

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

Name of Manufacturer	Kunming Pharmaceutical Corporation
Unit number	Phytochemistry Plant No.4 (PCP4)
Production Block	Phytochemistry Plant No.4 (PCP4)
Physical address	Qigongli, West Suburb, Kunming City 650100, Yunnan Province, P.R. China
Contact person and email address.	Dr. Caesar B. Schmidlin Tel.: +86(0)871 8171380 caesar.schmidlin@holley.cn
Date of inspection	25 to 28 June 2012
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Artemether (APIMF125) under company code DS00 Artemether API under company codes DS 04 and DS 12 for use in oral solid dosage forms
Summary of the activities performed by the manufacturer	Production and quality control of APIs

Part 2: Summary

General information about the company and site

Kunming Pharmaceutical Corporation (hereafter be abbreviated as “KPC”) was established in 1951. The company has one joint venture, four subsidiary companies, one drug research institute, and one manufacturing centre. The overall KPC site employed over 2800 staff members with the manufacturing site located in Qigongli, west suburb of Kunming City. The manufacturing centre covers an area of 120,000 square meters with a floor area of 60,500 square meters, and a staff of more than 950 employees. Antimalarial products – Artemisinin and its derivatives had been produced by the companies for many years with the company being amongst the first developing these materials.

The Artemether API is manufactured in No. 4 Phytochemistry Plant (hereafter be abbreviated as “PCP4”), which was first commissioned in 2005.

History of WHO and/or regulatory agency inspections

The site was previously inspected by WHO in 2004 for PCP1 and 2009 for PCP4 for Artemether. PCP4 was also inspected by US FDA in November 2008 for Artemether API (DS04).

Focus of the inspection

The inspection focused on the production and control of Artemether. 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.

The company manufactures Artemether API under a number of company codes depending upon the customer and the Artemisinin source(s). DS04 and DS12 are manufactured for WHO Prequalified OSDs (these codes have the same specification but differ in the approved Artemisinin sources) whilst DS00 is the grade approved in APIMF125.

Inspection program and the areas inspected

Introductory Meeting

Overview of activities at site

Personnel

- Organization chart
- Job description
- Staff training programme & records

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

- Warehousing and storage
- 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, protocols
- Process validation
- Cleaning and cleaning validation

Production facility & equipment management

- Purified Water
- Maintenance program
- Qualification and calibration program
- HAVC

Post inspection summary meeting

2.1 QUALITY MANAGEMENT

General

The following key QMS documents were reviewed.

- SOP on annual product review
- SOP on Release of intermediate and finished product of Artemether API
- SOP on Handling of deviations
- SOP on Change control
- SOP on Document control

Quality management systems were established, documented and implemented with procedures being present for all key QMS elements. Production and quality control procedures were generally satisfactorily defined and were being followed in general.

Product Quality Review

The Artemether APIs produced in PCP 4 were assigned three different material codes depending upon the status of the raw material and client requirements.

The 2011 Annual product quality review of Artemether DS04 was reviewed.

2.2 PERSONNEL

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

The number of personnel working in the Artemether API production was 120.

Job descriptions

Key personnel responsibilities were specified in job descriptions. The described responsibilities for the following key personnel were reviewed. The product release procedure and its associated authorisation were reviewed in conjunction with the job descriptions of the key personnel to assure consistency and lack of ambiguity in this critical activity.

- Director of Quality
- QA & QC Manager
- QA Manager
- QC Manager

Personnel hygiene

The gowning and changing rules when entering the clean areas were described in standard operating procedures.

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

2.3 BUILDINGS AND FACILITIES

The inspected production block and the production equipment were dedicated as only one API product Artemether was manufactured at PCP4. The workshop and the facilities inspected were maintained to be acceptable in general.

The production area is on the second floor of PCP 4. The final crystallization, drying, milling and blending, as well as final packaging are performed in the clean area which was claimed to comply with grade D.

Utilities

The pipelines were identified with flow directions indicated.

Purified water

Purified Water was used for processing and cleaning equipment. The specifications and testing method of the water met the requirements of the Chinese pharmacopeia.

Containment

There is a joint venture Kunming Baker Norton Pharma. Co.Ltd. located within the KPC site which produces cephalosporin FPP.

Examination of the exterior of the Baker Norton Building and the location means that it is probably low risk except in the situation of a major failure of containment equipment in that facility but needs to be verified by the corporate QA group.

HVAC systems

The environmental conditions in the clean areas (Crystallization, Centrifugation, drying) were maintained by means of HVAC systems. These systems appeared adequate for their intended purpose.

2.4 PROCESS EQUIPMENT

General

The equipment used to manufacture of Artemether were dedicated. The process equipment was identified and kept in an acceptable condition in general.

Maintenance program and Cleaning

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

Cleaning procedures subject to different equipment and records of the cleaning of equipment and facilities were available for inspection. The SOP for cleaning centrifuge bag was inspected.

Calibration

The calibration record of the balance in the clean area was inspected, observation was made.

Computerized Systems

Other than for individual pieces of equipment, such as the HPLC and GC equipment, no computerized systems were used in the warehouse, production or QC lab.

Electricity power supply

The reliability of power supplies to the site were discussed especially in relation to the sterile operations and critical equipment such as cold rooms and stability rooms. The site was not equipped with a backup power supply, but there were UPSs for short term solution in certain instances.

2.5 DOCUMENTATION AND RECORDS

The site documentation system was paper based. The procedure for document control was inspected.

2.6 MATERIALS MANAGEMENT

Procedures

There were written procedures describing the receipt, labelling, quarantine, storage, and handling of materials, as well as the procedures for sampling, testing and approval or rejection of materials. Each raw material was assigned an identification code. In general the procedures seen were adequate.

Vendor qualification

Materials used for manufacturing of Artemether were required to be purchased from approved vendors. A list of approved vendors was available.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

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

In-process controls were conducted at different stages to monitor performance of the process, 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 and only one product was handled in the labelling room at any time,

2.9 STORAGE AND DISTRIBUTION

RM/PM warehouse and finished product warehouse

The raw material warehouse was located on the ground and 1st.floor of a separate building. Access was via a stairway to a basic but adequate change zone and a step over barrier after donning overshoes, bonnets and gowns.

There was a depiction of the change procedure was displayed on the wall. Entry to all areas was locked doors with the supervisor holding keys. There was a separate area for reject materials that was empty at the time of the inspection.

The warehouse was conditioned and whilst rather old adequately maintained. Temperature and RH measurement were monitored with sensors calibrated by an external agency.

Records of pest control and temperature mapping were not attempted during this inspection.

The separate cold stores for both raw material and finished API temperature was continually monitored and alarmed for excursions. There were no back up coolers in the stores seen but in the event of failure of one room the other was of adequate size to accommodate the levels of stock seen during the inspection.

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.

The microbiological laboratory was on the fifth floor of the main building. The media preparation and sterilization was inspected.

The validation of analytical method was done by the FPP manufacturer based on the agreement. The testing monograph for Artemether DS (drug substance) was reviewed.

Sample receiving and distribution procedure and records were inspected.

Reference materials

The room to keep reference standards was visited.

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, 2°C to 8°C stability chamber for Artemether.

Handling of out of specification (OOS) results

The OOS investigation procedure was available for inspection. The SOP was reviewed during the inspection.

2.11 VALIDATION

Cleaning validation

Validation was performed for Artemether DS12 caused by the new supplier of Artemisinin. Due to the time limit, the validation document and the data was not reviewed during the inspection.

2.12 CHANGE CONTROL

A procedure for change control was according to the SOP. The change control register and records were maintained.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovered solvents were not used at the PCP4 according to the company.

Reprocessing and reworking are both allowed as per SOP on handling of unqualified products.

2.14 COMPLAINTS AND RECALLS

The standard operating procedures to handle the complaints and recall were available. SOP on Consultation and complaint and SOP on product recall were available for inspection.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The contracts for manufacturing of API Artemether between KPC and FPP manufacturers were reviewed during the inspection.

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 (APIMF125) and other grades of Artemether API for use in oral solid dosage forms manufactured at Kunming Pharmaceutical Corporation, Qigongli, West Suburb, Kunming City 650100, Yunnan Province, P.R. was 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.