

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

API manufacturer

Part 1: General information

Name of manufacture	Chongqing Holley Wulingshan Pharmaceutical Co., Ltd
Unit number	N/A
Production block	Building 1 and 2
Physical address	108 Cuiping Street, Zhongduo Town, Youyang County, Chongqing, China
Contact person and email address	Mr. Alex Zheng, Regulatory Manager Beijing Holley-Cotec Pharmaceuticals Co. Ltd zhengzhi@cotec.com.cn
Date of inspection	24, 25 and 26 November 2010
Type of Inspection	Routine GMP inspection
.Active Pharmaceutical Ingredient(s) included in the inspection	Active Pharmaceutical Ingredients against Malaria
Summary of the activities performed by the manufacturer	Manufacturing of APIs and intermediates, using Chemical synthesis processes.

Part 2: Summary

General information about the company and the site

Chongqing Holley Wulingshan Pharmaceutical Co., Ltd has several manufacturing sites. According to the Site Master File and the presentation given at the opening meeting, Chongqing Holley Wulingshan Pharmaceutical Co., Ltd was located in Youyang County, Chongqing and established in 1986. Chongqing Holley Wulingshan was acquired by Chongqing Holleypharm in the year 2000. The company is specialized in antimalarial APIs and its derivative APIs. The facility was also manufacturing liquid dosage forms produced from artemisinin or its derivatives. All the production activities were carried out in dedicated facilities.

Chongqing Holley Wulingshan had 3 production buildings in separate blocks with separate air handling systems.

The manufacturer was licensed by the Chongqing Food and Drug Administration Authority (CFDA) on September 29th, 2007.

The production facility manufactures several active pharmaceutical ingredients (APIs): the list of the APIs manufactured in Youyang city, was presented.

A GMP certificate was issued by the CFDA for the manufacture of certain APIs.

All the phases of the process and the release laboratory analyses (physico-chemical and microbiological) were performed at the site.

The areas covered during the inspection included: warehouses, receiving, sampling and dispensing areas, production plants (synthesis), physico-chemical QC laboratories, water production and air handling units.

History of WHO or regulatory agencies inspections

This inspection of Chongqing Holley Wulingshan Pharmaceutical Co., Ltd was the second WHO inspection of the site. It was inspected in 2005 for anti-malarial APIs.

Focus of the inspection

The inspection focused on the production and control of Building 1 and 2 of anti-malaria APIs. The inspection covered all the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

On the first day, the inspection started with an opening meeting, during which the company staff and the inspectors and observers introduced themselves, followed by an overall company presentation and also a presentation of the site activity with its quality assurance system. The lead inspector explained the purpose and focus of the routine inspection.

The activity and the location, especially the manufacturing process of the API was presented and the proposed inspection plan was discussed.

The annual product quality review reports for 2008 and 2009 were inspected and were followed by the inspection of the warehouse for starting materials, packaging materials, sampling and dispensing areas, as well as the tank farm, the chemical drums stores, and the purified water system in the afternoon.

Several documents were reviewed including training and personnel files, SOP for SOP, trainings, job descriptions, vendor qualification, and self inspection.

On the second day, several documents were reviewed and the manufacturing process was presented by the company along with the location of the different workshops concerned with the process showed on the plant layout. Buildings 1 and 2 including raw material processing area, workshop used for the manufacturing process and the HVAC system dedicated to the processing area were inspected.

Batch records were reviewed along with analytical data.

On the third day the quality control laboratory was inspected as well as the stability testing chambers and the retain samples area.

The manufacturing process of the API was also inspected. This was followed by a closing meeting where a summary of the inspection was presented.

Areas inspected

- Warehouse of dry starting materials, packaging materials and API tank farm ;
- Chemical drum stores ;
- Building 1: Extraction, Column separation, Crystallization, Dissolution, Filtration, Re-Crystallization
- Building 2: Synthesis, Crystallization, Dissolution, Crystallization
- Water system and HVAC system ;
- Quality control laboratory (except microbiology part).

2.1 QUALITY MANAGEMENT

The quality assurance system was presented. Chongqing Holley Wulingshan Pharmaceutical Co., Ltd performs all manufacturing, testing, packaging and holding of APIs in accordance with the requirements of the GMP principles as described in WHO GMP. The quality management department has the overall responsibility. All changes which directly or indirectly have the potential to affect product quality were reviewed and approved by quality management department.

Internal Audits (Self Inspection)

The self inspection plan for 2010 and the standard operating procedure “Internal audit” were presented and reviewed.

Product Quality Review

The product quality review (PQR) for year 2009 (January to December) and 2008 were presented. There was no complaint, recall, return or OOS result reported in 2009. One deviation was reported during the manufacturing. The deviation was inspected.

2.2 PERSONNEL

There were 139 staff members working on the site. The organisational chart was presented. The standard operating procedure “Department Training procedure”, training plan 2009/2010 and training master plan were presented. The training records of a selected analyst were reviewed.

2.3 BUILDINGS AND FACILITIES

Design and Construction

Buildings 1 and 2 used to manufacture active substance was inspected. The workshops and the facilities associated were clean and well maintained. The last stages of the process were carried out in a clean isolated area equipped with terminal HEPA filters.

Water

Production Buildings 1 and 2 were equipped each with a purified water system consisting of a multi-media filter, carbon filter and 2 pass reverse osmosis system for purification.

Sanitation and Maintenance

Warehouse and production areas were generally clean.

2.4 PROCESS EQUIPMENT

The workshops and the facilities inspected were clean and well maintained. 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.

The last stages of the process were carried out in clean isolated areas (class 100,000) equipped with terminal HEPA filters.

Calibration

Calibration of devices (temperature, pressure etc.) was conducted according to the established program.

Computerized Systems

Only the HPLC, FTIR, GC and UV instruments were computerized.

2.5 DOCUMENTATION AND RECORDS

Documentation System and Specifications

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, computer printouts etc. SOPs and specifications for the product existed. Several SOPs were reviewed pertaining to the activities associated with the product processing, cleaning of equipment and returns.

The annual product quality review reports for 2009 and 2008 and the procedure “Preparation, review and control of standard operating procedures” were reviewed.

Equipment Cleaning and Use Record

Equipment cleaning and use records were generally in place.

Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

Records including an approved vendors list (listing general raw materials and key materials respectively) were available.

Batch Production Records

The selected batch production records manufactured in 2009 was reviewed.

Laboratory Control Records

Analytical control records (results for raw materials) were available and were presented for inspection. Source data were verified for testing including working reference standards, test procedures, use logs and instrument registers. The stability chambers and the list of samples in the chambers were verified.

2.6 MATERIALS MANAGEMENT

General Controls, Receipt and Quarantine, Sampling and Testing of Incoming Production Materials, Storage

Materials were received and checked prior to storage. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use.

An approved vendors list existed.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production processes were guided by documented procedures and detailed instructions. Production processes were conducted in dedicated facilities and dedicated equipment. There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. The processes used were 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 cross-contamination.

Reactors and vessels were suitable to carry out or hold reaction mass during reaction and workup. Cleaning procedures were generally validated. Pressure cascades were in place and the AHUs were designed for supply air. The inspected AHUs were designed with re-circulation of air.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging and labelling operations were conducted as per standard operating procedures. After batch release the QC person affixed approved labels and handed over the release intimation to production department. Production department transferred the material in the warehouse along with transfer note and the finished product was then dispatched from the warehouse.

2.9 STORAGE AND DISTRIBUTION

Chongqing Holley Wulingshan Pharmaceutical had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Some conditions of storage were not monitored. Appropriate records for stock and distribution for those monitored were maintained.

2.10 LABORATORY CONTROLS

The main QC laboratory was situated on the first floor of the administration block. 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, hot areas and balance room. There were adequate pieces of equipment with up to date calibration status.

Records of sample receipt and allocation, analysis were maintained. Records of analysis could facilitate traceability of the reagents, standards and equipment used.

The quality control laboratory was inspected focusing on the control of reference standards, testing procedures and data verification of a selected batch. Source data, equipment use logs, temperature and RH records for the stability chambers were reviewed.

Chongqing Helloy Wulingshan Pharmaceutical Co., Ltd, used working reference standards, tested against official standards.

The microbiology laboratory was separated from the chemical laboratory.

Certificates of Analysis

An example of certificate of analysis was presented. The information such as name, address and results with specifications were indicated.

2.11 VALIDATION

Chongqing Holley Wulingshan Pharmaceutical Co., Ltd manufacturer had policy, procedures, protocols and reports for validation and qualification of processes, procedures, equipment, utilities etc.

Only selected validation and qualification protocols and reports were inspected.

Qualification

Major pieces of equipment were qualified as per the written installation and operational qualification protocols before taking them for product processing. In general, qualification reports were available.

The QI, QO and QP reports of the Waters HPLC were verified.

Cleaning Validation

The company had procedures, protocols and reports for the cleaning validation.

2.12 CHANGE CONTROL

There was a procedure for change control which included evaluation on 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.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovery of solvents and materials at different stages of synthesis was done according to documented instructions and were tested to meet predefined specifications. Solvent recovery was done on site. The in house recovery processes were validated as part of the process validation.

2.14 COMPLAINTS AND RECALLS

The standard operating procedure “Customer Quality Complaint” was checked. According to the 2008 and 2009 product quality reviews, there was no recall or complaint for the API being inspected.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

According to the company, there were no contracted manufacturing and analytical 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, **Chongqing Holley Wulingshan Pharmaceutical Co., Ltd**, 108 Cuiping Street, Zhongduo Town, Youyang County, Chongqing, China was considered to be operating at an acceptable level of compliance with WHO GMP guidelines 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.