufacturing may result in rejection. Allnon-compliancesof the Medical device GMP requirements should be noted by inspectors and classified as

critical or major or minordeficiency (other deficiency). The grading of the non-compliances are done by the inspection team and reviewed by the medical device GMP inspection quality assurance task force.

Critical deficiency is a deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human patient or a product which could result in a harmful residue. A critical deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation of falsification of products or data.

Major deficiencyis a deficiency that is not critical deficiency but which has produced or may produce a product which does not comply with any of the applicable regulatory requirements, ordoes not ensure effective implementation of the required GMP control measures and consists of several “other related deficiencies ,none of which on its own may be ‘Major’, but which may together represent a “major “deficiency or systems failure and should be explained and reported as such.

A deficiencythat is not classified as either “critical” or “major”, but indicates a departure from Good manufacturing practice classified as minor or other deficiency. A deficiency may be judged as other because there is insufficient information to classify it as “Critical” or “Major”.

Manufacturer with even single critical noncompliance shall be refused from GMP compliance certificate. If a total of six and more major non-compliances are found in one or more of the critical QMS subsystems (Design and Development, Product documentation, Production and Process control, and Quality Control) are observed, manufacturer shall be refused from GMP certification. If the total major non-compliance are more than 15 irrespective of the subsystems, the authority may refuse the manufacturer from GMP certification.

The corrective and preventive measures taken by the manufacturer may be submitted to the Authority within 90 working days after receiving formal report for Non-compliance of major and other observations. However, onsite re-inspection may be required to decide the compliance of the facility. If the company is not granted GMP compliance

certificate, the company can apply for re-inspection along with the previous inspection CAPA program and report.

## 7.5 Inspection Report Writing, Reviewing and Approval Process

The inspection observation shall be recorded immediately on each day after completing the daily inspections.The compiled report shall be submitted to MFID within 15 calendar days upon completion of inspection and return back home.The Inspection report shall be specific and provided with sufficient details in order to allow an independent assessment, comprehension and easy decision making.The MFID of the Authority shall distribute the foreign facility report for reviewing process to GMP quality assurance task force within 3 working days upon receipt from the inspection team.The GMP quality assurance task force shall review the report within ten working days of receipt.

The MFID on behalf of the Authority shall submit the final inspection report to the inspected manufacturer within forty five calendar days from the last day of the inspection.

## 7.6 GMP quality assurance

The members of the GMP Quality Assurance task force will be proposed by Medicine facility Inspection Directoratedirector and approved and formed by respective Deputy Director General. For the purpose of efficiency and monitoring of activities, the GMP Quality Assurance shall be within Medicine Facility Inspection Directorate. The validity period of membership is five years.

The GMP quality assurance task force will prepare its own terms of reference. GMP quality assurance task force is responsible to evaluate final inspection report, as incase requested by the Directorate, and give advice on final decision for MFID before distributing to manufacturer. The task force may propose internal capacity building program, evaluation of inspector and different strategies related to GMP inspection.

## 7.7 Role of Director General and Deputy Director General in Coordinating of Activities

The inspection activities shall be supervised with respective Deputy Director General of the Authority, and whenever necessary, the Director General may get involved to clear complain, proposing future strategies and promoting overall regulatory activities. In addition, the respective DDG and DG may travel to the manufacturing site to supervise, monitor, and have a look of the inspection.

The respective DDG and DG may give necessary direction based on the trend reports of successive inspection report statistically evaluated for further regulatory measures.

# 8 Administrative Measures and Complaint Handling Procedures

## 8.1 Administrative Measure

### 8.1.1 Inspectors and Lead Inspectors

There may be different administrative measures to be taken on the inspectors when violating any of the required codes of conduct.

#### *8.1.1.1 Corrective Notification*

Corrective notification shall be given by the MFID director when violations are significant enough for the issuance of a corrective notification letter and reasonable expectation exist that the inspector will correct the violation. The notification shall be given in written form immediately after completion of the inspection.

#### *8.1.1.2Issuance of warning letter*

The respective Deputy Director General may give a warning letter to the inspector when the inspector committed one or more of the following minor violations.

a) If the inspector or lead inspector did not submit the inspection report within the time-frame.

b) If the inspector or lead inspector did not follow the inspection report writing procedure.

c) If the inspector or lead inspector did not follow the roles and responsibilities stated in this guideline.

d) If the inspector or lead inspector did not followthe requirements of conflict of interest and confidentiality.

The warning letter shall be issued within a reasonable period of time not exceeding ten working days of the knowledge of the violation by respective Deputy Director General.

#### *8.1.1.3 Rigorous disciplinary measure*

Any rigorous violation of the inspector shall be considered as rigorous disciplinary violation and shall be governed by the Federal Civil Servants Proclamation No.1064/2017 and appropriate measures should be taken according to the violation of the law. The disciplinary violations shall be presented to the Authority's Disciplinary Committee based on Federal Government Regulation No. 77/94.

### 8.1.2 Manufacturer

Any manufacturer who tries to corrupt or deceive the inspectors in which the authority has an evidence of such act shall be subjected to rejection of inspection for at least five years. In addition, a manufacturer who provided false information as an evidence of compliance for cGMP shall be rejected and blacklisted for consecutive three years.

Any manufacturer who became absent deliberately during the inspection process shall be considered as inspected and it shall be rejected. If the rejected manufacturer wants to be inspected in the future, it shall pay the inspection fee based on the information on Service fee Regulation. A manufacturer who showed or tried to show a manufacturing facility other than the site located on site master file is subjected to rejection.

## 8.2 Complaint Handling Procedures

### 8.2.1 Complaint related to assignment of inspector

Any candidate inspector shall submit complaint on his/her assignment of inspection to the respective Deputy Director General within two working days after the announcement of the assignment. The complaint shall be prepared in written form and shall also provide appropriate documentary evidence and other evidences relevant to the case. Where the complaint fulfills the above stated requirements, the respective Deputy Director General shall notify its final decision to the complainant within 2 days from the receipt of the complaint. The decision to the submitted complaint shall at least, include the reason why the complaint should not be acceptable for any reasonable ground.

If the candidate inspector does not accept and is not satisfied with the decision of Deputy Director General, she/he may take the complaint to the authority's complaint handling committee.

### 8.2.2 Complaint related to inspection finding and decision

Any manufacturer may appeal against any decision of the Authority within 30 working days from the receipt of inspection report from the Authority. The complaint prepared shall, at least state, the Authorities' alleged reason to take the measure, decision of the Authority, reasons of the complainant why he/she believes the decision is unjustifiable or inappropriate and shall be signed and dated by the complainant. The complaint shall be in written form and shall also provide appropriate documentary evidence and other evidences relevant to the case.

Where the complaint fulfills the above stated requirements, the DG shall submit to complaint handling committee or other appropriate body.The complaint handling committee or other appropriate body shall review the complaint within 60 days and shall present the decision to DG of the Authority. The DG of the Authority shall present the final decision of the submitted complaint to the manufacturer within 5 days after the complaint handling committee or other appropriate body has presented the review output.

The manufacturer can appeal to court incase if still not satisfied by the final decision made by the Director General of the Authority.

# 9 Miscellaneous

## 9.1 Record handling

The Medicine Facilities inspection directorate shall keep all relevant documents pertaining to GMP inspection activities including inspection report for at least until re-inspection is done.

## 9.2 Service Fee

A manufacturer who seeks the GMP compliance inspection by the Authority shall pay an appropriate service (GMP inspection service fee).

## 10 Annex-1 Allocated Number of Inspection days

| **Facility Type and Inspection type** | **Number of Days allocated for Inspection** |
|---|---|
| New Inspection of manufacturers producing single medical devices (e.g. only Male and/or female condoms or only medical gloves) | **3** |
| New Inspection of manufacturers producing different medical devices of the same category (eg. examination and surgical gloves) | **3** |
| New Inspection of manufacturers producing two different medical devices of different category (eg. Gloves and Condom) | **4** |
| New Inspection of manufacturers producing more than two different medical devices of different category. | **5** |
| New, Renewal, Special, and Investigation Inspection of manufacturers producing not more than 6 types of test kits. | **3** |
| New, Renewal, Special, and Investigation Inspection of manufacturers producing 6 to 11 types of test kits. | **4** |
| New, Renewal, Special, and Investigation Inspection of manufacturers producing more than 11 types of test kits. | **5** |
| For non-English speaking countries | **Additional 1 day** |
| Report Writing | **1 (For every 2.5 Facilities)** |