

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

Name of Manufacturer	Swiss Pharma Nigeria Limited
Unit number	NA
Production Block	NA
Physical address	5 Dopemu Road, Agege, Lagos, Nigeria
Contact address	Mr Colin Cummings – Chairman/CEO E-mail: swipha@swiphanigeria.com Tel.: +234-80-34022640
Date of inspection	15 – 17 April 2013 – Initial audit (WHO + NAFDAC) 09 - 10 October 2013 – follow-up (WHO + NAFDAC) 10 - 11 February 2014 – CAPA verification (NAFDAC)
Type of inspection	WHO PQP Pre-submission Audit
Dosage forms(s) included in the inspection	Oral Solid Dosage forms (Tablets)
WHO product categories covered by the inspection	No submission yet but there are products under development with WHO-PQT Technical Assistance.
Summary of the activities performed by the manufacturer	Manufacturing, Packaging, Quality Control and Batch release of Finished Pharmaceutical products (FPPs) in oral solid (tablets) and liquid dosage forms. Toll manufacturing of FPPs in oral solid dosage forms (tablets) Importation and distribution of FPPs.

Part 2: Summary

General information about the company and site

Swiss Pharma Nigeria Limited, hereafter also known as Swipha, was incorporated as a pharmaceutical company in Nigeria on 31st January 1976 (RC 16806). Company manufactures own brands as well as toll manufactures and distributes for local and multinational companies.

According to the presentation made by company at the start of the inspection, the facility is sited on a total area of about 40,000sqm of which 15.72% is total built-up area. Swipha maintains depot operations in nine strategic locations across the country. The warehouse is managed at the head office in Lagos while the depots are outsourced.

Company has been producing pharmaceuticals for the past thirty years and is currently in the process of obtaining WHO prequalification for one of her tablet formulations.

History of WHO and/or regulatory agency inspections

The initial audit was conducted by WHO-PQT inspection team in conjunction with NAFDAC between 15th and 17th April 2013 with a follow-up between 09th and 10th October 2013. With agreement with WHO-PQT, NAFDAC conducted another audit between 10th and 11th February 2014 to verify implementation of Corrective and Preventive Actions (CAPAs). The company had also been audited at various times by NAFDAC, Standards Organization of Nigeria (SON) and Pharmacists Council of Nigeria (PCN).

The company also had an advisory GAP analysis audit by a team of WHO consultants in 2011 with NAFDAC inspectors present as observers.

Focus of the inspection

The inspections focused on the production and control of oral solid dosage forms (tablets).

The inspections were WHO PQP Pre-submission Audits. The initial inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities. The subsequent inspections focused on verification of implementation of CAPAs to the observations of the initial inspection.

Inspected Areas

Day I: 15th April 2013

On arrival, an opening meeting was held with key personnel and after introduction of the company representatives by the Deputy Managing Director, the company made a presentation of the company profile.

The WHO inspector then introduced himself and gave a brief summary of his background and experience. He explained that since the company had not submitted an application for a specific product, the inspection would focus on general systems for production of oral solid dosage forms (immediate release tablets), an area from which the company had indicated intention to submit to WHO-PQ. However, the audit would be conducted in much the same manner as a certifying inspection but with an opportunity for lapses to be discussed. The inspection will also serve as a GAP analysis, to help company compare its actual performance to potential performance while revealing areas to be improved on. It was further clarified that WHO-PQT does not issue GMP certificates but a closing letter and a WHOPIR in case of a positive outcome. In view of this, at the end of the exercise, the company would be issued with a closing letter and a modified WHOPIR.

The inspection plan included a walk-through of some parts of the facility followed by an evaluation of the Quality system with emphasis on Deviations, Root Cause Analysis, Failure investigations and OOS/OOT.

During the walk-through of the facility, the following issues were observed:

Warehouse

- While going through the ambient raw materials/packaging materials warehouse, it was noted that the company had different suppliers for starting materials. This can lead to variability in the functionality of excipients. Using ingredients from different sources can affect the pharmaceutical properties e.g. gelling properties of the material and affect the granulation process. Subsequent visits indicated that steps have been taken to strengthen material management and vendor qualification.
- Temperature mapping and monitoring of the ambient warehouse had not been concluded. This was subsequently improved to ensure identification of worst case locations and steps put in place to ensure they are monitored accordingly.
- The cold room for storing starting materials at 2-8°C had to be reorganised to reduce the overcrowding and to permit effective cleaning and proper segregation of released and quarantined/rejected items. In addition back-up for the chillers in

the cold room had to be put in place should there be system failure. Steps were also initiated to include disinfection in the procedure for cleaning the cold room especially with the presence of materials packed in cardboard containers which could be sources of spores. CAPAs and subsequent visits indicated that cooling systems, segregation and cleaning procedures in the warehouse were effectively improved accordingly.

Production Area

- Initially, there was no dedicated area for the cleaning of the down flow dispensing booth pre-filters of the Air Handling Unit. A dedicated AHU filter cleaning area was subsequently put in place.
- Prior to the audit, granules for tablet production were scooped manually into the blender. This is a dust-generating operation with a high tendency of deposition of the API on the operators' sleeves and transfer of this into other products or other parts of the facility. Product specific and dedicated arm sleeve protectors are now used by dispensing operatives.
- Cleaning validation for the Legacy compression machine was not done and operators seen dismantling the machine for cleaning after the compression of tablets did not wear gloves. This could be a potential source of contamination to the machine. A lot of dust from the product was also seen on the machine as it was being dismantled. This could be transmitted to other products through operator clothing posing a high risk of cross-contamination. Cleaning validation has been initiated following acceptable protocols. Operators dismantling the machine for cleaning after the compression of have now been provided with appropriate personnel protection gowning, gloves and goggles.
- A generator served as back up when power was lost and it had a recovery time of three to five minutes. However the effect of power outage was not considered during equipment qualification e.g.it was not determined if an equipment timer would stop during power outage or not. Subsequently, equipment qualification has been initiated to address the impact of power outage and computer back up procedures have been established to prevent data loss.

Otherwise, other production facilities and premises were generally acceptable as elaborated in sections 2.12 and 2.16 below.

Quality Management System Review

A review of some Quality system documents e.g. the Management review process, Agenda of management review meetings, Summary of findings of the meetings, self-inspection reports and Annual Product Reviews revealed the following:

- The company management had observed that several complaints received related to imported products. Follow-up audit of this manufacturer by Swipha by the first

quarter of 2013 had not been done and a deviation to this effect had not been document. Subsequently the complaint handling procedure was strengthened and firm arrangements to audit the affected manufacturer have been put in place.

- Management review also noted a process performance deviation with the Fluid Bed Dryer (FBD) where it was observed that the inlet and exhaust air temperatures were out of range. The problem persisted after initial repairs. Root Cause Analysis (RCA) identified a change in the logic setting of the equipment software. Review of the Root Cause Analysis (RCA) and repairs to resolve the issue revealed gaps in the original qualification and its related documentation plus lack of procedure for software introduction. Subsequently, the problems with the PLC of the FBD have been resolved. A new procedure for management of software has also been established which requires that original configuration must be documented and controlled.
- Subsequent to observations of the inspection, the manual operation of the FBD equipment which had been provided as a back-up option in case of equipment malfunction was included in the master batch document and template for batch production record.
- In the third quarter of 2012, company had to recall one of their products, due to problems with coating and colour variation. An in-depth RCA was not carried out as the problem was merely attributed to the fact that the new technology used in the manufacturing of the product had not been mastered. An SOP on deviation management to allow an in depth RCA has now been established and is in use.

Day II: 16th April 2013

The plan for the day was discussed and included a review of the Batch Manufacturing Records (BMR) for the product of interest, training records for some key personnel and a tour of the packaging section and water treatment plant of the facility.

BMR and Training Records

Review of the BMR and training records revealed the following issues:

- The plan on Critical Process Parameters and Associated Control Points with Monitoring Program for Solid Production Process goes through the production process starting from the first production operation. The plan did not consider other activities that come up before production operations e.g. API and excipient selection. Subsequently, the two documents that included the plan on critical process parameters and associated control points with monitoring of program for solid production process were harmonized to provide all information in a single document.
- Item codes were not consistently and comprehensively used for process documents and specifications e.g. raw material codes were included in the BMR

while packaging material codes were not. Subsequent efforts have ensured that material codes now appear in the revised BMRs and specifications.

- Prior to the inspection, cleaning status labels for the dispensary were filled, endorsed and counter-signed by the same individual. The company's policy on endorsement was not clear as to whether the operator performs the job and signs while the supervisor checks that the job was done and then countersigns, or whether the supervisor alone signs that he witnessed the job as it was done. Company has now trained operators, Quality Assurance and Quality Control staff on good documentation practice and appropriate changes are in place.
- Following observations of the inspection checklists used for equipment cleaning during line clearance are now bound and the use of loose sheets which could easily be misplaced has stopped.
- The rooms in which equipment are located have now been indicated in BMR alongside the list of equipment to be used for particular operations in production.
- The master formula for certain tablets indicated that hot purified water (40-60°C) should be used for binder mucilage preparation. Stainless steel thermometers are now used instead of glass thermometers to check temperature and this check is now documented in the BMR.
- Prior to the inspection, spare punches were used to replace defective punches of the compression machine in routine use without conducting height checks on the newly-introduced ones. Such punches may be longer than the ones in routine use and can lead to variations in tablet hardness. Appropriate SOP has now been enhanced ensuring uniformity of punch heights.
- Prior to the inspection, the number of tablets tested during set up of compression machine was not representative of the performance of all the punches on the machine. A new procedure and log sheet detailing results of three revolutions of the press is now implemented with a tableting start up worksheet now established.
- Senior Systems Compliance Manager's job description has now been enhanced including responsibility of product release as against product release only in the absence of the Quality Manager.
- Review of training records of selected staff showed that training records were not regularly updated. There was also no program to serve as a reminder for records to be updated. Furthermore, training records, which merely showed that trainings were conducted, were the basis for the implementation of training programs. There was no monitoring system in place to assess the effectiveness of the trainings. However, training records have now been updated and the SOP on training has been updated assigning the Senior System Compliance manager the responsibility to ensure timely update of training records and establishing a method to assess the effectiveness of the trainings.

Packaging Section and Water Treatment Plant

The tour of the Packaging section and water treatment plant revealed the following issues;

- Prior to the inspection, on issuance of the Batch Packaging Record (BPR) by the Quality Assurance (QA) department, the BPR number was stated only on the first page of the document while the other pages were filled during QA review of the BPR. It was noted that this could lead to mix-ups in a situation where products were packed differently for specific markets. The BPR number now appears on each page at the time of issuance.
- In Line Clearance for blistering operations, the Batch number printing blocs were not removed from the blistering machine immediately after the operation was completed. It was left until the next operation giving room for the possibility of printing the wrong batch information on the product. Improved system now in place, the batch number printing blocks are now removed immediately after each operation to avoid mix up
- Printing of batch information on the secondary packaging material was usually done in runs. This was to avoid printing packages in excess in order to save costs. This posed a risk of printing the wrong information since the printer was not dedicated to any product and could lead to mix-ups. Improved systems are now in place. Full issuance of printed materials is now carried out per batch according to enhanced SOP.
- The intensity of the UV rays in the germicidal lamp of the water treatment plant was not checked to ensure the effectiveness of the lamp. Subsequently, a UV intensity meter was procured to check this.

Day III: 17th April 2013

The inspection plan for the day was a review of the Validation Master Plan (VMP), Process validation for the product of interest, Cleaning validation and a tour of the Quality Control (QC) laboratories.

Review of Validation Documents

The following were the issues arising from the review of the Validation documents:

- The Validation Master Plan Matrix has been updated to include all elements related to equipment e.g. Hardness Tester, that require validation (e.g. operating procedure, preventive maintenance, cleaning etc.).
- Process Validation for the product of interest had not been completed as validation of the analytical methods was still ongoing as at the time of first inspection but this has now been concluded.
- The acceptance limits for residues in cleaning validation did not consider paediatric products like the product being prepared for prequalification, which

contains smaller quantities of the API. These limits have subsequently been established in the cleaning validation master plan.

- During the first inspection, it was noticed that the company had no formal procedure in place for the introduction of new products into the site. It was noted that in 2011, a product was introduced without any documented risk assessment program. SOP for this procedure is now established.
- Company produces other products. These were not included in the selection of a worst-case product during the cleaning validation program. Company also did not have a procedure in place for the introduction of a new product in the cleaning validation plan. Issues of occupational hazard, risk of sensitizing materials etc. would normally be considered when introducing new products. In addition to the SOP on introduction of a new product referred to above, a cleaning validation matrix has been improved to accommodate toxicity, solubility, low therapeutic index for actives amongst others covering all products handled on site.

QC Laboratories

While conducting the tour of the QC laboratories, the following observations were made:

- When facility limitations in analysis arose e.g. analyses requiring Gas Chromatography, materials were released at risk based on identification tests and assay. Such materials were accepted based on these minimal parameters and the certificate of analysis from the supplier. However, the basis for acceptance of the supplier's certificate of analysis had not been established. In the interim, a contract with quality agreement has been established with a reference laboratory to cover the identified gaps while for a long term basis, a GC and FTIR have been purchased and installed for use once fully qualified. The FTIR had been qualified and already in use as at the last CAPA verification by NAFDAC.
- It was the practice to, on occasions, substitute raw materials from different suppliers without going through the change or deviation management program. There is however now established a robust supplier list with adequate deviation management.
- Samples of API taken for testing from the cold room under a storage condition of 2-8°C were stored in a cabinet drawer which had no temperature control. Two Pharma refrigerators with built audiovisual alarms have now been installed to address this matter.
- The QC sampling work sheet did not include a provision for the inclusion of the manufacturer or broker of the API/excipients. Sampling sheets now include manufacturers name and site amongst other details.
- The software for the company's HPLC dates back to 2002. To use the HPLC for analysis, the analysts log on to the software on the system administrator platform/mode. This implies an unlimited access to data on the system and possible loss or manipulation of data. The HPLC is now restricted only to analysts

with log on passwords and activated audit trail, therefore every activity can be tracked to the operator.

- The company had two HPLCs and several non-dedicated columns used in the analysis of materials and products, but there was no logbook for recording the columns used in a particular HPLC, the materials analysed on the columns and the number injections into each of the columns. Subsequently, there is now a dedicated logbook for each HPLC, with details of raw material or FPP analysed by specific columns and a separate logbook for columns use and number of injections.

2.1 QUALITY ASSURANCE

The company has a procedure for evaluation and monitoring of product performance and quality of the systems through annual product reviews. There were procedures in place for the qualification of some equipment and systems and validation of some procedures and processes. At the time of the initial inspection, the quality system was not adequately implemented and demonstrated especially in the areas of handling deviations, change control and root cause analysis. The system has now been strengthened in the area of handling deviations, change control plus elaborate on tools to assist for root cause in-depth assessment and deviation management.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The facility was a spacious, reasonably laid-out and effective single product facility with good quality equipment and because of the single granulation room available; there is little risk of product contamination. The system was designed to support the manufacture and control of the product of interest in 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, warehouse, corridors and cloak room were clean and tidy.

2.4 QUALIFICATION AND VALIDATION

The validation master plan was in place and from the working document it was observed that several procedures and processes had been validated while others were at different stages in the validation process. Process validation for the product being prepared for prequalification will be executed on completion of on-going accelerated stability studies while the analytical methods validation is now complete. Also, the

cleaning validation acceptance limits for residues has been established including consideration for paediatric doses.

2.5 COMPLAINTS

It was noted from the annual product review that a reasonable proportion of the complaints received in the year under review were on products from one supplier but the recommended action was not implemented and there was no project plan in place to track all the issues at a glance. Now in place is an SOP for formal review of product quality complaint. The manufacturing site producing the product generating complaint has been audited by Swipha.

2.6 PRODUCT RECALLS

Procedures for product recall have been put in place to include parameters for exported products. The procedure provides for indication of who will be responsible for the recall in the importing country .in order to liaise with the regulatory authorities.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Although the company undertakes toll manufacturing for both local and multinational companies, this area was not covered in this inspection.

2.8 SELF INSPECTION AND QUALITY AUDIT

The company has an adequate self-audit program as audits are conducted and closed after the audit report but non-conformances are tracked in the company's CAPA program till they are all closed out.

2.9 PERSONNEL

The company personnel were generally knowledgeable and cooperative but it was noted that there was a lot of expertise in key personnel and how well the expertise is passed down in the system may be a cause for concern. Subsequent to the initial inspection, a management strategy on succession planning was established and is currently being implemented.

2.10 TRAINING

A training programme was in place, although at the time of the initial training, review of some of the personnel training records, indicated that the records were not duly updated as some training received was not documented in the records reviewed. Also there was no formal assessment of the effectiveness of the trainings conducted. Training system is now robust, training records have now been updated and the SOP on training has been updated assigning the Senior System Compliance manager the responsibility to ensure timely update of training records and establishing a method to assess the effectiveness of the trainings.

2.11 PERSONAL HYGIENE

A satisfactory level of personal hygiene of the personnel was observed as they wore clean apparel including head coverings where required, as appropriate to the duties performed.

2.12 PREMISES

The premises were well laid-out and appropriately designed, constructed, maintained and cleaned to suit the operations carried out and facilitate sanitation except for the cold room which was observed to be inadequate in size. The HVAC system was suitably designed, installed and maintained as well as the water treatment plant which was found to be generally adequate.

2.13 EQUIPMENT

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

2.14 MATERIALS

Receipt, storage and dispensing of materials were generally satisfactory and robust supplier qualification is on-going.

2.15 DOCUMENTATION

The company has a document issuance and authorization system in place with further improvements in documentation practises implemented following observations of the initial inspection. Also item codes are now consistently and comprehensively used in process documents and specifications.

2.16 GOOD PRACTICES IN PRODUCTION

Generally, production activities were carried out satisfactorily as they were performed in accordance with batch documentation and in line with GMP principles.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The Quality department carries out the requisite functions of the Quality Control Unit as regards sampling, testing, organization, documentation and release of materials and products. Facility limitation in analysis prior to the initial inspection had led the company to utilize supplier Certificate of Analysis (C of A) results for release of certain APIs. Whilst the release and agreement had followed discussion at an appropriate level in QA, this practice had not been formally handled through the change/deviation management and supplier assurance program. In the interim, a contract with quality agreement has been established with a reference laboratory to cover the identified gaps while for a long term basis, a GC and FTIR have been purchased and installed for use once fully qualified.

There were also some observations on data management on the HPLC system. The HPLC is now restricted only to analysts with log on passwords and activated audit trail, therefore every activity can be tracked to the operator.

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, **Swiss Pharma Nigeria Limited, 5, Dopemu Road, Agege, Lagos, 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 2 years, provided that the outcome of any inspection conducted during this period is positive.