

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

Name of Manufacturer	Guilin Pharmaceutical Co., Ltd.
Unit number	API I and API II
Production Block	API I and API II
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	16 to 18 July 2012
Type of inspection	Routine inspection (New site)
Active Pharmaceutical Ingredient(s) included in the inspection	Artemether (APIMF181) Artesunate (API for FPP) Amodiaquine Hydrochloride (API for FPP)
Summary of the activities performed by the manufacturer	Production and quality control of APIs

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 has recently completed the construction of its new manufacturing workshops (API I and API II) on the site located at No.43 Qilidian Road, Guilin, China. The OSD and API units, QC, Warehouse operations have been transferred from the No.17 Shanghai Road, Guilin to this new site in the first half of this year. The old site will be closed as planned. The site is located about 40km from the Guilin Liangjiang International airport.

History of WHO and/or regulatory agency inspections

The site has a number of older facilities on the campus and a number of these have been inspected by WHO including those for Artesunate powder for injections and SVA/SVP in November 2010 and November 2011. This is the first WHO inspection to the newly constructed API units at this site.

Focus of the inspection

The inspection focused on the production and control of the APIs Artemether, Artesunate, and Amodiaquine Hydrochloride in the blocks API I and API II. The Artemether and Artesunate are also used as non sterile intermediates for the manufacture of sterile FPP. The inspection covered most of the sections of WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Inspection program and the areas inspected

Introductory Meeting

Overview of activities at site

Personnel

- Organization chart
- Job description
- Staff training

Quality Assurance and Quality Management System

- Product Quality Reviews (PQR)
- Change Control
- Deviations
- Complaints
- Recalls
- Document control
- Self-inspections
- Retention Samples

- Review of batch documents
- Inspection of Production Operations & Facilities
- Production operations
 - Packaging and labelling operations
- Quality Control
- In-process sampling and controls
 - QC Labs (physic-chemical and microbiology)
 - Sampling
 - Testing of the API and intermediates (IPC)
 - Out of Specification investigations
 - Reference substance and working standards
 - Stability program
- Validation
- Validation master plan
 - Cleaning and cleaning validation
- Production facility & equipment management
- Purified Water
 - Maintenance program
- Post inspection summary meeting

2.1 QUALITY MANAGEMENT

General

Quality management systems were established, documented and implemented in general.

The QA/QC department was independent from production.

The production and quality control procedures were generally satisfactorily defined and were followed. Three APIs were produced in the two new blocks (API I and API II) of the site.

Product Quality Review

The product quality review followed the procedure written in the SMP. The PQR of the inspected APIs were reviewed.

The following documents were reviewed.

- Factory layout diagram
- Organization chart
- Annual quality review of products SMP
- Quality risk management procedure SMP
- Product release SMP

2.2 PERSONNEL

An organization chart was available. The quality assurance and quality control department were independent from the production department.

The number of personnel working at the site was 1028 as total.

Job descriptions

Key personnel responsibilities were specified in job descriptions. The responsibilities for product release of the following key personnel were reviewed:

- Quality Director
- Deputy QA Manager
- API product release
- Quality Control Manager

Personnel hygiene

The changing rooms for the clean areas were equipped with hand wash facilities. The gowning and changing procedure when entering the clean areas was displayed on the wall.

Training

Personnel were qualified by education and training. The responsible person was interviewed regarding the training before and after site transfer and found to be acceptable in general.

2.3 BUILDINGS AND FACILITIES

General

The inspected production blocks API-I and API-II are mainly multipurpose plants. The plants and the facilities inspected were seen to be in good condition however these being very new it was difficult to assess the long term effectiveness of maintenance programme.

Production workshop

The Production blocks of the inspected APIs:

API-I and API-II:

The installation of the manufacturing equipment supports the vertical material flow of materials as the process is completed. The initial steps of synthesis were performed in a “non-controlled” reactor hall area (in terms of the formal GMP cleanliness class). The final recrystallization, drying and packing were performed in the segregated clean area.

Utilities

The pipelines were identified with flow directions indicated and valves properly identified.

Purified water

Purified Water was used for processing with the source water supplied by the government. After initial pre-treatment, water was treated through two ROs, and then pumped to two distribution tanks and circulated continuously through the two separate distribution loops. The following documents were reviewed.

- Flow chart of Purified Water (PW) station
- SOP for water

Containment

There were blocks of penicillin and cephalosporin finished products located on the same site, the risk assessment issue has been discussed with the company. The inspectors considered that there was minimal risk to the API facilities from these activities due to the separation of these two sets of activities and there being no shared activity.

HVAC systems

The environmental conditions in the controlled areas (Crystallization, Centrifugation, drying) were maintained by means of HVAC systems. These were inspected and considered fit for purpose.

2.4 PROCESS EQUIPMENT

General

The equipment used to manufacture of the inspected APIs are multi-purpose equipment.

The process equipment was identified and kept by means of periodic qualification, calibration, and maintenance and cleaning.

Maintenance program

The equipment maintenance was accomplished based on an annual maintenance program and approved maintenance protocols.

Cleaning

Cleaning procedures subject to different equipment and records of the cleaning of equipment and facilities were available for inspection.

Computerized Systems

Computerized system was used in the warehouse.

2.5 DOCUMENTATION AND RECORDS

Documentation system

The site documentation system was paper based. The procedure for document control was available. GMP documentation included standard operating procedures, specifications, master batch manufacturing records, etc.

2.6 MATERIALS MANAGEMENT

Procedures

There were written procedures describing the receipt, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials.

Vendor qualification

Materials used for manufacturing of the APIs inspected were required to be purchased from an approved vendor. The supply of key raw material Artemisinin used for the production of Artemether and Artesunate was mainly from its own subsidiary company.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production process was guided by documented procedures and instructions. Production process including synthesis, purification, crystallization, drying etc. were conducted in the specified facilities and equipment. Clean areas were available for the final steps of the API's manufacture and were maintained at a satisfactory level.

Production of the Artesunate and intermediate in the API-I unit as well as Amodiaquine Hydrochloride in the API-II unit were in operation during this inspection.

In-process controls were conducted at different stages to monitor performance of the process and quality of the intermediates. Sampling of the API for release testing was done after drying and before final packing in the clean area.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging and labelling operations were conducted as per standard operating procedures in clean areas.

The labelling operations were designed to prevent mix-ups as only one product was handled in the labelling room at the time.

2.9 STORAGE AND DISTRIBUTION

Incoming materials, quarantine and acceptance/rejection in the warehouse was controlled by a computer system and was considered to be acceptable. The materials status were saved in the computer system and controlled by a code reader. The cold temperature and cool temperature storage rooms were inspected and found acceptable with no major concerns.

2.10 LABORATORY CONTROL

General

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, products (API's), environmental monitoring samples, purified water samples.

Sample receiving and distribution of Artesunate were inspected and found to be acceptable in general.

Stability testing

The QC department was responsible for stability testing of finished APIs.

The stability samples were taken according to the defined program/protocol and stored in a long-term 25°C/60% RH, and 2°C to 8°C stability chamber in the case of Artemether,

Handling of out of specification (OOS) results

The SMP described the OOS, OOT and abnormal data investigation procedure has been reviewed.

2.11 VALIDATION

Manufacturing process validation

The manufacturing process of Artemether was revalidated in 2012. The process validation was performed to verify the process in the new facility and with new equipment.

The report of Artemether API was reviewed.

2.12 CHANGE CONTROL

A procedure for change control was available for inspection. As the facility is new there were few changes noted in the log.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovered solvents and mother liquid were used at the site according to the production process. The specification of the recovered acetone was same as the fresh one as claimed by the company.

2.14 COMPLAINTS AND RECALLS

The standard operating procedures to handle the complaints and recall followed the procedures as per written procedures.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the company, there were no contracted manufacturing and testing activities.

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, Artemether (APIMF181), Artesunate (API for FPP) and Amodiaquine Hydrochloride (API for FPP) manufactured at Guilin Pharmaceutical Co., Ltd., No.43, Qilidian Road, Guilin, Guangxi, China were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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.