



**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)**

**Active Pharmaceutical Ingredient Manufacturer**

**Part 1: General information**

Name of Manufacturer	<b>Kunming Pharmaceutical Corporation (KPC)</b>
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
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Date of inspection	<b>14, 15 and 16 September 2009</b>
Type of inspection	Routine inspection
WHO product categories covered by the inspection	<b>APIs for use in products against malaria (MA)</b>
Active Pharmaceutical Ingredient(s) included in the inspection	Active Pharmaceutical Ingredients against Malaria (MA)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, control and release of Anti-Anti-Malarial active pharmaceutical ingredients.

## **Part 2: Summary**

### *General information about the company and site*

### *General information about the company and site*

The site inspected was **Kunming Pharmaceutical Corporation, Qigongli, West Suburb, Kunming City 650100, Yunnan Province, P.R. China, hereafter called KPC**. The focus of the inspection was Phytochemistry Plant No. 4 (PCP4). The company corporate office was located at Plot No.166 Key Road, State New and High Technology Development Zone, Kunming650106, Yunnan Province, P.R. China.

According to the Site Master File effective 25 August 2009 and the presentation given at the opening meeting, **KPC** was established in 1951. In 2000, it was listed on the Shanghai stock exchange and the major shareholders were Holley Group in Zhejiang Province (22%), Provincial Industrial Investment Co., Ltd and Hongta Group. KPC owns 1 sub-pharmaceutical sale, 7 pharmaceutical holding companies, 1 Joint venture company, 4 manufacturing factories, 1 drug research institute and 1 pharmaceutical engineering design institute.

The site of **KPC** was about 170,000m<sup>2</sup> in size with a built up area of 100,000m<sup>2</sup>. The manufacturing facilities at the site included:

- ⇒ Oral dosage plant manufacturing several products including antinfectives.
- ⇒ Oral dosage forms belonging to Kunming Becker-Norton Pharmaceutical Co., Ltd, a joint venture company with Teva Pharmaceuticals, which produces generic penicillin finished pharmaceutical products.
- ⇒ Two injection Plants,
- ⇒ 4 Phytochemistry Plants (PCP) for APIs:
  - PCP1: old production plant.
  - PCP2: plant dedicated to a certain series of APIs.
  - PCP3: extraction and concentration plant (2 blocks).
  - PCP4: new production plant.

PCP4, which was the focus of inspection was built in 2005 and was dedicated to production of one API through 4 steps:

- ⇒ **Step I: Reduction.**
- ⇒ **Step II: Methylation and crystallization.**
- ⇒ **Step III: Dissolution and recrystallization.**
- ⇒ **Step IV: Milling and blending.**

The API under focus was produced under two codes.

1. **One (DS04)** produced solely for a specific customer.
2. **Another (DS00)** produced up to step III for KPC and other customers. The steps of synthesis, manufacturing instructions, reactors and specifications used for DS00 were similar to those for DS04 except there was no step IV (milling and blending) and the specifications of the key intermediates were based on Chinese Pharmacopoeia (Ch.P2005).

### *History of WHO and/or regulatory agency inspections*

According to the SMF and company presentation, KPC got GMP certificates issued by the State Food and Drug Administration of China (SFDA) for Active Pharmaceutical Ingredient, Powder for Injection, Small Volume Injection, and Oral Dosage. It was stated also that:

- ⇒ PCP4 passed the GMP inspection by US FDA in Nov. 2008 focusing the API the specific customer (DS04).
- ⇒ PCPI passed GMP inspection by TGA in 2001 and 2005.

PCP1 was previously inspected by WHO-PQ in September 2004 and subsequently approved.

### *Focus of the inspection*

The inspection focused on the production and control of the API for the specific customer (DS04) in PCP4. The inspection covered all the sections of ICH Q7, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

### *Inspected Areas*

#### **Day 1**

The inspection started with an opening meeting in the conference room, where the inspectors introduced themselves and exchanged business cards with the key staff of KPC. The inspectors explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection and timelines for the processing the report and company responses to the inspection observations. The procedures for closing the inspection including the WHO public inspection report (WHOPIR), Notice of Concern (NOC), Notice of Suspension (NOS) were explained. The tentative inspection plan was discussed and confirmed. This was followed by a presentation from KPC about the company and the site to be inspected. The presentation highlighted the capacities, Quality Management Systems and inspection history of the site. The synthesis and purification process of the API starting from key API starting material were presented highlighting the starting materials, the equipment used (reactors, filters, tanks centrifuges, dryers, mills and blender) and their location, key process parameters, and batch sizes at different stages of the process. A copy of the presentation was obtained and will be filed in the company file.

The inspectors proceeded with a detailed review of the following areas of the quality management systems and related documents and records:

1. SOP on the procedure for allocating batch numbers to intermediates and final API in PCP4. The batch numbering format was CODE YYYY P XXX: Where:
  - CODE was the product code, which differed according to the API code and plant used.
  - YYYY was the year of production, e.g. 2008.
  - P was the production type:
    - 1 = Normal production batch.
    - 2 = Trial production batch.
    - 3 = Reworked batch.
    - 4 = Validation batch.



- 5 = Batch reprocessed once.
  - 6 = Batch reprocessed the second time.
2. Batch sizes.
  3. SOP on the procedure for handling unqualified intermediates and final API in PCP4. The procedure described the conditions and procedures for reprocessing and reworking. A batch could be reprocessed twice and but reworking could only be done once. Reworking was only allowed if the API before milling and blending failed the test for clarity. There was an approved procedure for reworking (effective 06.09.2008) which included re-purification by addition of filter aids. Reworked or reprocessed batches could be identified from their batch numbers.
  4. Specifications of key API starting material, intermediates and final API. Although the specifications of the key starting material and finished API for the different codes (DS04 and DS00) used different specifications, their intermediates used the same specifications.
  5. SOP on the annual product quality review (APQR) for DSO4 and DS00 for all the 4 steps for the years 2005, 2006, 2007 and 2008. The content of polymorph A in most of batches was 100% and none was less than 99%.
  6. Deviation and control procedures with the following examples reviewed in detail:
    - ⇒ One where potable water instead of purified water was used in the first step of 5 batches to assess the impact of ozone on the quality of the key intermediate.
    - ⇒ One to distinguish the master batch processing instructions and related records for DS04 and DS00 following starting to manufacture DS00 in PCP4. Hitherto in PCP1, the same batch processing instructions and records were used for DS04 and DS00.
    - ⇒ One for introduction of cool storage for the API before milling and blending.
    - ⇒ One for change of several process parameters and update the Master batch processing instruction. Evidence of submission and approval of the changes to responsible DRA was available.
  7. Supplier audit, qualification and approval and list of approved suppliers for starting materials and solvents used in the manufacture of the API. The process involved evaluation of a questionnaire filled by the supplied, full analysis of samples from several batches and audit of the facilities and systems of the supplier. There were different suppliers of key starting material for DS04 and DS00. The customer for DS04 was responsible for the approval of the suppliers for key starting material for DS04 and it was first collected in a central warehouse managed by an agent on behalf of the customer and only transferred to KPC according to production the schedule. Some of the key starting material used in the manufacture of DS00 used to be extracted on site and some was still purified on site. Suppliers of the other starting materials and solvents were identified and approved by KPC.
  8. SOP on Complaints handling.
  9. SOP on Product Recall.
  10. SOP on Artemether API batch release.
  11. SOP on management of documents.
  12. SOP on how to write an SOP.
  13. Organization charts and job description of selected employees, namely:
    - Head of QA/QC
    - Head of QA.
    - Head of QC.

The inspectors proceeded to inspect the warehouses used to store finished API (Cold room), solid starting materials, key starting material (and related sampling and dispensing room), reagents and a quick visit to PCP1.

The inspection ended late in the evening so the review of the progress of the activities of the day, and giving the day's feed back were differed to the next day.

## **Day 2**

The inspectors started by reviewing the areas inspected the previous day and gave feed back on the observations made.

The production activities in the common production area for steps I and II and clean area for steps III and IV of PCP4 were inspected. The corresponding documents in the area were reviewed including use and cleaning log books, batch processing instructions and records. The intermediate storage area and washing areas of equipment, tools and filters bags for the filters and centrifuge were inspected. The API was stored in the fridge before milling and blending operations. The IPQC lab was inspected followed by review batch records of selected batches DSB and its intermediates as well as DS00 and its intermediates. The stock control book showed that all the batches of DS00 were transferred to the KPC injection plant.

The monitoring of holding time for unmilled API after removal from the fridge was reviewed as described in the corresponding SOP.

The inspection ended late in the day so the review of the progress of the activities of the day, and giving the day's feed back were differed to the next day.

## **Day 3**

The inspectors started by reviewing the areas inspected the previous day and gave feed back on the observations made.

The morning was dedicated to the inspection of the QC laboratory. The following labs were inspected:

- ⇒ First Floor (Ground floor) : sample receiving area
- ⇒ Second Floor: Stability chambers room, Retention samples room and Packaging material testing lab.
- ⇒ Third Floor: Raw material wet chemistry testing laboratory, instruments laboratory, samples preparation room
- ⇒ Fourth Floor: Standard solution preparation lab, UV analysis lab.
- ⇒ Fifth Floor: Microbiology testing lab: separate labs for limit test and purified water analysis.

## **2.1 QUALITY MANAGEMENT**

KPC had an acceptable documentation system consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. The responsibilities of the Quality and production units were defined. There was a system and records for Annual product quality review.

One of the key customers had supported KPC in establishing a comprehensive quality management system and had been involved in its regular monitoring and continuous improvement.

## **2.2 PERSONNEL**

KPC had adequate numbers of qualified and experienced personnel to carry out the tasks in accordance to the applicable GMP. Individual responsibilities were generally defined in the organograms and individual job descriptions.

The heads of production and quality control were independent of each other.

Personnel interviewed reflected that they were aware of the principles of GMP although the routine GMP training could be strengthened further. Entry to critical production, storage and quality control areas was restricted to only authorized personnel. Personnel were provided with appropriate protective clothing.

## **2.3 BUILDINGS AND FACILITIES**

The building and facilities of PCP4 were designed to facilitate logical flow of production activities and to avoid contamination. The building and facilities were in a good state of repair and were adequately cleaned. They were dedicated to the synthesis and purification of the API in focus.

The clean areas for purification stage were separate from those for the synthesis stages and floors, walls and ceilings were smooth to facilitate cleaning. The areas where highly flammable materials like nitrogen were used were separated by explosion proof doors and were under negative pressure compared to the surrounding areas.

All the production areas were supplied with appropriately filter air and purified water. The pressure differentials, temperature and relative humidity were regularly monitored.

## **2.4 PROCESS EQUIPMENT**

The process equipment were designed and installed to facilitate containment and logical flow of production. They were regularly cleaned and maintained according to approved procedures and records were maintained. There was a system to indicate the status of the equipment.

## **2.5 DOCUMENTATION AND RECORDS**

There was a system for documentation in form of SOPs, manufacturing procedures, log books, specifications, testing procedures. These were designed, approved and controlled according to established SOPs.

## **2.6 MATERIALS MANAGEMENT**

Materials were sourced from approved suppliers. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use, although a weakness was

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identified in inspecting the labels of received solvents. The storage of starting materials, intermediates and finished APIs was generally adequate and the storage conditions were regularly monitored. Materials under a different status and stage of processing were adequately segregated.

Materials at different stages processing were identified with a unique batch numbers and stage of processing.

## **2.7 PRODUCTION AND IN-PROCESS CONTROLS**

Production processes were guided by well documented procedures and detailed instructions. Production processes were conducted in dedicated facilities. There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. The process used was generally similar to those outlined in the dossiers submitted to WHO. The cleaning procedures, design of the buildings and equipment, plus the planning of production facilitated prevention of possible contamination.

## **2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

Materials at different stages processing were identified with a unique batch numbers and stage of processing. Intermediates and finished APIs were packed using packaging materials meeting the relevant specifications. Packaging operations took place in segregated areas. There was appropriate reconciliation of packaging materials at the end of each packaging operation. The label for final API needed to be improved (see deficiencies).

## **2.9 STORAGE AND DISTRIBUTION**

KPC had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Conditions of storage were monitored and appropriate records for stock and distribution were maintained. The records could support traceability of the batches distributed.

## **2.10 LABORATORY CONTROLS**

There was a separate block for QC and QA department. The premises, facilities and utilities were separate from production and were in a good state of repair. There were dedicated rooms for activities like sample receipt and storage, wet chemistry, instrumentation and balance room. There were adequate pieces of equipment with up to date calibration status.

Records of sample receipt and allocation, analysis were maintained. The assembly of records of analysis could be improved.

The microbiology laboratory was separated from the chemical laboratory. It had adequate room for segregation of different activities.

There were stability chambers for the different storage conditions and records of charging and withdrawal of samples for testing were available and consistent with the protocols and regulatory requirements.

## **2.11 VALIDATION**

Validation of manufacturing processes had been done and the relevant protocols and reports were available. These protocols were well designed and executed. All validation stages were preceded with an elaborate quality risk analysis to identify the critical process parameters and their acceptance limits. Generally, the conclusions reached were supported by the results of validation and they were used to design routine process instructions and related in-process controls.

Major pieces of equipment had been qualified and records of qualification of selected equipment showed that the programme was comprehensively executed.

## **2.12 CHANGE CONTROL**

There was a procedure for change control which included evaluation of the validation status of the system and prescribed appropriate control measures to preserve the validated status. There was a change control register and appropriate records were maintained. Several changes were reviewed which proved that the change control in place was well designed and adequately implemented.

The introduction of synthesis of DS00 in PCP4 was done through a well documented change procedure.

## **2.13 REJECTION AND RE-USE OF MATERIALS**

No recovered solvents were used in any stage of synthesis or purification. All solvents and mother liquors from PCP4 were collected in several tanks in PCP3 and sold to an outside client. An agreement with this vendor was in place and records of dispatch of the solvents were reviewed and no matter of concern was observed.

Reprocessing of materials was allowed at all stages of synthesis and purification. This was guided by well documented procedures which had been covered during validation. Reprocessed material had to meet the same specifications as routine materials but they were identified by a different batch number. The policy allowed materials to be reprocessed up to a maximum of two times.

Reworking was only allowed in case of the un-milled API failing to comply with specifications for clarity. The rework process was well documented and required careful evaluation and more testing and stability testing if found necessary. Up to date, no batch had been reworked.

## **2.14 COMPLAINTS AND RECALLS**

There were procedures for handling customer and market complaints and product recall. No complaints or recalls had been encountered since the last inspection.

## **2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

There was no contract manufacturing done for the API under focus. Specialized test in QC were contracted out but the agreements with the vendors were not reviewed. The contracts with the WHO Public Inspection Report (WHOPIR)

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vendor used to handle waste solvents for 2008 and 2009 were reviewed. The responsibilities of KPC and the vendor were well spelt out.

### **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, **Kunming Pharmaceutical Corporation, Workshop PCP4, Qigongli, West Suburb, Kunming City 650100, Yunnan Province, P.R. China**, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines and in particular, ICH Q7: Good Manufacturing Practice Guide 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.