

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

Name of Manufacturer	Guilin Pharmaceutical Co. Ltd.
Unit number	OSD-I
Production Block	Same as above
Physical address	No.43, Qilidian Road, Guilin, Guangxi, China, 541004
Contact person and email address.	Mr. Jimmy He Tel: +86-773-3675053 E-mail: Hem@guilinpharma.com
Date of inspection	19 to 21 July 2012
Type of inspection	Routine Inspection (New site)
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	Malaria
Summary of the activities performed by the manufacturer	Manufacturing and quality control of FPP

Part 2: Summary

General information about the company and site

Guilin Pharmaceutical Co., Ltd. is a subsidiary company affiliated to Shanghai Fosun Pharmaceutical (Group) Co., Ltd. The company's newly constructed manufacturing factory is located in No.43 Qilidian Road, Guilin, China. The OSD and API units, QC, Warehouse are in the process of being transferred to this new site from the No.17 Shanghai Road, Guilin with most of the technology transfers completed in the first second quarter of this year. The old site will be closed as planned on conclusion of the transfers and the necessary approvals for variations to add the new site to the various filings the company holds. The new OSD and API site is located about 40km from the Guilin Shuangjiang airport on the outskirts of the city on an existing campus where Artesunate Injection is already manufactured in a separate workshop.

History of WHO and/or regulatory agency inspections

The campus on which the new factory for OSDs and new API workshops has been constructed also has a number of older facilities and several of these have been inspected by WHO including those for Sterile Artesunate powder for injections and SVA/ SVP (small volume parenteral) in November 2010 and November 2011.

OSD products are currently manufactured at the No.17 Shanghai Road, Guilin which has also been inspected on a number of occasions. This is the first WHO inspection to the new OSD unit at this site.

At the time of the inspection validation batches had been manufactured at the new site according to the validation matrix agreed previously with the assessors, but full validation of all processes for other products to be manufactured on site was still on-going along with further transfers of other Non-PQP product from the No.17 Shanghai Road, Guilin site.

Focus of the inspection

The inspection focused on general principles of GMP and the production and control of three PQ FPP tablet products. The inspection was performed back to back with that of the company's new API operations also relocated to this campus. The inspection of the API operations is reported separately. The OSD inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Warehouses including sampling areas
- OSD I production facilities
- QC facilities (physico-chemical) including storage of retention samples
- Document review
 - o Facility layouts

- o Organogram
- o Product Quality Reviews
- o Change control
- o Deviation control
- o Complaints
- o Recall
- o Supplier's Approval
- o Product release control
- o Document control
- o OOS investigation
- o Self-inspection

Document review (production) including

- o BMR's of the inspected products
- o Manufacturing process validation
- o Cleaning validation
- o Manufacturing equipment calibration, qualification and maintenance
- o Water system
- o Waste treatment

Document review (QC, physico-chemical), including

- o Sample handling and testing
- o Handling of reference standards
- o Analytical instrument calibration, qualification, maintenance
- o Recording of analytical tests, handling of raw data, reporting

2.1 QUALITY ASSURANCE

Quality management system of the company was established in form of the organisational structure, standard operational procedures and related resources. There was a quality unit composed of the quality assurance and Quality control departments which were independent of production. Managerial responsibilities were generally well specified in job descriptions. There was a system for self-inspection and its effectiveness was not significantly in question given the observations of the inspection which were mainly of a minor nature.

There was an SOP describing the requirements for product quality reviews.

A number of SOPs were reviewed during the inspection, including:

- Organization chart
- Annual quality review of products
- Quality risk management procedure
- Product release
- Customer complaints handling
- Product recall management procedure

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The production was performed in a multi-product facility and production equipment was not dedicated. Validations, qualifications were performed according to the site policy and documented procedures.

Adequate premises and equipment were available for production, in-process quality control and storage.

Manufacturing processes and quality control test requirements were generally well defined in approved documents.

There were three OSD units located in the one building. All the PQ OSD was manufactured in the OSD-I. Within the building OSD is physically separated from the other two OSD facilities which are used for the manufacture and packaging of other non-PQP products.

2.3 SANITATION AND HYGIENE

The facilities and procedures for sanitation and hygiene established on the site were found to be adequate to ensure that premises and equipment were properly cleaned. All equipment inspected was in an appropriate condition.

The gowning and changing procedures for entry into the manufacturing facilities were satisfactory and adequately described in SOPs (illustrated) which were displayed on the wall.

2.4 QUALIFICATION AND VALIDATION

The Validation Master Plan was a general document that stated the company's validation policy. The manufacturing process and equipment have been validated when production transferred from the old site to this new site. Some of these activities were still on going at the time of the inspection with adequate plans in place to assure completion.

A list of major equipment together with identification numbers was available for the inspection. It provided the information of the equipment newly installed in the site and the old ones transferred from the original site. Calibration/qualification and maintenance programs were in place for critical manufacturing and quality control equipment and water systems.

Cleaning validation was based on the physic-chemical attributes of the products and APIs (strength, potency, solubility).

The manufacturing process and cleaning validation protocols also serve as validation report master record forms.

Separate “validation reports” were issued for the 3 consecutive validation batches and the results were summarized in a “Summary report”. Validation batches were reviewed.

2.5 COMPLAINTS

SOP on handling of market complaints was available and found to be acceptable.

2.6 PRODUCT RECALLS

SOP on handling product recalls was available and found to be acceptable. It provided for a classification of recalls into class I, II, and III with corresponding times for implementing a recall specified. The recall procedure and effectiveness of above mentioned product has been reviewed and found satisfactory.

2.7.1 CONTRACT PRODUCTION AND ANALYSIS

There was no manufacturing activity contracted out for the inspected products.

2.8 SELF INSPECTION AND QUALITY AUDIT

There was a system for self-inspection and its effectiveness was not significantly in question given the observations of the inspection which were mainly of a minor nature. Self-inspections were conducted as per SOP.

Vendors were qualified as per written procedure. QA was responsible for assessing the need and coordinating audits of vendors. The APIs for prequalified products were manufactured and supplied mainly by company itself.

2.9.1 PERSONNEL

Personnel in GMP areas (production, warehousing, quality assurance, quality control) were full-time employees. The site appeared to have an adequate number of personnel to perform the site operations.

There were facilities to ensure personnel hygiene and they were provided with appropriate clothing suitable for the manufacturing activities. There were separate dinning for use by staff for eating and drinking.

Organization charts and job descriptions were in place. Individual responsibilities were defined and recorded as written job descriptions. Delegated duties were defined. The people met during inspection appeared competent and had a good understanding of GMP requirements.

2.10 TRAINING

Training programmes were in place but the observations of the inspection put in question its effectiveness. Training was conducted as per written procedure and training has been performed during production transfer to the new site. A schedule for on-going training was available.

2.11 PERSONAL HYGIENE

The level of hygiene observed and the measures taken to maintain the facility were considered acceptable.

Photos describing the gowning procedures were appended to the changing procedures and provided on the walls of changing rooms.

2.12 PREMISES

There premises for manufacturing, storage and quality control of the inspected products were generally of a satisfactory standard. Layouts of the facilities were available and up-to-date.

The production facilities of OSD-I were multi-products facilities together with OSD-II and OSD-III situated in one building.

Warehouses were situated in a separate building and controlled by computer system. Cold storage room was in place. The environmental conditions (temperature, humidity) at the different storage facilities were maintained and recorded.

The premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. The company claimed that there are no other highly active products or non-pharmaceutical products are manufactured in the OSD-I.

Air in processing areas where products are exposed were supplied by AHU with HEAP. Pressure differentials between zones were specified and monitored by Magnehelic gauges. The pressure in the corridor was designed higher than the individual production room.

2.13 EQUIPMENT

Process equipment was installed and maintained in a way that minimizes risk of contamination and cross contamination. Production equipment was identified as to its content or purpose and cleanliness status by label. The majority of the equipment is of European origin with granulation equipment from Glatt and compressing machines from Fette.

A qualification/calibration and preventive maintenance program was in place and was followed. Cleaning procedures for critical manufacturing equipment were available.

Cleaning procedure and numbering of bins was inspected.

2.14 MATERIALS

Materials were controlled by a computerized system. Written procedures for the receipt, identification, quarantine, storage, handling, sampling, approval or rejection of materials were inspected.

The storage conditions (temperature and humidity) of the inspected products were controlled between below 30°C.

Materials were tested according to the material code of the initial order.

The water system had been qualified and maintained and was being monitored. The validation programme was conventional with there been a phased approach to qualification. At the time of the inspection the system was undergoing low term monitoring as part of the qualification approach.

2.15 DOCUMENTATION

An SOP for document control was available and acceptable in general. Documentation was maintained and reviewed according to the written procedure. Documentation included: batch master formula, specifications for raw materials, packaging materials and packaging components, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and various standard operating procedures and protocols. There were corresponding records in the form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

The QA department was responsible for the control of the preparation, review, approval, distribution and of documents. QA was responsible for the final release of finished products and this was documented.

2.16 GOOD PRACTICES IN PRODUCTION

The inspected finished dosage form facilities were multi-product facilities. For the eight PQ products, the compression of the two-layer tablets of Artesunate and Amodiaquine Hydrochloride were in production during the inspection.

The site inspection of the production areas covered following areas:

OSD-I:

- Granulation
- Blending
- Compression
- In-process controls
- Coating
- Packing lines

Validated manufacturing procedures were followed. The three validation BMRs for Artesunate 50mg tablets were reviewed.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The physico-chemical QC laboratory was situated in an independent building. A microbiology laboratory was in the different floor of the same building. The QC Laboratories were adequately equipped for the work being carried out. The site inspection of QC activities covered the following areas:

- Sample preparation
- Specifications, test methods and records
- Chromatography (HPLC) laboratory
- Retention samples room
- Reference Standards

The quality specifications contained the requirements and the test methods to be followed. The operation and calibration of the HPLC was reviewed. It had been qualified in April 2012 with appropriate records kept.

Retention samples room was visited, the log book vs. retention samples of the Artesunate 50mg tablets were inspected.

Documentation relating to HPLC instrumentation was generally satisfactory. When not in use, columns were correctly stored. Related logbooks included those for column use and, a register of those approved for use in the laboratory. Logbooks were retained by QA.

Sample receiving and distribution register was reviewed. OOSs handling SOP was reviewed.

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, Guilin Pharmaceutical Co. Ltd. No.43, Qilidian Road, Guilin, Guangxi, China 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.