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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Quality Control Laboratory

Part 1	**General information**
Inspected laboratory details	
Name of Laboratory	National Agency for Food and Drug Administration and Control (NAFDAC) Central Drug Control Laboratory, Yaba Lagos.
Address of inspected laboratory site	8/10 Merret Road, Medical Compound, Yaba, Lagos-State, Nigeria.
Inspection details	
Dates of inspection	15 – 17 February 2023
Type of inspection	Follow up
Introduction	

Brief description of testing activities

Type of Analysis	**Finished Products**	**Active pharmaceutical ingredients**
Physical/Chemical analysis	pH, uniformity of dosage unit (mass, content), Mass uniformity (uniformity of weight), disintegration, loss on drying, water content (Karl Fischer), dimensions, viscosity, specific gravity, optical rotation, net content (fill volume/deliverable volume), residue on ignition, friability, hardness, physical description	Melting point, pH, loss on drying, water content (Karl Fischer), viscosity, ash content, specific gravity, optical rotation, physical description.
Identification tests	HPLC, Spectrophotometric, IR, TLC.	HPLC, Spectrophotometric, IR, TLC.
Assay, impurities and related substances	HPLC (UV-VIS detection, DAD, RID, fluorescence), spectrophotometry, GC, polarimetry, volumetric titrations.	HPLC (UV-VIS detection, DAD, RID, fluorescence), spectrophotometry, GC, polarimetry, volumetric titrations.

		determination of related substances/impurities and degradation products	determination of related substances/impurities and degradation products
General information about the laboratory	The Central Drug Control Laboratory of the National Agency for Food and Drug Administration and Control (NAFDAC) is the official reference laboratory for medicines for NAFDAC which is the Medicines Regulatory Authority (MRA) of the Federal Republic of Nigeria. The Central Drug Laboratory commenced operation in 1978 under the department of Food and Drug Administration of Nigeria's Federal Ministry of Health. It later became Central Drug Control and Vaccine Laboratory (CDCVCL) when NAFDAC was established in 1993, and in 2009 as Central Drug Quality Control Laboratory (CDQCL) with the vaccine unit established as a separate and independent laboratory. In 2013 its name was changed to Central Drug Control Laboratory (CDCL). In 2018, following an organizational restructuring for greater efficiency, Laboratory Services Directorate Drug and Vaccines was created, which comprised three of the seven (7) laboratories in NAFDAC – CDCL and two others (NCLVB and MAL). In 2022, the National Control Laboratory for Vaccines and other Biologicals (NCLVB) became an independent laboratory and Directorate known as the Vaccines, Biologics and Medical Devices, Laboratory Services Directorate (VBM-LSD), and therefore CDCL became Laboratory Services – Drug Directorate. The Central Drug Control Laboratory, Yaba conducts regulatory testing of medicines and cosmetics.		
History	This was the second WHO PQ inspection. The first inspection took place in February 2019. The last ISO/IEC 17025:2017 audit was carried out in November.,2022. The last ISO 9001: 2015 was carried out in November,2022.		
Brief report of inspection activities undertaken – Scope and limitations			
Areas inspected	Quality Management System - Management Review Quality Assurance and complaints Personnel Training and Safety Documentation and Records, including sample processing and OOS handling Premises and Equipment, including calibration Validation – Qualification of computerized systems Validation of analytical methods Evaluation of test results Laboratory Practices Reference standards – Reagents – Water		
Restrictions	N/A		
Out of scope	Testing operations relating to food/nutritional products, medical devices, biologicals, stability, microbiology and pharmacology were out of the scope		

	of this inspection

Abbreviations	**Meaning**
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometry or spectrophotometer
GMP	Good manufacturing practices
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
KF	Karl Fisher titration
LIMS	Laboratory information management system
MB	Microbiology
MR	Management review
NC	Non conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometry or spectrophotometer

Part 2	Summary of the findings and comments

1. Organization and Management

The laboratory had an independent Quality Assurance unit covering of all QMS activities. The QA unit had defined roles and responsibilities for key personnel. It reported directly to the Director of Laboratory Services – Drug Directorate. Organizational and managerial structures were defined in organizational charts. The laboratory had managerial and technical personnel with the authority and resources needed to carry out their duties. Management review meetings were annually held according to a written procedure including a follow up meeting within three months of the annual meeting. The agenda of the meeting was communicated at least 7 days in advance, and it included a set list of topics. Minutes were maintained. Quality meetings were held quarterly while heads of units' meetings were organized monthly.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

2. Quality management system

The laboratory had established, implemented, and maintained a quality management system according to ISO 17025, ISO 13485, ISO 9001 and WHO guidelines. The latest QM was presented and it described the policies, systems, programs, procedures, and instructions of the laboratory's QMS. The QM was applicable to all 7 NAFDAC laboratories. The QM also included the management's commitment to impartiality, confidentiality, and continual improvement of the QMS.

Self-inspection

Operations and activities of the laboratory were systematically and periodically audited according to a written procedure. Audits were differentiated to self-assessments and internal audits. The self-assessment was a formal audit conducted by each unit within the laboratory. The self-audit team was made up of members of the unit. On the other hand, the internal audit was a scheduled audit for all the units in the laboratory. The team was led by the Head of QA and comprised of members from different units. Audit reports were generated and CAPA were identified and monitored for implementation.

Deviations.

A procedure on non-conforming work and deviations was in place and it described the system for registering and investigating deviations and non-conformances. The Quality Assurance Unit Head and respective department Head were responsible to evaluate the impact of all non-conformities and perform root cause analysis. The responsible Unit Head was responsible for preparing corrective actions.

Deviations were classified as critical, major, or minor depending on the impact on the accuracy, and reliability of the laboratory test reports. Deviation forms and registration logs were available, and all deviations were to be approved by the Quality Assurance Head. The timeline for review of deviations was stipulated as 3 months. Several examples of deviation handling were reviewed

CAPA

There was an SOP in place providing instructions for the identification, implementation, and evaluation of corrective actions. Root causes of non-conformances were to be established and documented. All corrective actions were to be closed within 30 working days after identification of non-conformances. Results of corrective actions were to be monitored by additional audits when necessary to ensure they were effective. It was the responsibility of the Quality Assurance Head to monitor the implementation of corrective actions. Several examples of CAPA implementation were reviewed

Complaints

The procedure for handling of complaints was reviewed. A complaints investigation form, showing the investigation process and responsible parties was annexed to the SOP. The Quality Assurance Head was responsible for the investigation of complaints in collaboration with the responsible unit Head. Investigations and root cause analysis had to be completed within 45 working days. Complaints' investigation outcomes were to be periodically reviewed and presented in management review meetings. The complaints investigation register showed that two complaints had been recorded in 2022. No complaints were registered in 2023, until the time of the inspection. The relevant records were reviewed.

All the non-compliances observed during the inspection regarding the QMS and the areas described above were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR

3. Control of documentation

The hierarchy of documentation was described in the QM. Four levels were identified (level I: QM/ Policies, level II: Procedures, level III: Work instructions, level IV: records). In addition, there were procedures in place defining the QMS requirements, authorities and responsibilities for the control, issue, update, distribution, storage, and withdrawal of documents. The Head QA was responsible for the management and control of all documentation generated and used in the laboratory. The laboratory had two types of procedures in place, namely Harmonized Procedures (applicable to all NAFDAC laboratories) and Laboratory Location Specific Procedures (applicable only to CDCL). The Laboratory's policies and procedures for coordinating all its activities were contained in a series of documents of internal and external origin, the "Master List of documents". Master documents and other quality documents were maintained by the quality assurance unit. A historical set of obsolete documents was also maintained with proper identification

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR

4. Records

A procedure was in place for managing records. The procedure defined retention periods for all classes/levels of documentation. The ALCOA principles were adequately described in the procedure. The retention time of records was different for different documents as determined by the regulatory, statutory and laboratory specific requirements. The Head of QA was responsible for maintaining a list of record types and their retention time.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

5. Data processing equipment

The laboratory had a system in place for ensuring that IT hardware and software, automated tests and equipment for the collection, processing, recording, reporting, storage, or retrieval of test- and/or calibration data were appropriately maintained and qualified. Most of the laboratory equipment and software were maintained and qualified/calibrated by external contractors.

The laboratory used Laboratory Information Management System (LIMS) for the registration and management of samples. LIMS was operated based on a detailed procedure.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

6. Personnel

The great majority of personnel were hired on permanent contracts and had the necessary education, training, technical knowledge, and experience for their assigned functions. Responsibility, authority, and interrelationship of personnel were specified in their job descriptions and the organization chart. The laboratory maintained job descriptions for all personnel. A code of conduct/confidentiality agreement was signed by all personnel to ensure they were free from any conflict of interest and pressure that would interfere with the quality of results. The principles of impartiality and confidentiality were described in detail in a written procedure. The Head of QA was responsible for issuing and collecting the Confidentiality and Non-Disclosure agreement form to each member of staff, contractor, or consultant.

Training was conducted according to a written procedure. The procedure outlined the steps for determining competency requirements, planning, conducting, and evaluating training. A competency matrix was used to identify the skills and training required for a position and determine training needs. Each Unit Head was responsible for identifying the training needs for the Unit's personnel. Training was classified as internal training (including induction training and re-training), external training and supplementary training.

There was a procedure in place describing the principles for the evaluation of personnel laboratory competencies and skills. A competency assessment plan was prepared every December for the following year by the Head of QA. In general, a competency assessment was initially conducted 2 months after the assignment of responsibilities, at 6 months and every 3 years thereafter, unless otherwise indicated. Four competence levels were defined based on the ability of an analyst to perform testing using different methods and equipment and interpret test results. The 2022 competency assessment plan was reviewed in detail.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

7. Premises

Different rooms and laboratories were established on different floors of the building. In general, laboratory facilities were of appropriate size and design to serve the functions and to perform the operations to be conducted in them. Environmental conditions were generally monitored. Separate storage facilities were maintained for secure storage of samples, retained samples, reagents, laboratory accessories and reference substances, if necessary, under refrigeration and deep freeze temperatures.

Some discrepancies were identified regarding the refrigeration conditions and monitoring. These were also identified during the previous inspection.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

8. Equipment, instruments and other devices

In general, equipment, instruments, and other measuring devices used for testing, calibrations, validations, and verifications were suitable for use as they met relevant standard specifications. Some new laboratory equipment had been procured since the last inspection. Equipment was timely qualified and/or calibrated either internally or by external contractors but these exercises and reports did not always meet regulatory requirements. Logbooks for use were available. Records of calibration and qualification were maintained.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

9. Contracts

In general, there was no subcontracting of testing with the exception to sister NAFDAC laboratories certified for ISO 17025 for the relevant test methods. On some occasions the laboratory was carrying out testing on products provided by International Organizations and NGOs. Contracts or MoUs were established by the legal department of NAFDAC and in general, included responsibilities for each party including but not limited to the provision of analytical methods, analytical method transfer and OOS investigations.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR

10. Reagents

In general, reagents used in the laboratory were of appropriate quality and correctly labelled. The laboratory maintained an inventory of reagents; their stocks were monitored. Solutions prepared in the laboratory were labeled and stored appropriately; preparation records were available.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

11. Reference substances and reference materials

Primary and secondary standards were available and used in the testing of product samples. An SOP for receipt, handling, and management of reference standards was in place and described the management of reference standards at NAFDAC laboratory. Monitoring of the valid lot for reference standards was performed monthly. Records for the month of January were verified. Logs were maintained for the use of reference standards. Three cold chain refrigerators were available for the storage of reference standards at refrigerator (2-8^{0}C) and freezer conditions. These were observed to have valid calibration dates.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

12. Calibration, verification of performance and qualification of equipment, instruments and other devices

Generally, equipment was observed to be labelled with calibration stickers showing the calibration status and dates when recalibration was due. Calibration records for the HPLC equipment and daily verification records for the analytical weighing balance, were sampled for review. Due to time constraints soft copies of the qualification of Agilent GC 8890 and the Karl-Fischer apparatus YDL-ANCH II-KF-002 were requested and reviewed after the on-site inspection. It is noted that issues relating to qualification of instrumentation were identified and some of these issues were considered recurrent since equipment qualification/calibration was found deficient in the previous inspection.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR

13. Traceability

There was a procedure in place for monitoring timelines for laboratory processes. Analytical results were generally traceable to the equipment and reference materials used in testing of products. Records related to tests performed on the HPLC equipment were verified.

All the non-compliances observed during the inspection that were listed in the full report were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR

14. Incoming samples

NAFDAC received samples for either compliance testing or investigative purposes. The SOP "Management of test items", described the steps taken during receipt, allocation, distribution, storage of retention samples and disposal. The sampling guide for NAFDAC regulated products, described the quantities of different product dosage forms required for testing. Samples were registered in the LIMS system and coded. An area for the transit storage of samples was available on the 2nd floor of the laboratory. A sample movement register was in place to track samples.

Allocation of samples was performed in the specification and archives room located on the 3rd floor of the building. This included selection of the test methods to be used for testing samples based on the product specifications provided by the customer (i.e., pharmacopeial or in-house). However, test specifications were not always verified against the product dossier.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

15. Analytical worksheet

Analytical worksheets were maintained for each product tested. Details included product sample codes, dates for performing tests, test results and responsible analysts and reviewers.

16. Validation of analytical procedures

Analytical methods were verified prior to use in testing of products. The relevant SOP provided guidance on parameters to be verified for analytical methods. Examples of method verification protocols, and relevant results were reviewed. The parameters verified were linearity, accuracy, and precision.

17. Testing

There was a procedure in place for risk-based testing referring to the PQM guidance for implementing risk-based post-marketing quality surveillance in low and middle-income countries. A soft copy of the procedure was provided to the inspectors for review after the on-site inspection. The procedure categorized medicinal products into 3 risk categories, where low-risk products intended for retention samples were not tested, unless necessary. High-risk medicinal products were subjected to full testing according to specifications while medium-risk products were only tested for physical parameters, dissolution, and identification.

The laboratory participated in proficiency testing schemes. A procedure was in place. A proficiency test/ Inter-laboratory comparison plan was elaborated every 4 years and annually reviewed. The expectation was that each test method was qualified at least once every 4 years. There was no provision to alternate qualified analysts when participating in proficiency testing of the same method. The 2020-2023 plan was reviewed as well as the results of proficiency tests which were carried out. All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR were addressed by the laboratory, to a satisfactory level, prior to the publication of the WHOPIR.

18. Evaluation of test results

Test results and raw data were reviewed by the section Head and approved by the Laboratory director. Appropriate procedures were in place for the management of OOS results.

19. Certificate of analysis

Certificates of analysis for each product detailing the product-specific details and conclusion as to whether the samples were found to meet declared specifications or not were prepared following the completion and approval of test results.

20. Retained samples

Retained samples adequate for two re-analyses for each product were maintained and appropriately stored**.**

21. Safety

General safety rules including wearing appropriate protective clothing, gloves, masks, and eye protection were in place. Emergency showers were installed and appropriately located.

Part 3	Conclusion – Inspection outcome

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***National Agency for Food and Drug Administration and Control (NAFDAC) Central Drug Control Laboratory,*** located at ***8/10 Merret Road, Medical Compound, Yaba, Lagos-State, Nigeria***was considered to be operating at an acceptable level of compliance with WHO GPPQCL Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 5	List of WHO Guidelines referenced in the inspection report

1. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1. ***Short name: WHO TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2. ***Short name: WHO TRS No. 961, Annex 2***
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4. ***Short name: WHO TRS No. 937, Annex 4***
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

5. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***
   http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

6. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7. ***Short name: WHO TRS No. 961, Annex 7***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

7. WHO Guidelines for preparing a laboratory information file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report. Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 2011), Annex 13. ***Short name: WHO TRS 961, Annex 13***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPreparingLaboratoryInformationFileTRS961Annex13.pdf?ua=1TRS%20961:%20Annex%2013:%20WHO%20guidelines%20for%20preparing%20a%20laboratory%20information%20file

8. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10. ***Short name: WHO TRS No. 1010, Annex 10***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

9. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***
https://www.who.int/publications-detail/978-92-4-000182-4

10. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3. ***Short name: WHO TRS 1033, Annex 3***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

11. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS 1033, Annex 4***
https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations