Inspector's Guide to GMP Inspection of Manufacturing Facilities

2023 Edition

Table of Contents ……...…I

Acronyms

API	Active Pharmaceutical Ingredient
AHU	Air Handling Unit
CAPA	Corrective Action and Preventive Action
DER	Drug Evaluation and Research
DQ	Design Qualification
FEFO/FIFO	First Expired First Out/First In, First Out
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
HPLC	High-Performance Liquid Chromatography
HVAC	Heating Ventilation and Air Conditioning
ID	Identity
IQ	Installation Qualification
NAFDAC	National Agency for Food and Drug Administration and Control
NC	Non Conformance
OOS	Out-Of-Specification
OQ	Operational Qualification
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QSIT	Quality System Inspection Technique
RH	Relative Humidity
SMF	Site Master File
SOP	Standard Operating Procedure
SKU	Stock Keeping Unit

Definition of Terms

Absorptive	A substance that absorbs components of materials it is in contact with
Additive	A substance that is added extraneously to materials it is in contact with
Aide-memoir	A written reminder of summary or outline of important items of proposed pattern of proceedings
Beginner Inspector (BI)	An inspector who has complied with Agency's requirements for expression of interest to be a Pharma GMP inspector and is designated to observe inspection for the purpose of capacity building
Beta Lactams	A class of broad-spectrum antibiotics, consisting of all antibiotic agents that contain a beta-lactam ring in their molecular structures, including penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems
Calibration	The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure and the corresponding known values of a reference
Co-Inspector (CI)	An inspector who plays a supportive role during the proceedings of an inspection as delegated by the Lead Inspector and who in certain instances, may assume a Lead Inspector role as defined by relevant formal procedure in which case the Co-Inspector will be referred to as the Team Lead.
Consultant	A professional who provides expert advice in a particular area
Critical deficiency	Describes a situation that is likely to result in a product that may result in an immediate or latent health risk (such as death, injury or hospitalization) or that involves fraud, misrepresentation or falsification of processes, products or data.
Critical Step	A step or action that, if performed improperly, will cause irreversible harm to plant equipment or people or will significantly impact operations
Deficiency	An observation to GMPs noted by an inspector during the inspection of a manufacturing establishment and confirmed in writing to the company in the inspection report or raised during exit meeting. Observations are assigned a risk classification ranging from critical, major or other deficiency.
Deionization	Removal of charged atoms or molecules (ions) from a liquid
Deviation	Departing from an established/approved, procedure, or standard
Direct Impact System	A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice (GEP) and, in addition, are subject to qualification practices
Diverters	Strategies and responses intended to deflect legitimate necessary inspection inquiries
Endotoxins	A heat-stable toxin associated with the outer membranes of certain gram-negative bacteria
Exit Meeting	A meeting with the representatives of the establishment and the inspection team under inspection that comes at the conclusion of the inspection and before departure of the inspection team at the end of inspection to discuss inspection findings.
Finished Product	A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling

Follow-up Inspection	An inspection to ascertain compliance with issues highlighted during a previous inspection
GMP Reassessment Inspection	An inspection to reconfirm the adequacy of GMP Compliance of an establishment
Hired Impostors	Hired casuals dressed up and fronted as regular employees for the singular purpose of deceiving GMP Inspectors about the actual personnel strength of an establishment under inspection
Homeopathic Drug Product	Drugs and related materials used in homeopathic medicine (related to the medical philosophy and practice based on the idea that the body has the ability to heal itself)
Incident Report	A form for recording details of an unusual event that occurs in the course of production to the point of use of a regulated product
Indirect Impact System	This is a system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to GEP only
In-process Material	Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for and used in the preparation of a medicinal product
Inspector's Notebook	An entry notebook issued by Inspectors for recording on-the-spot observations and related entries during an inspection
Investigative Inspection	An inspection to ascertain specific facts related to issues under investigation
Lead Inspector (LI)	An officer who is designated by virtue of evaluated competence and experience with responsibility to coordinate and direct inspection procedures by an Inspection Team and also train other cadres of inspectors
Lot Number, Control Number, or Batch Number	Any distinctive combination of letters, numbers, or symbols (or any combination of them) used for identification, such that the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of medicinal product or other material can be determined
Major Deficiency	Describes a situation that may result in the production of a drug not consistently meeting its marketing authorization. Some major deficiencies may be upgraded to critical deficiency, for example in cases where the issues identified is not isolated to one area or system. Generally more than 5 deficiencies in a system may be upgraded to a critical deficiency
Management	Decisionmaker(s) who set the strategy of an organization and coordinate(s) the efforts of its employees (or of volunteers) to accomplish its objectives through the application of available resources, such as financial, natural, technological, and human resources
Marketing Authorization	A legal document issued by the NAFDAC that establishes the detailed composition and formulation of the product and the pharmacopeia or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life; also implies product license and registration certificate

Materials	A general term used to denote components, raw materials/starting materials, reagents, solvents, process aids, intermediates, active pharmaceutical ingredients, product containers, closures, packaging and labelling materials, and in-process materials
Non-sterile	Not free from germs or microorganisms
Open Non-contained System	A system that regularly exchanges feedback with its external environment
Operations	A process or series of acts involved in a particular form of production of a regulated product
Packaging Component	Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment; referred to as primary or secondary depending upon whether they are intended to be in direct contact with the product
Particulate Microbial Contaminant	A foreign particle or infectious foreign particles, material or their toxins and by-products unintentionally or accidentally introduced into a substance or product
pH meter	A scientific instrument that measures the hydrogen-ion activity in water-based solutions, indicating its acidity or alkalinity expressed as Ph
Post-Market Surveillance/ Post-Marketing Surveillance	The practice of monitoring the safety and efficacy of a pharmaceutical drug or medical device after it has been released on the market
Pre-production Inspection	An inspection done before commencement of production activities leading to issuance of manufacturing authorization and usually carried out before Pre-registration Inspection which applies to particular pharmaceutical products
Pre-registration Inspection	An inspection required as prerequisite before product registration which applies to pharmaceutical products
Production Inspection	An inspection to ascertain compliance with GMP requirements and usually applies to cosmetics, medical devices, herbal medicines, and nutraceuticals
Pyrogens	A substance, such as a thermostable bacterial toxin, that produces a rise in temperature in a human or animal
Quality Risk Management	A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product throughout the product lifecycle.
Qualification	An action of proving that any premises, systems, and items of equipment work correctly and actually lead to the expected results; the word *validation* incorporates the concept of qualification
Quarantine	The status of starting or packaging materials, intermediate, bulk, or finished products isolated physically or by other effective means while awaiting a decision on their release or refusal
Raw Data	Data that have not been processed for use
Reactive	A substance that reacts with materials it comes in contact with

Reference Standard (Primary)	A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be obtained from an officially recognized source, prepared by independent synthesis, obtained from existing production material of high purity, or prepared by further purification of existing production material.
Regulated Product	A product requiring NADFAC approval before lawful use, manufacture, distribution, sale or use in the Nigerian market
Related Material	A material whose quality can impact the operations and product of a manufacturing establishment
Reprocessing	Subjecting all or part of a batch or lot of an in-process medicine, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological medicines and, in such cases, are validated and pre-approved as part of the marketing authorization.
Reworking	Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization. Reworking is not allowed by relevant NAFDAC guidelines for manufacture of small molecules.
Risk Assessment	Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards
Risk Status	Defines the risk score of a manufacturer based on intrinsic and compliance risk score after the conduct of a full or routine GMP inspection or as defined by the relevant formal procedure e.g. For Drug manufacturers can attain any of the following risk status; Acceptable Operation (AO), Needs Improvement (NI), Official Action Indicated (AOI). A manufacturer's risk status may also be upgraded or downgraded following a regulatory audit.
Routine Inspection	An inspection of a registered product manufacturing establishment to ascertain continued cGMP compliance. It may be announced or unannounced.
Sanction Activity	A restraining or punitive regulatory measure on deviant and nonconforming establishments
Special Inspection	An inspection scheduled toward special ends by Inspecting Team (e.g. Advisory inspection, Surveillance inspection, Sampling inspection, Placement and Removal of hold label, Layout Review, Desk assessment in lieu of onsite inspection)
Starting Material	Any substance used in the production of a medicinal product, excluding packaging materials
Sterile	A substance that is free from bacteria or other viable microorganisms.
Thermometer	A device that measures temperature or a temperature gradient
Trainee Inspector (TI)	An Inspector who largely observes an inspection for the purpose of capacity building but may also actively participate in inspection activities (such as questioning, data verification, document review etc.) if he/she possesses identifiable/acceptable level of expertise in any GMP component.

Validation	a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined criteria

FOREWORD

The National Agency for Food and Drug Administration and Control (NAFDAC) is an organization that was established by decree No.15 of 1993, now NAFDAC Act CAP N1, LFN 2004. The enabling Act saddles the Agency with the responsibilities of regulation and control of manufacture, importation, exportation, distribution, advertisement, sale and use of food, drugs, cosmetics, medical devices, packaged water and chemicals.

Within the purview of the organization's responsibilities, the Agency through appropriate regulatory practices, controls and enforcement; is able to vigorously pursue her objective of safeguarding the health of the nation by protecting citizens from the consumption of substandard and falsified medicines, unwholesome foods and other regulated products.

The Agency also has the responsibility of making pronouncements on the quality and safety of foods, drugs, cosmetics, medical devices and other regulated products after undertaking relevant evaluation.

With the growing challenges of sustaining the health and wellbeing of the Nigerian populace, the need to attain global regulatory compliance and ensure consistent availability of quality regulated products, it has become expedient to evolve standards and guidelines for achieving the organization's set goal. One of such guidelines is the NAFDAC Inspector's Guide to Good Manufacturing Practice (GMP) Inspection of Manufacturing Facilities.

The current edition of the NAFDAC Inspector's Guide to Good Manufacturing Practice (GMP) Inspection of Manufacturing Facilities is intended to serve as a handy reference or pocket guide for the NAFDAC GMP Inspectors. The intended objective of the handbook is to provide adequate guidance to the Inspector throughout the inspection cycle covering preparation for and conducting the inspection, report-writing and follow up activities. It is also targeted for use in combination with relevant GMP resource materials for induction training of new Inspectors and as well as for refresher training for experienced Inspectors.

The provisions of this Guide will certainly assist the Inspectors to perform more effectively in carrying out factory inspections so as to achieve better regulatory compliance of pharmaceutical, cosmetics, medical devices, herbal medicines and nutraceutical manufacturing companies and thus contribute to the vision of safeguarding the health of the nation.

This pocket guide only contains the essential elements of GMP to enable ease of use for the NAFDAC Inspectors while on the field.

It is therefore expected that all NAFDAC Pharmaceutical GMP Inspectors, as well as other GMP Inspectors should diligently deploy the use of this Guide to drive GMP compliance in our domestic facilities and those exporting into our country.

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Introduction

What Is GMP?

Good manufacturing practice (GMP) is that part of quality management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation, clinical trial authorisation or product specification. GMP is concerned with both production and Quality Control (QC). GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture.

The basic principles for enforcing GMP is to ensure that the desired products are manufactured, processed, packaged, or held so that they meet the quality, identity, purity, strength, safety, and efficacy that they claim to possess.

These requirements form the basis upon which a product is granted registration or marketing authorisation by the National Agency for Food and Drug Administration and Control (NAFDAC).

This guidance document describes general principles and a recommended format for inspection preparation, report writing, and follow-up for use by NAFDAC inspectors. The purpose is to provide transparency to facilitate inspection practices and the information sharing, which builds trust among the inspectors, NAFDAC, manufacturers, relevant stakeholders, and the public at large.

The GMP inspector, as a patriot and responsible officer is the eyes and ears of the community, and this public trust must be taken seriously. It is the duty of the inspector to ascertain, to the extent possible, whether inspected facility meets minimum requirements and operating in compliance with extant GMP regulations (including packing, holding, or distribution). Otherwise, there exist potential for sale, distribution, and use of ineffective, unsafe, or downright dangerous product for the citizenry.

What Happens during GMP Inspection?

Simply put, a GMP inspection is really a “verification” exercise for the real-time implementation of quality on practice. The NAFDAC Inspector, is the “verifier.”

The inspector is expected to carefully verify that products have been manufactured, packed, held, and distributed under GMP conditions.

Inspectors are to enforce current NAFDAC GMP for Medicinal Products Regulations by evaluating compliance through onsite inspections of manufacturing/holding facilities, review of documentation, and sometimes sampling of regulated products and related materials for laboratory testing.

Before the Inspection

Adequate planning and preparation are critical for achieving the goals set for any GMP inspection.

Planning

Adequate planning is paramount for the successful execution of Good Manufacturing Practice (GMP) inspections. Reference to the SOP for Conducting GMP Inspections (DER-808-03) and SOP for Booking and Scheduling of GMP/GSP inspections (DER-807-03) outlined the key steps and considerations for planning GMP inspections. The inspector should therefore acquaint him/herself with the prescriptions of the stated formal procedure.

Preparation

The minimum duration of GMP inspection usually varies within 1-3 days depending on the purpose or scope, type of inspection and the class of regulated product involved using a risk-based approach. Generally, Table 1 below presents information on the various types of inspection and their corresponding minimum number of duration.

Table 1: Types of Inspection

S/N	Type of Inspection	Scope and Purpose	Typical Minimum Number of Days Required
1	Production Inspection	GMP assessment, at the instance of the applicant, all processes related with manufacturing of the product is witnessed, samples are drawn if audit is satisfactory. Applies to non-Pharma inspection	1 day
2	Pre-Production Inspection	A new pharma facility, applicant notified, Assessment of quality system, equipment qualification, assessment of facility for intended use, Issuance of authority to manufacture on successful audit.	2-3 days
3	Pre-Registration Inspection	Applicant notified, conducted after a satisfactory pre-production audit, manufacturing lines operational, all aspects of GMP assessed in line with extant requirements. Production process witnessed; Samples are drawn when audit is satisfactory using a risk-based approach. Outcome leads to recommendation for issuance of marketing authorization	2-3 days
4	Routine Inspection	An announced or unannounced full inspection depending purpose of inspection. Usually the scope of inspection covers the entire 17 quality elements.	2-3 days
5	Investigative Inspection	Audit driven by a complaint, pharmacovigilance alert, laboratory failure arising from submission of registration samples or post marketing surveillance, etc. Auditees are not notified and focus areas and other related areas assessed.	1–2 days
6	Follow-up Inspection	A fallout of an unsatisfactory audit. Onsite verification of CAPA implementation and adequacy. To ensure all critical and major nonconformances have been closed out and risk associated with deficiencies have been acceptably mitigated.	1–2 days

7	GMP Reassessment Inspection (e.g., Licence Renewal)	Applicant notified, at the expiration of marketing authorization. All aspect of GMP assessed	2-3 days
8	Special Inspection	As defined under definition of terms (see above)	1–2 days

In general, to prepare for an inspection, the following steps should be taken:

- Determine the type(s) of products and processes at the facility. For example:
    - Is this an active pharmaceutical ingredient (API) or a dosage form facility?
    - Do they manufacture sterile or non-sterile products?
- Remember that different dosage forms (e.g., oral liquid, solids, semisolids, sterile, parenteral, ophthalmic, and beta lactams) may have certain specific requirements.
- Each member of the inspection team must review the site master file, quality manual, site validation master plan or other equivalent documentation in advance.
- Review the manufacturer's past compliance history, but this should not bias the inspector's view.
- Review relevant sections of GMP regulations for the particular inspection.
- Ensure relevant documents (e.g., application letter, marketing authorization, receipt of payment) are obtained from the concerned manufacturer.
- Consider any available post-marketing surveillance information.
- Draw up the inspection aide memoire and tentative inspection plan highlighting the following information:
    - Names of the Inspection Team members and their respective roles.
    - Time, date, and place for the opening meeting.
    - Organizational units to be inspected, taking into consideration whether the company has multiple sites.
    - Expected time and duration for each major inspection activity.
    - Schedule of meetings, including a daily briefing to be held with company management.
    - Tentative list of documents for review (as attachment to the plan).
    - Tentative time, date, and place for the final meeting.

The Inspection Team

Inspectors who are adequately qualified and possess knowledge of the systems, processes, and procedures involved should be selected. Less experienced inspectors should be paired with more experienced team members. Reference to SOP for designation of GMP/GCP inspectors

Note: All members of the inspection team must have been trained (with supporting documentation) on the respective Drug Evaluation and Research (DER) standard operating procedures (SOPs) relating to GMP.

The DER Directorate will form the inspection team and appoint the inspection team leader (also called Lead Inspector). In addition to the defined attributes of a lead inspector he/she should posses the qualities listed below:

- Be a senior staff member with an appropriate track record of GMP training and good conduct.
- Be honest, firm and meticulous.
- Have the ability and capacity to conduct good data analytical interpretation.
- Have a good understanding of pharmaceutical manufacturing and quality control.
- Possess appropriate behavioural skills and understand the required etiquette of his/her job

The team will prepare the inspection agenda after reviewing the company's site master file, other documents earlier listed and the marketing authorisation application. The inspection plan will follow the format presented in Annex 1.

Prior to the inspection, the Lead Inspector must summon a team meeting to plan and discuss details of the inspection. The responsibilities of each inspection team member—before, during, and after the inspection—must be understood and agreed upon by the team at this meeting. There should be no gaps in the assignment of responsibilities and follow-up action. The inspection plan should be rehearsed, and strategies for addressing unforeseen circumstances must be agreed upon. Prior to the meeting, each team member must understand the *NAFDAC Code of Ethics/Conduct for Inspectors;* questions must be clarified at the pre-inspection meeting while roles must also be assigned to the team members by the lead inspector.

Conflicts of Interest

Team members must disclose any potential conflicts of interest so that these may be resolved ahead of the inspection. Examples of conflicts of interest include but not limited to the following: prior sponsorship from a company, previous encounter with a company, personal conflict, relative(s) employed by the company, ownership of stock in the company by self or close relative(s).

Inspection Logistics

Important logistic issues that can make or mar an inspection must be addressed.

Foreign Inspection Logistics

Take care of visas, air tickets, hotels, local transportation, insurance (e.g., health and unforeseen emergencies).

- Check the weather/news to be prepared for climatic/weather conditions.
- Wear warm clothes for winter and lighter ones for summer.
- Wear comfortable formal shoes for long walks during the inspection.

- To prevent language barriers, the Lead Inspector must communicate ahead of time that the inspection language is English, if necessary the Lead Inspector should request interpreters.
- Be alert to security, especially at busy train stations or airports.

Domestic Inspection Logistics

- Arrange for adequate transportation and other logistics for the inspection, including airline tickets, if necessary.
- Get the right directions to the location and allow for adequate time to be punctual.

Things to Assemble

- GMP Inspector's Guide for every member as quick reference during inspection.
- Documentation and writing materials (e.g., inspector's notebook, pens).
- Identification cards for all inspection team members.

Must Read/Must Know

- All GMP inspection-related SOPs.
- All documents submitted by the company (e.g., SMF, VMP, last inspection report where applicable, previously existing documents on the company.
- GMP regulations. Inspectors must strive to correctly reference the relevant parts of the GMP regulations where necessary while conducting an inspection.
- Inspection Aide memoir(where applicable)
- NAFDAC Inspector's Guide.

Arrival at the Facility

Make sure you arrive punctually—about 10 minutes ahead of when you plan to start. Announce yourself at the gate and ask to see the appropriate facility official. Please remember that jewellery and perfume are not to be worn by any inspectors.

During The Inspection

Remember that the inspection visit provides the inspector with a first-hand opportunity to verify and assess the facility's compliance with GMP.

Carrying out the inspection well will assist in providing answers to the question: Are systems, processes, and procedures at the inspected facility in compliance with GMP?

The onsite inspection process can be divided into three main stages:

- Opening meeting
- Detailed site inspection

- Closing/exit meeting

Opening Meeting

Upon arrival at the company, arrange an opening meeting with the company's management and key personnel. The purpose of this meeting is to:

- Introduce the members of the inspection team.
- Outline the purpose, type, and scope of the inspection and documentation you would like to review. (In some situations, you might not be free to reveal the purpose/target of your inspection beyond a "routine GMP").
- Discuss the proposed inspection plan and make the necessary adjustments.
- Review the company's organizational structure and general information about the manufacturer /site, if not done prior to inspection.
- Discuss any previous inspections and which corrective and preventative measures were implemented. Discuss any significant changes in facilities, equipment, products, and personnel since the last inspection, if applicable.
- Give the company the opportunity to present a short (maximum of 10 -20 minutes) overview of the quality management system and to discuss current and proposed activities.

Note: For ease of identification, inspectors should wear visible name tags/ID.

A record should be made of the main persons met during the inspection, including those attending the opening and final meetings.

Remember to carefully and accurately record information in your Inspector's Notebook because inspection documents might need to be tendered as evidence in a court of law if and when the need arises.

Detailed Site Inspection

- Conduct the inspection using the Quality System Inspection Technique (QSIT) considering the scope of the inspection.
- Assess whether the facilities and equipment are of suitable layout and design, are maintained properly, and are suitable for the intended operations. (To consult the previously conducted desk review on the layout of facility)?
- Examine the relevant dosage form or API manufacturing process. Determine the most critical steps in terms of the success of the overall process. Assess how these steps are controlled, monitored, and recorded, taking into account detailed GMP guidelines.
- Focus on higher-risk activities, known problems, and deviations (including list of complaints within the 2 two years) from standard practices; examine the Product Quality Review reports from the last 2 years.

- Confirm that the company is effectively implementing its current procedures.
- Interview all levels of personnel, as necessary. Likewise, request any pertinent documents (e.g., procedures, records, raw data, and personnel training records).
- Confirm the accuracy of observed deficiencies with the immediate supervisory personnel. Keep management informed of the deficiencies (e.g., during the wrap-up meeting at the end of each day).
- Depending on the size of the site, time at disposal, and other factors, partial dividing the inspection team may be considered as an option.

Observations Made During the Inspection

- Bring observed deviations to the attention of key personnel promptly; avoid arguments.
- Give the manufacturer an adequate chance to explain or answer other questions.
- Ask follow-up questions as needed until there is clarity. Listen attentively.
- Watch out for "time wasters," "diverters," and other tricks in response to questions. Address these politely with a strong emphasis on inspection scope coverage.

Taking Samples

During the inspection, inspectors may sample starting, in-process materials or finished products for independent testing by NAFDAC, as necessary.

Digging Deeper: Systems, Processes, and Procedures—How Do They Work?

The rest of this Inspector's Guide serves as reminder of key elements in the GMP regulations and actions needed to verify compliance, which you must be familiar with.

Organization and Personnel

- NAFDAC GMP for Medicinal Products Regulations 2021, section 3(3).
- NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 2

Tip! Be alert to detect hired impostors (e.g., "employees for a day").

- Manufacturing of drug and related products under GMP conditions and the requisite quality assurance systems ultimately rely upon having qualified people. For this reason:
    - There must be a sufficient number of qualified personnel.
    - Responsibilities must be clearly defined.
    - Job descriptions must be documented and understood by affected personnel.
    - All personnel must receive initial and continuing training on their specific job, GMP, sanitation, and hygiene.
    - All personnel must be appropriately clothed and outfitted for their tasks.

- Any consultants who advise in any area of GMP operations must have documented relevant educational qualifications, experience, and training in the areas of GMP operations for which they render consulting services. Verify records of consultant qualifications, training, and experience. Review organograms (organization chart), SOPs, job descriptions, and training records. Ask questions to ensure that:
    - Job descriptions are clearly defined for QA/QC and production managers.
    - Quality Control Unit Head reports to management, independent of the Production Manager.
- Assess the scope of operation and automation to determine whether personnel numbers are adequate for operations.

Buildings and Facilities

NAFDAC GMP for Medicinal Products Regulations 2021, section 5
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 3

- Premises and facilities must be designed, located, constructed, and maintained to suit the operations to be carried out.
- Layout and design must aim to minimize risk of errors and to facilitate cleaning and maintenance to avoid cross-contamination, build-up of dust, dirt, and other adverse effects on the quality of products.
- Make visual observations, review documentation, ask questions, listen, and take notes.
- Check that there are clear restriction signs on doors to restricted areas.
- Verify orderly placement of equipment and materials to prevent mix-ups and contamination, especially for open non-contained systems.
- Confirm visible, clear, and logical provisions for flow of materials, products, processes, personnel, and waste to prevent mix-ups and contamination.
- Verify smooth, cleanable floors and walls, seamless corners, and ceiling and fittings that prevent build-up of dust and dirt.
- Are operating areas of adequate size to prevent contamination or mix-ups?
- Confirm availability of defined areas or other control systems for:
    - Receipt, identification, sampling, and quarantine of incoming materials and intermediates before release/rejection.
    - Holding rejected materials before disposition (e.g., return, reprocessing, destruction).
    - Storage of released materials.
    - Production, laboratory, packaging, and labelling operations.
    - Adequacy of ancillary area, utility/maintenance space.
- Is ventilation, air filtration, air heating and cooling, and exhaust systems adequate?
- Is lighting adequate for operations? Review schedule for lighting maintenance (e.g., changing bulbs).
- Confirm that adequate particulate and microbial control is achieved.

- Confirm adequacy of air filtration systems, where needed.
- Check air pressure differential gauges and flow directions as you cross different levels of clean areas.
- Check air control monitoring and air system validation records.
- Verify adequacy of air controls/exhaust systems in dusty operations (e.g., weighing, production).

Water Supply

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 7.5

- Check water and plumbing systems, monitoring and control records.
- Confirm clear identification of pipe work, (e.g., markings, documentation, computer control systems) to prevent contamination and facilitate cleaning.
- Confirm adequacy and cleanliness of drains: no back siphoning, no build-up of contaminants.
- Check water standards requirement for operations: potable/higher purity (e.g., sterile preparations).
- Check procedures, records, pyrogen test (e.g., deionisation, particulate/microbial contaminant, endotoxins).

Hygiene/Sanitation

NAFDAC GMP for Medicinal Products Regulations 2021, section 4(4)
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 2.24-2.32

- Review SOPs for hygiene, gowning; visit cloak rooms, toilets; ask questions.
- Review SOPs, schedules, and records for sanitation, washing, and use of toilet facilities.
- Check availability/adequacy of facilities for toilet, showers, clothing, and laundry.
- Verify that hygiene, gowning, and other relevant SOPs are available in all areas and are followed.
- Review health policy; check pre-employment and routine health records.

Pest Control, Sewage, and Waste Disposal

NAFDAC GMP for Medicinal Products Regulations 2021, section 9(4)
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, sections 3.4, 7.2

- Verify evidence of safe and sanitary disposal of sewage, refuse, and other wastes in/from building and immediate premises.
- Are responsibilities assigned? Are SOPs, cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities available? Are SOPs followed?

- Do SOPs exist for use of **s**uitable rodenticides, insecticides, fungicides, and cleaning and sanitizing agents? Is there documented evidence that are followed?
- Confirm evidence that any rodenticides, insecticides, or fungicides used for pest control are approved by NAFDAC and other appropriate governmental agencies for such use.
- Review/note procedures to protect personnel and prevent contamination of equipment, components, drug product containers, closures, packaging, labelling materials, or drug products during application and use of pest control agents.

Building Maintenance

NAFDAC GMP for Medicinal Products Regulations 2021, section 5(1)(2)
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 3.17 J (IV)

- Confirm that buildings are designed so that maintenance does not pose a risk to products.
- Review maintenance records to confirm that schedules are followed.
- Observe facility to confirm status of maintenance.

Equipment: Design, Construction, Size, and Location

NAFDAC GMP for Medicinal Products Regulations 2021, section 5(1)
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 3.64-3.77

- Equipment shall be of appropriate design, adequate size, and suitable location to facilitate intended operations, cleaning, sanitation (if needed), and maintenance.
- Equipment surfaces in contact with product must not be reactive, additive, or absorptive or alter quality, identity, purity, safety, or strength of regulated products and related materials beyond official or other established specifications.
- Review list of equipment submitted in SMF before inspection; confirm availability and adequacy of equipment; review SOPs, validation/calibration records, etc.
- Is equipment of appropriate design? Adequate size? Suitably located to facilitate operations, cleaning, and maintenance?
- Confirm that equipment is constructed with materials and of specifications to meet standards.
- Examine SOPs for cleaning, sanitation, and maintenance of equipment and utensils; confirm SOPs are followed.
- Review records for maintenance, inspection, and calibration (if needed) for automatic, mechanical, and electronic equipment.
- Are filters (where used) fibre releasing?

Control of Materials

NAFDAC GMP for Medicinal Products Regulations 2021, section 9(2)(3)
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 7.3, 7.4. 7.6

- Ensure that SOPs on sourcing, receipt, identification, storage, handling, sampling, testing, and approval or rejection of materials are established and followed. Materials shall at all times be handled in a manner to prevent degradation and contamination.
- Check the SOP index. View all SOPs if possible. Review some SOPs (e.g., sampling and testing of materials).
- Pick a key SOP; if possible, find where, on a Batch Record, a batch of material has been processed as per that SOP. Ask the employee who performed that task to tell you how that specific operation was performed. Compare their account with the SOP. Does the SOP confirm that the Quality Unit approves the SOP? Check records.

Materials Management

NAFDAC GMP for Medicinal Products Regulations 2021, section 9
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 7

- Verify that documented procedures exist for sourcing, receipt, identification, storage, handling, sampling, testing, and approval or rejection of materials.
- Confirm that standards and specifications for materials are documented and complied with.
- Verify adequacy of the process in place for the testing and approval/rejection of materials
- Verify that adequate controls are in place to rotate materials approved for use (e.g., FEFO/FIFO).
- Verify that materials are retested or re-examined, as appropriate, for identity, strength, quality, and purity and approved /rejected by quality unit (e.g., after exposure to extreme conditions).
- Verify that rejected materials are identified and controlled by a quarantine system designed to stop their use in any operations for which they are unsuitable.
- Review procedures for supplier certification and records.

Production and Process Controls

NAFDAC GMP for Medicinal Products Regulations 2021, section 8
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 6

- There shall be SOPs for production and process control designed to ensure that the regulated products and related materials have the identity, strength, quality, and purity they purport (*, section 29*).
- Review documents (e.g., SOPs, batch manufacturing records, record of yield) and signatures of head of quality unit/independent person verifying activities.

- Confirm availability, adequacy, and implementation of SOP for production and process control.
- Verify that systems are in place and followed for report, investigation, and justification of any deviation from SOPs and that quality unit approval is obtained for such deviations.
- Confirm procedures exists for identification, documentation, review, and approval of changes in raw material, components, specification, analytical methods, facilities, equipment, computer hard/software, and processing steps.
- Confirm SOPs for control procedures include batch requirements, component handling, verification, and supervision of operations.
- Verify that each container of components issued for manufacturing, each component added to batch, and calculations performed by one person are independently verified by a second person.
- Review procedure to ensure that actual yield and percentage of theoretical yield are calculated at the end of the appropriate phase of manufacturing, processing, packing, or holding of regulated products and related materials.
- Verify how equipment identification requirements are met.
- Verify there are written procedures for in-process controls, as well as tests or examinations for conducting on appropriate samples of in-process materials of each batch. Are the SOPs followed?
- Confirm that time limits are established to assure the quality of the regulated products and related materials; check records for proof of adherence to time limits for completion of each phase of production.
- Confirm that written procedures are established and followed, prescribing a system for handling batches that fail to meet specifications.
- Are procedures implemented to control microbiological contamination?
- Is any reprocessing done? Who authorises it? SOP?
- Verify the batch numbering system.

Packaging and Labelling Controls

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 6.46-6.49

- Detailed SOPs for the receipt, identification, storage, handling, sampling, examination, and/or testing of labelling and packaging materials shall be established and followed *(*
- Are labelling and packaging materials representatively sampled examined and tested upon receipt and before use?
- Are out-of-specification (OOS) material rejected and quarantined?
- Check SOPs for receipt, identification, storage, handling, sampling, testing, and examination of labelling and packaging materials.

- Is there an implemented process for the control of labels issued?
- Examine implementation of SOPs to assure that correct labels, labelling, and packaging materials are used for drugs and related products.
- Review implementation of SOPs for tamper-evident packaging requirements.
- Review documented and implemented SOPs for inspection of drugs and related products. Check for documented SOP for assignment of expiration date.
- Verify that regulated products have expiration dates on labels as required.
- Verify process outlining standards/specifications (e.g., protective, non-reactive, clean/sterile) for drug product containers and closures.

Holding and Distribution

NAFDAC GMP for Medicinal Products Regulations 2021, section 13
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 1.16-1.17

- Warehousing and distribution of SOPs for drug products shall be established and followed. SOPs shall include quarantine before release; storage under appropriate conditions of temperature; and light and humidity to maintain the quality, identity, purity, and strength of the drug product.
- Check SOPs; check storage conditions; interview personnel on recall and other relevant warehousing and distribution procedures.
- Audit warehouse: ask to see records of temperature and humidity to check storage under appropriate conditions of temperature, humidity, and light.
- Confirm SOP exists to manage stock to ensure that oldest approved stock of drug product and related product is distributed first. Check distribution register to verify.
- Is there a documented system for traceability of distribution of each batch of drug product to facilitate recall? Ask to see it.

Laboratory Controls

NAFDAC GMP for Medicinal Products Regulations 2021, section 10
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 8

- Review analysts' notebooks, records of equipment qualification and process validation.
- Review training records and personnel qualification records
- Verify that the Quality Unit and other personnel are trained, qualified, and experienced.
- Examine training records to verify initial and continual training on GMP, hygiene and sanitation, and specific job functions.
- Interview trained staff on training.
- Examine consultant records for proof of experience/qualification.

- Check laboratory SOPs index.
- Review a couple of laboratory SOPs
- Do appropriate and scientifically sound specifications exist for all products manufactured at the site?
- Do sampling plans exist?
- Do test procedures exist?
- Does the laboratory perform identity tests (Id) on APIs and excipients as required?
- Review a test procedure (test method) for the most important product manufactured at the facility.
    - Is it approved?
    - Is it followed exactly as written?
    - Check against a batch record of product released 2 months ago, 12 months ago, and 18 months ago (or 2, 6, and 12 months ago).
- What are your findings?
- Verify the following: (examine actual examples, probe, and ask for explanations)
    - Do appropriate written specifications exist for the acceptance of each batch of:
        - API?
        - Starting materials?
        - Packaging components?
        - In-process materials?
        - Finished products?
    - Do specifications include a description of the sampling and testing procedures to be used?
    - How are ***samples*** taken?
        - By whom?
        - Verify chain of custody.
        - Are samples representative of the batch? How?
        - Do sampling plans specify the number of units per batch to be tested?
        - Are samples labelled and identified?
    - How are samples stored to avoid deterioration, cross-contamination, or mix-up?
    - Are samples stored under lock and key?
    - Is there retesting of any material that is subject to deterioration?
- Verify that the laboratory conducts tests on each batch of raw materials, in-process goods, and finished drug products (check products manufactured 2, 12, and 18 months ago).
- Who determines whether a given batch of material conforms to written specifications or should be rejected?
    - Production manager?
    - Quality Unit (QA/QC) manager?
    - Plant manager?
    - Some other company official?

  - Check against documents on released or rejected batches to see who really makes the decisions.
- How are rejected batches disposed of? Ask to see an example!
- Review verification of compendia methods.

Microbiology

- Verify training on job specification and periodic performance evaluation to determine competence (e.g., plating, aseptic techniques).
- What biological indicators are purchased?
- Are population of organisms confirmed before use? Is there an SOP?
- Are SOPs for media preparation and storage available?
- How is the number of passages for working culture tracked?
- Are growth promotion tests carried out? Review SOPs.
- Review environmental monitoring results and SOPs.
- With regard to SOPs for analysis of water and other ingredients or drug and related products that are susceptible to microbial contamination, is there appropriate laboratory testing, as necessary, of each batch to determine absence of objectionable micro-organisms and/or levels of pyrogens and endotoxins?

Instrument Calibration and Preventive Maintenance

- Are instruments, apparatus, gauges, and recording devices (e.g., analytical balances, ovens, pipettes, and other analytical volumetric glassware; stop watches; pH meters; thermometers; high-performance liquid chromatography (HPLC) pumps, HPLC detectors, spectrophotometers) calibrated at suitable intervals?
- Is there a written SOP for equipment calibration?
- Has a calibration schedule been established for all equipment subject to calibration? Is it followed?
- Check the analytical balance calibration log.
- Verify that it was calibrated on the days when each of the batches you checked earlier (manufactured 2, 12, and 18 months ago) was weighed in the laboratory during testing.
- Is there a preventive maintenance SOP and schedule for equipment? Is it followed? Verify!

Out-of-Specification (OOS) and Investigations

- Ask to see the SOP for OOS
- Examine the Laboratory Investigations Log.
- How many open investigations are there?

- Frequent OOS test results should raise a red flag!

Method Validation
NAFDAC GMP for Medicinal Products Regulations 2021, section 6.2
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 8.37

- Does the company have a method validation SOP? Is it followed? Ask to see evidence!
- Ask to see validation (or verification) report of the Assay and Degradation Products Test Methods or the Stability Test Methods for the company's product from a risk based perspective
- Reprocessed Materials

  Does the company have an approved reprocessing SOP? Ask to see test results on a recently reprocessed batch, if any. *Remember, prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria*.

Stability Testing
NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 8.62-8.80

- Recall that:
  - A written stability testing program is required by GMP regulations.
  - The results of these tests must be used to determine the labelled storage conditions and expiration dates.
  - The tests must be carried out in the container closure system(s) in which the product is marketed.
- Verify that a stability testing SOP with appropriate details exists and is followed.
  - Ask to see the stability storage chambers.
  - Are the chambers appropriately labelled for temperature and humidity conditions?
  - Are temperature and humidity conditions monitored and recorded?
  - Ask to see the records supporting these items.
  - Are the chambers validated? Ask to see the validation reports and data.
- Does the manufacturer place at least one batch of each product in its respective stock keeping unit (SKU) manufactured annually on stability monitoring?
- What happens when there is a stability test failure? How are these investigated?
- Ask to see an example. Interview the analysts.
- How long does it take from when a sample is pulled from the chamber to when testing begins? Ask to see records to verify this.
- Are stability samples awaiting testing after being pulled from the chamber appropriately stored? How and where? Verify SOP and practice.

- Does the manufacturer make homeopathic drug products? If stability testing is not feasible for such products, is there testing for ingredient compatibility to demonstrate that there is no degradation of the product in the market and market container during the labelled period of use?

Special Testing Requirements

Sterile Products

- Does the facility manufacture sterile and/or pyrogen-free products? If so, verify that appropriate microbiological testing is done to assure compliance of each batch with written specifications for pyrogens, endotoxins, sterility, preservatives, and microbiological and other attributes.

Ophthalmic Ointments

- Does the facility manufacture ophthalmic ointments? If so verify that appropriate testing is done to check for the presence of foreign particles and harsh or abrasive substances in each batch of product. Are the test procedures in writing? Do test results conform to written specifications?

Modified Release Products

- Does the facility manufacture modified ("controlled") release dosage forms? If so, are the rates of release of each active ingredient verified for every batch of product?
- Are the test procedures and acceptance criteria in writing and approved? Verify. Do products conform? Check some recent batches (past 1–12 months).

Computerized Systems Used in the Laboratory

- Does the laboratory use computerized systems? These include computers, spreadsheets (e.g., Excel spreadsheets for calculating results), instruments (e.g., s spectrophotometers, auto-titrators, pH meters), equipment with disk systems and/or storage memory, chromatography data systems (e.g., "Empower"), and laboratory information management systems.
- If so, ask to see evidence that these systems have been validated?
- Do these systems have the capability to track who made changes to data and to prevent unauthorized changes to data (audit trail)?
- Have such functionalities been implemented? Ask to see evidence.

Tests Conducted by External (Contract) Laboratories

- Does the firm send out any material for testing by an external laboratory?
- If so, ask to see evidence that these laboratories are qualified to perform those tests and that the results are reliable.
- Is there a vendor qualification program in place? Is it being followed?

Data Governance and Security

- What procedures are in place to assure the integrity of laboratory data and prevent unauthorised changes not only to computerized data but also to notebooks, worksheets, completed batch records, etc.?
- Is an audit trail functional on the computerized system?
- Do these systems have access control?

Retention Samples

NAFDAC GMP for Medicinal Products Regulations 2021, section 10(4)

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 8.18-8.28Does the site keep retention samples of APIs and drug products in appropriate quantities and for the periods required by GMP?

- Ask to see the SOP.
- Verify where retention samples are stored. Are these appropriate?
- How often does the company carry out physical inspection of the samples? Ask to see the documented evidence of where it recently did this.
- Do you notice any "off-colour" or other evidence of deterioration? Dust?

Laboratory Animals

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 8.58

- Does the site use laboratory animals for testing? Are these animals maintained and controlled in a manner that ensures their suitability for their intended use?
- Ask to see the SOP and verify adherence.
- Are animals identified, and are adequate records kept showing the history of their use?
- Verify documentation.

Beta-Lactam Contamination

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 3.18, 3.46, 6.22a, 8.59

- Does the firm manufacture beta-lactam and other highly sensitizing products? If so, are the operations carried out in a separate facility? Is there any real or possible cross-contamination of other products with these highly sensitizing products? Verify steps taken to prevent such an event.

Review of Documentation

1. Assess the company's overall documentation management system, including its change control practices. Evaluate the batch release procedure and the role of the person who is responsible for this duty.
2. Below is a (not exhaustive) list of documents that may be reviewed:
    - Site Master File
    - Quality Manual
    - Master formula and processing instructions
    - Specifications for starting materials, primary packaging materials intermediate, Bulk products and finished products.
    - Batch manufacturing records
    - Complaints
    - Deviation reports
    - Relevant SOPs and records (e.g., recall procedure)
    - Relevant contracts
    - Job descriptions and training records
    - Validation information
    - Laboratory books
    - Stability data (including ongoing stability)
    - Self-inspection program (self-inspection reports may not be reviewed; only check whether they are available)
    - Product Quality Review reports
    - Quality Risk Management reports
    - Management Review reports
    - Corporate corrective and prevention action (CAPA) program records
    - Vendor approval, qualification and maintenance system and list of approved vendors

Records and Reports

(, section 55)

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 5.12-5.13

- Records shall provide appropriate history of each batch of products, including its distribution and all other relevant circumstances pertinent to quality of final product.
- Verify SOP on records and reports; check traceability of a batch with personnel; confirm the role of the quality unit in review and approval of records and/or changes.
- Review SOP for handling and maintenance of records and reports. Is it followed?
- Verify SOP on managing container closure and labelling records (if not already done).
- Verify that records are maintained for all components, containers, closures, and labelling for appropriate periods.
- Verify written record of major equipment cleaning, maintenance, and use in individual equipment logs showing date, time, product, and batch number of each batch processed.

- Verify procedure developed and maintained for the preparation of master production and control records.
- Confirm that batch production and control records are prepared for each batch of drug product produced.
- Confirm that all drug product production and control records, including those for packaging and labelling, are reviewed and approved by the quality unit.
- Confirm that laboratory records include complete data from all tests necessary to assure compliance with established specifications and standards.
- Ensure that distribution records contain all required information, (name, strength, description of dosage form, name and address of consignee, date and quantity shipped, batch/control number, manufacture/expiry dates) of each batch.
- Ensure that there are written procedures describing the handling of all written and oral complaints regarding a drug or related product.

Returned Products and Product Salvaging

(2021, sections 65, 66)

NAFDAC Good Manufacturing Practices (GMP) Guidelines for Pharmaceutical Products 2021, section 7.57-7.60

- Returned products shall be identified as such and held. Where there is any doubt on quality of returned drug product, it shall be destroyed unless examination, testing, or other investigation proves that the product meets efficacy, quality, identity, potency, strength, and safety standards.
- Products that have been subjected to improper storage conditions or have expired shall not be salvaged or returned to the marketplace or for use (*2021, section 66*).
- Review SOP and records that manage return, handling, and salvaging of drug products. Are they followed?

Before the Closing/Exit Meeting

- The team members should meet alone to discuss their findings.
- Call Headquarters for guidance if in doubt or if faced with serious noncompliance requiring immediate action.
- List major findings to be presented to management at the closing/exit meeting.
- Begin with the most important findings.
- List findings of areas of strength, areas of deficiencies, and items that require immediate attention.
- Decide whether the Lead Inspector alone or other team members will present findings.

Closing/Exit Meeting

- At the end of the inspection, hold a closing/exit meeting with the company's management including QA, manufacturing, and others to discuss the outcome of the inspection.
- Complete the meeting attendance record.
- Present a summary of both the positive findings and the GMP deficiencies. The company may wish to further clarify some of the deficiencies. It is important to ensure that all of the deficiencies are accurate and are not subject to misinterpretation.
- Inform the company that a formal notification of the outcome of the inspection will be communicated to them within 20 working days.
- All points of contention should be discussed during this meeting. If the company does not accept a deficiency, inform them they can appeal by writing to the Director General.
- ***If applicable, make sure any documents are signed by the appropriate individuals.***
- ***The Lead Inspector should explain next steps to manufacturer personnel.***
- Thank the manufacturer personnel for their attention and cooperation.
- Depart.

After Inspection

Inspection Report

1. The report should be written using the approved DER Inspection Report Format (in Annex 4.
2. The contents of the report should be clear, concise, accurate, factual, objective, complete, written in the past tense, and not subject to misinterpretation.
3. The deficiencies listed in the report should be classified as described in the DER Inspection Report Format and referenced to a specific section of the *NAFDAC GMP for Medicinal Products Regulations 2021*.
4. Cover only one issue per observation. Multiple deficiencies dealing with the same issue should be combined.
5. Deficiencies that have been corrected during the inspection should be included in the inspection report with a statement that it has been corrected.
6. Each inspector should sign the report.
7. The timeframe for corrective measures may be dependent on the risk category of the deficiencies and the inspection rating. Generally, the company should be given 30 calendar days to respond to the inspection findings. See the CAPA format and risk categorization in Annexes 2 and 3.

Communication with Headquarters (HQ)

1. Inspection reports should be completed within 20 working days of conclusion of the inspection.
2. Send inspection reports to DER Headquarters within **5 working days of completion of the report,** unless otherwise directed.
3. Send a formal notification of the outcome of the inspection to the inspected company within 10 calendar days on conclusion for in country inspections by the Divisional Head or State Coordinator on behalf of the agency and 30 calendar days of conclusion of the inspection for foreign/ overseas countries by the DER Director
4. Address next steps to achieve closure on any issues requiring further action by the team.
    - Can the inspection be "closed"?
    - If so, is the inspection summary report (file) now complete, with no pending open issues? If not, what are the plans to address and close open issues? Defer to next inspection conduct follow-up inspection?
    - Is all documentation completed and filed?

Note: All activities required to achieve closure must be completed and any indicated follow-up action finalized within 60 calendars days from the day after the inspection.

Follow-Up

1. The company sends its response letter (including plan for corrective measures) to the DER Director. The latter sends it to the inspector team for review. If the company fails to respond to the inspection findings, the DER Director sends a reminder letter to the company.
2. Within 30 calendar days, the office of the DER Director prepares a response letter. This letter should:
    - Acknowledge receipt of the company's plan for corrective measures.
    - Provide an assessment of its corrective measures.
    - Include a statement of appreciation for cooperation with the inspection team.
    - Request for further correspondence, if needed.
3. Deficiencies may be considered as resolved if the company's response letter:
    - States that corrective and preventive measures have been implemented.
    - Includes supporting documentation.
    - If necessary, includes a written commitment, providing a clear and reasonable schedule for implementation of corrective and preventive measures.
4. If the corrective and preventive measures taken by the company are not considered acceptable, further correspondence between the office of the DER Director and the company may be necessary.
5. In the case of a non-conformance (NC) rating of the inspected site, the need for a follow-up inspection to ensure that corrective measures have been implemented should be discussed within the office of the DER Director and a decision taken. Such follow-up

inspection would represent a new inspection process to be dealt with according to this procedure.

Conclusion/Remarks

“Charge to inspectors”: This is a guide on what to look for and how to carry out GMP assessments.

Annex 1: Proposed Inspection Plan

Note: this template can be amended to fit purpose

Company name:

Full location address:

Date(s):

NAFDAC Inspection Team

Name of Lead Inspector:

Name(s) of other Inspector(s):

Scope of inspection:

Subjects and timings may change depending on the progress of the audit. Audit team may split to cover separate topics in parallel where required.

Day 1

Opening meeting

- Introductions
- Company presentation: Company overview, site description, production and QC capacities, quality management and assurance systems, summary of manufacturing processes, major equipment and product range, inspection history, major changes since the last inspection (where applicable). (15 minutes)
- Confirmation of proposed inspection plan/schedule.

Quality Management System review

- Site Master File
- Quality Manual
- Personnel Policies: Organization charts, Job descriptions, Training, Health and Hygiene.
- List of SOPs/SOP Index
- SOP preparation, review, approval and control
- Batch numbering system

- Product Quality Review SOP and reports
- Quality Risk Management SOP and reports
- Deviation and Change control SOPs + Registers
- OOS SOPs + Registers
- Self-inspection SOP plans and report.
- Minutes of Management Review + Corporate CAPA
- Complaints handling system SOPs + Register.
- Product recall system SOPs + Register
- Product Master Files, codes, specifications for APIs and FPPs
- Vendor approval, qualification, and maintenance system + list of approved vendors
- Finished product release SOP.

Validation Master Plan

- Qualification, validation and calibration policies, schedules and status.

Validation

- Process validation and revalidation: protocols and reports.
- Cleaning validation protocols and reports

Equipment qualification and preventive maintenance:

- Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment)
- Preventive maintenance schedules and records
- Calibration schedules and records

Review of the Heating Ventilation and Air Conditioning (HVAC) System:

- HVAC system schematic drawing and summary of specification for HVAC
- Qualification/Requalification/Monitoring the HVAC System
- Inspection of the HVAC + Dust extraction technical area.

Inspection of Receiving and storage areas + procedures:

- Receiving, quarantine, sampling and storage of starting materials and packaging materials including material flow and identification.
- Temperature + Relative Humidity (RH) mapping and monitoring
- Pest control procedures
- Inventory management procedures.

Summary of observations for the day

Day 2

Inspection of Water Treatment System (where water is critical to product quality)

- Water quality manual
- Key design parameters, schematic drawing of treatment plant
- Qualification/validation of the system
- Walk through of the treatment plant.
- Testing and monitoring

Inspection of Production activities:

- Site layout, Floor plans with material and personnel flow, area classification and pressure differentials, air handling units (AHU) distribution
- Dispensing
- Production, packaging and in process controls (charge-in etc.)
- Equipment identification
- Equipment use, maintenance, cleaning and incident logs.

- Review of Lot processing/Testing records – selected Lots
- Separation between packaging and labelling lines, Monitoring of printing devices.
- Line clearance
- Tamper-evident packaging requirement
- Finished goods warehouse + distribution records.

Quality Control Laboratory

- Analyst training and competencies
- Sample receipt, storage and allocation
- Wet chemistry laboratory
- Instrument laboratory
    - Qualification, calibration, preventive maintenance
- Laboratory materials management (Samples, Reagents Stock Solutions, Reference and Working Standards)
- Stability testing programme (Protocols, programme, records and data)
- Retention Samples
- Starting materials and finished products specifications, testing and release.
- Methods validation & verification
- Procedures
- Testing of Packaging Materials and Components.

Microbiological laboratory

- Room and equipment
- Media preparation and product testing
- Purified water (PW) monitoring
- Environmental monitoring

Review of any areas or outstanding documents.

Preparation for closing meeting.

Summary of observations for the day and closing meeting with company representatives

End of inspection activities.

Notes:

1. Lunch and tea breaks should be kept to a minimum.
2. The company should keep all relevant documents relating to the topics listed above ready for the inspection.
3. The plan is tentative and is subject to change, as circumstances dictate.
4. Additional documents may be requested during the inspection.

Annex 2: Corrective Action and Preventive Action Plan

Audit findings (observations)	Root cause analysis	Correction	Corrective Action(s)	Indicators for Completion	Timeline	Responsibility	CAPA Status

Annex 3: Risk Classification of Good Manufacturing Practices Observation

SCOPE:

To classify the observations noted during GMP inspections.

To inform the establishment of the situation(s) that the Agency (NAFDAC) considers unacceptable and that will generate a non-conformance rating following an inspection.

An overall recommendation will be based on the deviations from NAFDAC GMP Regulations observed during GMP inspection of an establishment.

The possible ratings are defined below.

1. **Compliant**
   At the time of the inspection, the auditee has demonstrated that its operations are in compliance with the NAFDAC GMP Regulations.

2. **Non – Compliant**

At the time of the inspection, the auditee has not demonstrated that its operations are in compliance with NAFDAC GMP Regulations.

The overall inspection rating assigned will be based on the risk involved taking into account the nature and extent of the deviation with the category of products evaluated.

Attribution of a Non- Compliant rating may have serious consequences for an establishment. Therefore, these situations of non-conformity have to be well defined, unambiguous and directly supported by the applicable Regulations

ASSIGNMENT OF RISK LEVEL TO AN OBSERVATION

The Risk assigned will be in relation to the nature of the deviation as well as the number of occurrences. The above principle should be applied in risk categorization because it is impossible to encompass every situation that may generate a risk.

Risks are categorized into;

Critical:

A Deficiency which has produced, or leads to a significant risk of producing a product which is harmful to the patient or has latent health risk.

OR

Any observation that involves fraud, misrepresentation or falsification of product or data.

Major:

A non-critical deficiency:

Which has produced or may produce a product, which does not comply with its marketing authorization?

OR

Which indicates a major deviation from NAFDAC current Good Manufacturing Practice Regulations.

OR

A major deviation from the terms of the manufacturing authorization.

OR

Which indicates a failure to carry out satisfactory procedures for release of batches or (within GMP Regulations) a failure of the authorized person to fulfil his/her required duties.

OR

a combination of several "other" deficiencies, none of which on their own be major, but which may together represent a major deficiency and should be explained and reported as such.

Certain major observations may be upgraded to critical.

Others:

Observation that is neither critical nor major but is a departure from GMPs. All other observations could be upgraded to major.

Assignment of Inspection Rating

A non- Compliant rating is assigned when critical observations are noted during an Inspection. Such situation is immediately brought to the attention of the company's officials and the Agency is to be notified in a timely manner.

A non-compliant rating may also be assigned when numerous major observations are noted during an inspection indicating that the company does not control its processes and operation sufficiently.

Repetition of many major and other observations noted during previous inspections indicates that company did not;

- Implement the corrective actions submitted following the previous inspection or;
- Did not put in place adequate preventive actions in a timely manner to avoids occurrence of such deviations.

When a Non-compliant rating is assigned, the inspector at the Exit meeting will inform the company of all the risks observed.

The status of compliance with NAFDAC GMP for Medicinal Products Regulations should be determined by the nature and number of deficiencies:

a. When there are critical or more than five (5) major deficiencies:

   i. The site is considered to be operating at an **unacceptable** level of compliance with NAFDAC GMP for Medicinal Products Regulations,

   ii. Another inspection will normally be required,

   iii. Regulatory actions are applied as necessary.

b. When there are other and less than six (6) major deficiencies:

   i. CAPAs are evaluated on paper and if actions implemented and/or planned, timelines and documented evidence of completion are found adequate, the site is rated to be compliant with NAFDAC GMP for Medicinal Products Regulations

   ii. If assessment of the CAPAs requires on-site verification, a follow-up inspection is conducted to ascertain level of compliance and effectiveness of corrective actions. A satisfactory outcome will infer compliance of the site with NAFDAC GMP for Medicinal Products Regulations

c. When there are other deficiencies only:

   i. The site is considered to be operating at an acceptable level of GMP compliance,

   ii. The manufacturer is expected to provide CAPAs,

   iii. CAPAs are evaluated and followed up during the next inspection.

Annex 4: DER Inspection Report Format

NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL (NAFDAC)

DRUG EVALUATION AND RESEARCH (DER) DIRECTORATE

This box should contain only the name of the Inspected Company. E.g. XYZ Pharmaceutical Limited

AUDIT DATE: This refers to Date(s) of the Inspection e.g. 24th August, 2017 or 24th and 25th August, 2017

REPORT DOC. NO: *This should be the abbreviation of the first letter of the first three words of the company name, the recognized abbreviation of the state of location of the company, type of Inspection conducted, its position for that year, and lastly the year in question e.g.*

MPI-AN-GRI-02-2021;

Where MPI represents Mandilas Pharmaceutical Industries Nig. Ltd.;

AN stands for Anambra State; (For foreign inspections, this should be the internationally recognized 2-letter code for the country based on ISO 3166 Standard International Naming Convention e.g. India – IN; Indonesia - ID)

GRI is GMP Reassessment Inspection;

02 is 2nd Inspection of that company in that year;

2021 is the year in question

DISTRIBUTION: **Director (DER)**
Company's copy
Director (PR&S) ***(for foreign inspections)***

Editor:	**DER Headquarters** *(this must always be the headquarters as shown)*
E-mail:	der.headquarters@nafdac.gov.ng *(This e-mail address and not individual State or Zonal office e-mail addresses must be used)*
Website:	**http://www.nafdac.gov.ng**

S/N	TYPE OF INSPECTION	CODE
1.	Pre-Production Inspection	PPI
2.	Pre-Registration Inspection	PRI
3.	Routine Inspection	RI
4.	Follow-Up (CAPA Effectiveness Verification) Inspection	FUI
5.	For Cause Inspection	FCI
6.	GMP Re-Assessment Inspection (Inspectors are to explain the reason for the re-assessment in the body of the report e.g. License Renewal, unsatisfactory lab. analysis etc.)	GRI
7.	Special Inspection (e.g. Advisory inspection, Surveillance inspection, Sampling inspection, Placement and Removal of hold label.	SI
8.	Monitoring Inspection (e.g. for co-packaging of products like Powder for injection and sterile water, printing of MAS code, overprinting of NRN on imported products etc.)	MI

General Information

Inspected site(s):	• ***Name and full address of the inspected site(s) (including telephone phone number(s), e-mail, fax & website)*** • ***Company's corporate address if different from that given above***
Activities carried out by company	• **Manufacture of Active Ingredient** ☐ • **Manufacture of Finished Product** ☐ • **Manufacture of Intermediate or bulk** ☐ • **Packaging** ☐ • **Importing** ☐ • **Laboratory Testing** ☐ • **Batch Control and Batch Release** ☐ **(Tick as appropriate)** **Others (please specify ……**
Inspection Details:	• **Date of Inspection -** ***Date(s), Month, Year*** • **Type of Inspection** • ***For foreign inspections, state whether the National Regulatory Authority of the country where the inspection took place was informed, and if they took part in the inspection.***
Inspectors:	***Names of the Inspectors, Designation, Directorate & Location in the Agency*** ***Name of Expert/Assessor (if applicable)***
References:	***GMP Regulation(s) and Guidelines used in assessing compliance should be listed***
Introduction: • ***Short description of company and its activities including product lines;*** • ***State if the product of interest is manufactured at the site under contract and the name and address of the contract giver.*** • ***Any use of outside scientific, analytical or other technical assistance in manufacturing and quality control.***	

- ***Date of previous inspection***
- **Type of previous inspection**
- **Names of inspectors involved in previous inspection**
- **Major changes in the facility since the previous inspection**

Brief report of the inspection activities undertaken: ***(italicized explanatory notes are to serve as a guide in writing the report and should be deleted from the report)***

Scope of Inspection:

Short description of the reason/purpose of the inspection. The reason for the inspection should be specified (e.g. general GMP assessment, new registration application, routine, investigation of product defect etc.)

Product(s) for which the inspection was carried out (where applicable). (Name, dosage form/formulation type, pack size, active ingredients & strengths, NRN, etc.)

Inspected area(s):

Each inspected area should be specified

Personnel met during the inspection:

The name and titles of key personnel met, their academic qualifications, years of experience, telephone numbers and email addresses should be specified.

Inspection Team's findings and observations (both positive & non-conformance observations):

Headings to be used are as shown below.

Note: Other relevant headings not mentioned may be introduced under separate headings.

1. **Pharmaceutical Quality System (PQS)**
   - **Management commitment to quality of products and attainment of quality objectives**
   - **Change Management (Request, review and approval)**
   - **Deviation Management (reporting, investigation and close out)**
   - **Root cause analysis & CAPA.**
   - **Product quality reviews**
   - **Quality Risk Management**
   - **Management Reviews**

2. Personnel

- ***Describe the organizational structure, personnel responsibilities, authorities, interrelationships and key personnel qualifications, availability of adequate numbers of sufficiently qualified and experienced personnel, clarity of their responsibilities, limits and reporting hierarchy. Qualifications, experience and responsibilities of key personnel (head of production, head(s) of the quality unit(s), authorized person) and procedures for delegation of their responsibilities***

- **Personnel Training:**
  Describe adequacy of procedures and records for induction, specialized and continual training and evaluation of its effectiveness; coverage of GMP and concepts of quality assurance during training; training of visitors and evaluation of consultants and contract staff

- **Personnel Hygiene**
  Description of the procedure and records in place for initial and regular health examination of staff appropriate to their responsibilities. Measures and facilities to impart, maintain and monitor knowledge of a high level of personal hygiene. Measures to ensure personnel do not become a source of contamination to the product, including hand-washing and gowning. Appropriate restriction of smoking, eating, drinking, chewing and related materials from production, laboratory and storage areas

3. Premises and Equipment

- ***Description of facility location (for new or additional facilities on existing sites)***
- ***Design and size of facility regarding adequacy of production, weighing, QC, storage and ancillary areas.***
- ***Nature of construction and finishes***
- ***Systems such as drainage, ventilation, air filtration, air-conditioning, supply of steam and gas, water systems.***
- ***Provision of self-contained facility for production of highly sensitizing and potent pharmaceutical products (where applicable)***
- ***Measures for dust control, prevention of contamination and cross contamination, appropriate segregation and restricted access to core processing areas.***
- ***Description of the procedure and records in place for sanitation activities, sewage and refuse disposal***
- ***Description of equipment location, design, identification, cleaning, calibration, maintenance, repair etc.***

4. Qualification and Validation

- ***Validation Master Plan***

- ***Qualification of critical production and laboratory equipment; protocols and reports***
- ***Process, cleaning and analytical method validation activities; protocols and reports***

5. Documentation

- ***Site Master File, Quality Manual, Specifications, protocols, reports on quality control, environmental control, and engineering.***
- ***Document control procedures***
- ***Standard operating procedures and records***
- ***Batch and document numbering system,***
- ***Measures to ensure data integrity, confidentiality and security,***
- ***Approved Master Formulae for all products***
- ***Standard testing procedures/instructions***
- ***Specifications for starting materials, packaging materials, bulk materials and finished products.***
- ***Batch manufacturing and processing records***
- ***Batch packaging records***
- ***Distribution records***

6. Production

- ***Dispensing, production, packaging activities***
- ***In-process controls (IPQC records)***
- ***Review of BMRs/BPRs of selected batches***
- ***Technical and organizational measures for avoidance of cross contamination***
- ***Deviation (reporting, investigation & approval)***
- ***Yield calculation and reconciliation (production & packaging)***
- ***Access control to production areas***
- ***Line clearance***
- ***Production equipment clean hold time.***
- ***Repair and maintenance of production equipment.***
- ***Checks on packaging operations and integrity of labeling operations, handling of unused batch coded and uncoded packaging materials.***
- ***Batch review and release procedure.***

7. Materials Management

- ***Vendor Qualification, Approval and maintenance system, list of approved vendors.***
- ***Receiving, sampling, quarantine, handling, storage, transport and use of starting materials, packaging materials, bulk and finished products.***
- ***Temperature + RH mapping and monitoring.***
- ***Returned and recalled goods management***
- ***Pest control procedures***

8. Quality Control

- ***Independence of QC from production and other departments***
- ***Availability of trained and competent personnel***
- ***Availability and use of approved specifications and testing procedures for sampling, inspecting, and testing of starting materials, packaging materials, and intermediate, bulk, and finished products***
- ***Periodic revisions of specifications as per new editions of pharmacopoeias***
- ***Availability of current pharmacopoeias, reference standards, reference organisms, reference spectra and other reference materials.***
- ***Laboratory records – sample, test, instrument/equipment records***
- ***Retention of samples of starting materials and finished products***
- ***Investigation of OOS and OOT***
- ***Stability studies***

9. Contract manufacture and analysis

- ***Availability of contract and quality agreement***
- ***Responsibilities of contract giver and contract acceptor***
- ***GMP/GPPQCL compliance of contract acceptor.***

10. Complaints and product recall

- ***Availability of a formal procedure for handling of complaints and recalls with designated responsible person(s)***
- ***Adequacy of complaints and recall procedures regarding exported products (for foreign inspections)***
- ***Escalation of complaints on product defects to several batches.***
- ***Review of complaint register or records.***
- ***Review of complaints record for recurring defects.***
- ***Handling of returned, recalled and salvaged products.***
- ***Communication with relevant and competent authorities on recalled products.***
- ***Reconciliation between the distributed and recovered quantities of the recalled products.***
- ***Procedure for mock recalls.***

11. Self-inspection

- ***Availability of formal procedure for self-inspection, self-inspection team, frequency of self-inspection, mechanism for escalation of self-inspection findings, follow-up actions.***

Distribution and shipment

Compliance with Good Distribution Practices.

State the name and address of company's distributor(s) where applicable

Miscellaneous:

Samples taken

State the names and pack sizes of products drawn (Product labels only for foreign inspections)

Distribution of Report

This refers to the different destinations to which the report should distributed. It should always be as follows;

- **Director (DER)**
- **Company's copy**
- **Director (PR&S)** ***for foreign inspections only***

Annexes attached:

List of any annexes attached e.g. Attendance sheets, list of company's products, company profile, memory stick and contents etc.

List of Deficiencies classified into critical, major and others:	**References**
All deficiencies found should be listed below even if corrective action had taken place straight away.	***The relevant reference to the NAFDAC GMP Regulations/Guide lines and other relevant guidelines listed in the section on references (pg. 3)***

		should be mentioned for each deficiency in this column
Critical		
S/N		
Major		
S/N		
Others		
S/N		
Recommendations: ***The recommendation of the inspection team should be based on the audit findings on the inspected site with a clear statement on the status of operations of the facility.***		
Summary and conclusions: ***The inspection team should give an overview of the operations of the facility, findings from the inspection and state if the company operates in accordance with the NAFDAC GMP Regulations/Guidelines.***		

The inspection report should be signed and dated by the inspectors who participated in the inspection. **Name:**	***Inspector 1***	**Inspector 2**	**Inspector 3**
Designation:			
Signature:			
Date:			

Annex 5: GMP Inspection Attendance Sheet

NATIONAL AGENCY FOR FOOD AND DRUG ADMINISTRATION AND CONTROL (NAFDAC)
Drug Evaluation & Research Directorate

NAME OF COMPANY:……

ADDRESS OF COMPANY:……

DATE OF INSPECTION:……...

S/N	NAME	DESIGNATION	QUALIFICATION & YEAR	YEARS OF EXPERIENCE	YEAR JOINED COMPANY	TEL. & E-MAIL ADDRESS	SIGN.

NAFDAC INSPECTORS:

1. ……..
2. ……..
3. ……..
4. ……..

CHANGE HISTORY & RATIONALE			
Effective Date of superseded Guidance document	Doc. Ref. No	Originator/Reviewer	Reason for Review
2018	DER-GDL-001-02	Pharma Operations Division	• Due for Review • Inclusion of "and the inspection team" (page iv) • Inclusion of "to discuss inspection findings." (page iv) • Replacement of "initial production" with "advisory inspection" (page v) • Replacement of "an" with "a special" (page v) • Inclusion of "to determine the company's readiness for the inspection and provide guidance" (page v) • Replacement of "the Agency" with "NAFDAC" (page v) • Inclusion of "usually carried out before preregistration which applies to pharmaceutical product" (page vi) • Inclusion of "which applies to pharmaceutical product" (page vi) • Replacement of "and" with "by" (page vi) • Replacement of "unadulterated" with "unsafe" (page 1) • Replacement of "1-2 days" with "not less than two days" (page 2) • Deletion of "1-2" (page 2) • Replacement of "1-2" with "2-3" (for pre-

			production inspection; Pre-registration; Routine Inspection; GMP Reassessment Inspection) (page 2) • Inclusion of "magnifying lens" (page 5) • Inclusion of "VMP," (page 5) • Replacement of "2009" with "2021" (page 6) • Inclusion of "2001" (page 16) • Inclusion of "2001" (page 17) • Inclusion of "2021" (page 21) • Correction of the Report Doc. No. Format