

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**
Finished Product Manufacturer
Part 1: General information

Name of Manufacturer	CHI Pharmaceuticals Limited
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Telephone Nos.	+234 – 1 - 2806770 – 9, +234 - 1 – 7740353
Date of inspection	1. 18 th – 19 th April 2013: First Pre-audit (WHO + NAFDAC) 2. 8 th - 10 th May 2014: Follow-up (WHO + NAFDAC) 3. 10 th & 11 th Sept. 2014: CAPA verification (NAFDAC)
Type of inspection	Pre-Audit towards WHO Pre-Qualification
Dosage form included in the inspection	Oral Solid Dosage forms (Tablets and powders for reconstitution for oral use)
WHO product numbers covered by the inspection	1. The company proposes to submit Zinc Sulphate 20mg dispersible tablet for WHO Prequalification and of interest to the UNCoLSC. 2. The company produces ORS which is of interest to UNCoLSC.
Summary of the activities performed by the manufacturer	The company carries out local manufacturing, quality control and batch release of Finished Pharmaceutical Products in oral solid dosage forms (tablets and capsules) Importation, distribution and marketing of Oral solid dosage forms (tablets and capsules) and insulin preparations

Part 2: Summary

General information about the company and site

CHI Pharmaceuticals Ltd is a part of TGI group which currently operates in nine countries in Africa.

The site was commissioned in 1990 for marketing and distribution of imported finished pharmaceutical products. The company now manufactures and markets its own range of pharmaceutical product lines consisting of tablet and capsule dosage forms. The factory is located in an industrial area of Ajao Estate, Oshodi in Lagos state of Nigeria. The company has adequate buildings and facilities in place. The company stated that the factory has an installed annual capacity of 360 Million tablets and 190 Million capsules with a provision for 30-50% expansion.

The factory building consists of three floors covering a total land mass of 5500 square meters as follows: 1). Ground floor - made up of material warehouse, production, laboratory and canteen, 2). First floor – Mezzanine (utilities and services), 3). Second floor – Administrative Offices.

History of WHO and/or regulatory agency inspections

There had been series of WHO advisory/ gap analysis inspections on the site. The last WHO pre- inspection was carried out between the 18th and 19th of April, 2013 which resulted in deficiencies put on notification to the company. The company has since developed and submitted a CAPA in response.

The factory site has been duly inspected, approved and issued with marketing authorization and GMP certificates by NAFDAC for its various dosage formulations which include oral solids and capsules prior to commencement of WHO visits.

Focus of the inspection

The inspection focused on the review and verification of the company's CAPA following the last audit conducted, as well as manufacturing and control procedures of OSDs in the facility with special focus on Zinc Sulphate 20mg dispersible tablet. It covered a review of all the six systems - Quality Management, Facilities and

Equipment, Materials, Production, Packaging and labelling, as well as laboratory controls.

Inspected Areas

Day I: 8th May 2014

The WHO inspectors accompanied by NAFDAC officers arrived at the site and had a pre- inspection meeting with key company officials. During the opening meeting the procedure and standards to be used for the inspection were discussed.

The WHO expert Inspector in his opening brief disclosed that the inspection would be used to look into the company's CAPA for the non-conformances observed during the last inspection conducted in April 2013. The WHO expert further explained that the outcome of the inspection would be used to assess the company's level of compliance with WHO GMP and in arriving at a decision on its final status. The procedure for the inspection was highlighted. This was to include a review of previous deficiencies, (CAPA) to be followed by a tour of the facility.

In an introductory brief after a formal introduction session of key personnel, the Company's MD mandated the Quality Assurance Manager to make a presentation of the company's profile and the overview of the site to be inspected as well as the manufacturing capacity of the company.

Thereafter, the company's CAPA for the previous observations was reviewed by the inspectors taking into account all the issues raised and how effectively they were addressed.

This review showed that some specific observations were adequately dealt with while for others, the root causes of the observations were treated symptomatically.

While reviewing the CAPA, the following documents were also reviewed:

- Incident/ Deviation reporting form
- Customer's complaint logbook
- Deviation and incident logbook
- SOP for Metal detection test
- Batch Manufacturing Record for Zinc Sulphate 20mg dispersible tablet

During the review, observations were made in the following areas:

- Reporting and handling of deviations and incidents.

- Consideration of variables like excipients and a range of other materials were in process validation
- Use of platform technology principle to standardize the use of minimum number of sieves to reduce variability and chances of error in operations.
- Traceability of material specifications and grades in the purchase orders for raw and packaging materials.
- Procedure for labeling of received packaging materials.
- Labelling of reels of primary packaging materials.
- Contract agreements with suppliers of packaging materials and related purchase orders/ lists.
- Security of Supply Chain Management (SCM).

Appropriate CAPAs to the above issues were proposed by the company, reviewed by WHO and NAFDAC inspectors and their implementation verified by NAFDAC inspectors in September 2014.

Day II: 9th May 2014

The review started with a re-cap of the observations made from the first day of the audit. The inspection plan was outlined to be a review of the company's Annual Product Review report (APR) and related documents, HVAC system schematic drawings and a tour of production areas, material warehouse (raw materials, packaging and finished products).

Documents reviewed included Annual Product Review report for Oral Rehydration Salt, SOP for writing Annual Product Report,

Observations were made in the following areas:

- Procedure for receipt of raw materials and its implementation.
- The numbering practice used for containers of materials under Quarantine.
- Status labeling and storage of the thief sampler for in process granules.
- System to highlight batch expiry dates for raw materials and excipients.
- Assigning of QC number to different batches and/consignments of PVC film rolls/reel.
- Labeling of materials returned from production to the packaging materials store.
- Security of approved primary packaging material in the store.
- Use of "Sampled" labels, adherence to sampling plans and traceability of samples to their actual containers.
- Individual container identification test for the containers of propylparaben and the methyl paraben.

- The sequence/ order in which materials (API and excipients) were dispensed and its documentation.
- Metal detection for compressed tablets.
- Humidity control and recording in the Oral Rehydration salt room.
- Pinhole test and detection for blister rolls used for ORS.
- Maintenance of the ORS packaging machine and protection some of its product contact surfaces after cleaning.
- Design of tops of stainless steel lockers in the cloak room.
- Visual aids for gowning during exit from production area.
- Hand washing facilities in the cloak room.
- Zero checks for Magnehelic gauges.
- Alarms for excursions in room pressure differentials.
- Protection of receiving bay from adverse weather conditions.
- Design of Air curtains at the entrances of warehousing and production area.
- Use of split Air conditioning units in the Raw Material quarantine room.
- Design of deferential pressure across the air lock before the dispensary room.
- The accuracy and range of the pressure gauge on the air filter in the UDLF sampling booth.
- The stability of the stainless steel table used for the digital weighing balance in the dispensary.
- Absence of wall guards in the staging room to prevent damage to wall panels by trolleys.
- The absence of air extractors in wash rooms to ensure that a negative pressure is maintained and does not lead to humidity overload.
- Design, cleaning and maintenance of the stainless steel floor drains in the key production areas, wash rooms and related areas.
- Status of temperature mapping in the finished product warehouse.
- Use of the staging area in the warehouse for both imported finished beta lactam products and the locally manufactured products.
- A beta lactam product (penicillin ointment) found in the first aid box in the corridor within the production area.
- Design and use of cleaning records/logbooks for equipment to provide a clear history of use and cleaning of equipment between batches and between products.
- Cleaning procedures and records for the equipment in the room with the sifter which had no localized dust extractor at point of use.
- The frequency of monitoring of the HEPA filter for the supply duct of hot air to the Fluid Bed Dryer (FBD) and the location of the monitoring panel for the filter.

- The procedure and practice of cleaning of difficult and recess areas of machines and equipment.
- Use of ball valve at the tap point for collection of purified water for granulation.
- Calibration of the hygro-thermometers used for monitoring room conditions (RH and Temp) in most operational areas.
- The procedure for the use, checking and polishing of dies.
- Areas not prescribed in the SOP to be covered in the Annual Product Review and resultant deficiencies in the prepared APRs.
- There was no adherence to any sampling plan for testing of raw materials.
- No pinhole checks for blister rolls/ sachets for in-process monitoring for ORS processing.
- Control of generation of label/package code and coding process.
- Supplies of hard gelatin capsules were not accompanied with TSE/BSE certificates.

Appropriate CAPAs to the above issues were proposed by the company, reviewed by WHO and NAFDAC inspectors and their implementation verified by NAFDAC inspectors in September 2014.

Day III: 10th May 2014

A brief on the observations made on the second day of the inspection was presented and the plan for the day was discussed. This included review of Personnel training and records, tour of the water systems, verification of the HVAC / pressure differential system in the interlock of the dispensary, and general review of AHU system layout, laboratories and review of QC documentation, conclusion of the review of the Batch Manufacturing Records (BMR) for ORS co-packed with Zinc Sulphate tablet, and the Stability program. The documents reviewed include: SOP for testing and assay of Zinc Sulphate tablet, Specification sheet for Zinc Sulphate tablet (old version and new draft), Certificate of Analysis for a batch of Zinc Sulphate Monohydrate (API), Analytical method for dispersible Zinc Sulphate tablet, Method of analysis for Oral Rehydration Salt (ORS), Logbook for stability chamber, and Sampling request forms.

During the review, observations were made in the following areas:

- Accuracy of HVAC drawings and keeping them up-to-date.
- The specification for pressure across the filter for monitoring the AHU filter.
- Design and installation of door to the AHU fan and cooling coil was not done to facilitate its opening for cleaning and maintenance.
- Labelling, procedures and monitoring the water system.

- Control of manual dampers used to control the amount of air supply and returned for pressure balancing.
- Procedures and records for AHU qualification documentation.
- Absence of a training matrix for the different areas of work and for the different staff and inadequacies in the method described for evaluation of training.
- No log book for retention samples of API or excipients or packaging materials are retained.
- Lack of standardization of names and specifications for APIs and excipients.
- There was no procedure in place for the verification of Certificate of Analysis (COA) from the API manufacturer.
- The analytical balance was not adequately verified for the weight range indicated on it (0.1mg - 220g).
- Lack of item codes in the specifications and method of analyses yet it was noted that there were two grades of Zinc sulphate on site. These were not currently interchangeable.
- Incomplete sampling plans and batch wise sampling records for individual materials (not clear which materials are to be sampled on a 100% or $\sqrt{N}+1$ or some other basis).
- Inadequate records for sample traceability from sampling plan through to laboratory receipt, to sample issue and analysis completion and eventual sample disposal.
- Inadequate handling of the change of specifications of the FPP.
- The individual results of the ID tests performed were not recorded.
- There were no print outs from the balances used in production and QC.
- Inadequate records to enhance traceability of the manufacturers and suppliers of raw materials, especially those supplied through vendors.
- BMRs for the lot reviewed:
 - The ordering of certain parts of the document did not logically follow process flow.
 - There were a number of missing signatures in the record reviewed.
 - There were a number of non-value added signatures and times recorded particularly in the general instructions at the beginning of processing stages.

Appropriate CAPAs to the above issues were proposed by the company, reviewed by WHO and NAFDAC inspectors and their implementation verified by NAFDAC inspectors in September 2014.

2.1 QUALITY MANAGEMENT SYSTEM

The key basic procedures were in place but most of the processes had not matured, because the extent to which they had been used had not been tested – change control, investigation and root cause analysis are not robust. These will need to be monitored from continuous improvement.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The facility was a spacious, well laid-out multi-product facility with good quality equipment designed to suit purpose. The system was designed to support the manufacture and control of the product of interest in compliance with good manufacturing practices however improvement in the functioning of the HVAC system to ensure adequate environmental controls in the core processing areas and effective facility maintenance will enhance compliance with good manufacturing practices.

2.3 SANITATION AND HYGIENE

There were cleaning procedures in place for the premises and equipment and the manufacturing areas, corridors and cloak room were clean and tidy. Cleaning logs for room and equipment were maintained in all areas in the factory. However, cleaning procedure for non-dust contained equipment did not consider the cleaning of surfaces of other equipment in the same room after use. Attention also was needed on the cleaning, monitoring and maintenance of floor drains.

Appropriate CAPAs to the above issues were proposed by the company, reviewed by WHO and NAFDAC inspectors and their implementation verified by NAFDAC inspectors in September 2014.

2.4 QUALIFICATION AND VALIDATION

The qualification records of the HVAC system and Process Validation were reviewed. The HVAC system though qualified had no record of raw data of the qualification performed.

The process validation was still on-going. The robustness of the validation had incorporated API from alternative source, but was yet to include variability from excipients. This area will need to be monitored for continuous improvement.

2.5 COMPLAINTS

There was a procedure in place for handling customer complaints but details were not covered during the inspection.

2.6 PRODUCT RECALLS

Procedures for product recall have been put in place but details of practices were not covered under the review.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The company is not engaged currently in any contract manufacturing.

2.8 SELF INSPECTION AND QUALITY AUDIT

This was not covered during the inspection.

2.9 PERSONNEL

The company personnel were enthusiastic and committed to the project. The production and support system operators were quite knowledgeable. However there was a knowledge and experience gap in other areas which needs to be improved upon by more training.

2.10 TRAINING

Though trainings were conducted, there was no use of training matrix for different categories of operators. The method described for evaluation of training was not comprehensive, systematic and could not be evaluated as effective. There was need for practical exposure and training in certain areas identified for the operators.

2.11 PERSONAL HYGIENE

There was high level of personal hygiene of personnel in the entire factory as operators in the different areas of activities were clad in clean apparel including personnel protective wears (PPPs) as appropriate.

2.12 PREMISES

The premises were clean, tidy and well laid-out. It was appropriately designed, constructed and maintained to suit the operations carried out. Attention was needed on the maintenance of HVAC system especially for pressure balancing.

Appropriate CAPA to this issue was proposed by the company, reviewed by WHO and NAFDAC inspectors and its implementation verified by NAFDAC inspectors in September 2014.

2.13 EQUIPMENT

The company had good quality pieces of equipment which were designed, qualified, located and maintained to suit the operations and permit effective cleaning and maintenance.

2.14 MATERIALS

Materials controls were inadequate and weak. Audit trail for material through processing was not robust. Standardization of material name was lacking - Zinc Sulphate Monohydrate of different specifications was used in documentation. The procedure for receipt of raw materials was inadequate as consignment delivery documents were not verified before receipt except physical examination of received materials. The numbering practice for material container identification was greatly flawed. Material codes and grades were not indicated on purchase order to suppliers. Packaging materials handling and control was not effective as same packaging material (PVC film) from different sources were assigned same QC control number. However this was not critical for the product under consideration for pre-qualification.

Appropriate CAPAs to the above issues were proposed by the company, reviewed by WHO and NAFDAC inspectors and their implementation verified by NAFDAC inspectors in September 2014.

2.15 DOCUMENTATION

The basic elements of good documentation practice were in place. Documents were well developed. SOPs and logbooks for various equipment, procedures and activities were maintained.

Document issuance and authorization system was in place and resides with the QA, however, it was noted that the documentation trail was fragmented making traceability cumbersome. Some inconsistency in completion of BMR was noted.

Laboratory prints outs were attached on BMR but not documented in laboratory records.

2.16 GOOD PRACTICES IN PRODUCTION

The production environment has tremendously improved. The equipment was good and production activities were carried out satisfactorily and performed in accordance with batch documentation and in line with GMP principles even though improvement in clarity of some areas of batch documentation is required.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The laboratories were equipped to handle the scope of tests required for starting materials, in-process and finished products of concern. The Quality Control carried out testing and evaluation for raw materials, in-process and finished products following established procedures. A system for final batch release which rests with the Quality Assurance (QA) was in place. It was noted that samples of APIs and Excipients were not retained except the finished products. Sample custody log was not maintained for samples distribution, analysis, retention and disposal. The sampling method for API was inadequate as the numbers of samples taken per container are not reflected.

The draft material specification for Zinc Sulphate Monohydrate was generated using USP expectation but the current specification is BP based. This made understanding extremely difficult to follow, moreover when the product specification was based on USP.

Also test records did not show evidence that any sampling plan was in use as neither 100% testing nor $\sqrt{N} + 1$ related records were visible.

Part 3: Conclusion

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, as well as the corrective actions taken and planned, **CHI Pharmaceuticals Limited, Plot 14, Chivita Avenue, Ajao Estate, Oshodi, Lagos State, Nigeria**, was considered to be operating at an acceptable level of compliance with WHO GMP 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.