



**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
API Manufacturer**

**Part 1: General information**

Name of Manufacturer	Zhejiang Medicine Co. Ltd.
Unit number	Units 207, 209, 218, 229
Production Block	Lumefantrine and artemether production blocks
Physical address	98 East Dadao Road, Xinchang, China
Date of inspection	October 13, 14, 15, 16, 2010
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Artemether, lumefantrine
Summary of the activities performed by the manufacturer	Production and quality control of artemether and lumefantrine for WHO prequalified products

## **Part 2: Summary**

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

Zhejiang Medicine Co. Ltd was founded in 1954 and has 3 production sites located in the province of Zhejiang: in Xinchang, Shaoxing and Shengzhou. The object of this inspection is the Xinchang Pharmaceutical Factory, which has about 25 different buildings involved in the production of vancomycin hydrochloride, carotenoids, CoQ10, vitamin E soft capsules, as well as the products that are covered by this inspection, lumefantrine and artemether.

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

The Xinchang manufacturing site was inspected by the USFDA for the same APIs in March 2009. The last WHO inspection was performed in October 2008.

### ***Focus of the inspection***

The inspection focused on the production and control of artemether and lumefantrine 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***

#### Day 1

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards. They explained the procedure for the WHO Prequalification Programme, the procedures and standards used for inspection and elaborated on the tentative inspection plan. After confirming the inspection plan, the company made a presentation about the company activities and the site to be inspected. The presentation highlighted the capacities, organizational chart, synthetic pathways and inspection history of the site. A copy of the presentation was obtained and will be filed in the company file.

The quality management system of the company was inspected along with recent product quality reviews. Other inspected areas included:

- complaints;
- the batch numbering system SOP;
- the general register for complaints;
- the evaluation procedure for material suppliers;
- raw material vendor audit procedures;
- approval of the a key raw material supplier;
- the list of approved suppliers;
- deviations.



The following areas were visited at the end of the day:

- raw material storage warehouse for incoming raw materials;
- the solvent tank farm.

### Day 2

The observations from the previous day were presented to the company.

Inspectors then proceeded to the inspection of the production areas for lumefantrine and for artemether as well as the finished API storage areas.

Documentary review was also performed at the end of the day. The self-inspection procedure was consulted as well as the GMP training of two operators.

Documents that were requested the day before were reviewed in areas such as raw material purchase contracts, deviations, cleaning records, logbooks for manufacturing equipment and batch distribution records.

According to an employee interviewed, the maintenance of the equipment was covered by the plan of each individual workshop. For calibration, there was one independent department which covered all of the different buildings.

Training records : the approach to GMP training was consulted for selected members of staff.

### Day 3

The full manufacturing process for artemether and lumefantrine was reviewed through the study of a full sequence of batch records. The associated CofAs were reviewed for each batch.

The general approach for equipment cleaning was reviewed. It included different SOPs and the available reports, for example justifying the company's cleaning intervals.

The filter cleaning and maintenance logbooks were checked.

There was no traceability between the supplier certificate for the titanium stick (batch number 080421045) used in filter F625 (lumefantrine IP) and the maintenance logbook recording the last change dated of 15/08/2010.

The utilities for building 218 and 207 (HVAC and purified water systems and control room for the monitoring of the AHUs in building 218) were inspected.

At the end of the day, the following documents were reviewed:

- the Change Control procedure QAP000024-7 and the change control recall M10013002 for the introduction of a new potassium borohydride supplier.
- the process validation VLD-VP207109 and report VLD-VR207219.

## Day 4

Additional documents supporting the change control M10013002 "Step 1 experimental protocol and report" were examined (No. ER/EP207104). The associated interim long-term stability study report STP100312 undertaken on the commercial batch of artemether corresponding to this new supplier (batch No. 100301) was presented. The starting point of this long-term stability study was March 12, 2010 and results for 3 months and 6 months were found to be acceptable.

The QC laboratory was inspected afterwards with examination of raw data for selected batches of raw materials and APIs. The general training approach and qualification for QC personnel was reviewed as well as one individual record.

The calibration department was examined. A presentation of the 2010 calibration plan for both 207 and 218 and verification of calibration of key equipment related sensor (temperature and pressure) were checked.

The maintenance office was visited in order to review some logbooks related to the maintenance of major pieces of equipment for buildings 207 and 218.

The presentation of the general approach followed by the company when restarting the production of artemether after a prolonged interruption, as well as the corresponding records (January 2010) were consulted. The training records and evaluation made before January 2010 was examined. The qualification plan and report for the reactor R302 building 207 located after its breakdown and reinstallation in the building.

Cleaning validation of equipment in workshop 220 after the C8 product protocol No VLD-CP-220-201 and the associated report (VLDCS-220-201) was inspected. In support of these documents, procedure SOP -VTP-000015 called "cleaning validation concept for API's and Intermediates" and procedure SOP VTP-000016 defining the calculation of limits for cleaning validation were also reviewed.

The stability facilities and reserve/retention samples storage areas were visited. The microbiological laboratory, however, was not inspected.

A series of batches (artemisinin, DHA, artemether crude, artemether IP and artemether DS10) was randomly picked and the batch production records were inspected.

The nitrogen production plant was visited in Unit 218. It contained an Ingersoll Rand air compressor.

Day 4 ended with the closing meeting where general impressions regarding compliance with the WHO GMP's for API's and other guidelines were discussed with the company, as well as the specific observations for day 3 and day 4.



## **2.1 QUALITY MANAGEMENT**

Quality management was adequately implemented. One deficiency regarding the management of the release of one batch prior to the closing of change control was noted. Furthermore, some improvement was necessary with regards to investigations related to deviations and complaints (root-cause analysis, preventive actions). The company proposed revised SOPs to address these issues.

## **2.2 PERSONNEL**

Personnel qualifications were adequate, as well as personnel hygiene and gowning for the different areas inspected. Training was well performed in general.

## **2.3 BUILDINGS AND FACILITIES**

In general buildings and facilities visited were appropriately designed for the different activities performed. The housekeeping was excellent as well as the maintenance.

Some minor issues were raised regarding the utilities. Namely, monitoring of pressure cascade between rooms of the clean area of building 218 was performed by operators through a computerized systems, but there was no automatic recording and no alarm system in place. Manual recording directly from the data values on the screens was performed twice per shift. Inspection of the qualification of this system was not covered due to a lack of time.

The water treatment unit No. 4 was state-of-the-art. Nevertheless, a few minor deficiencies were noted regarding start-up after extended shutdown periods and periodic maintenance.

## **2.4 PROCESS EQUIPMENT**

The process equipment was well designed with adequate space to accommodate the flow of personnel and materials. The identification system that was in place for the equipment was robust, with the exception of some minor deficiencies related to the identification of equipment status. Some deficiencies were also noted regarding the cleaning practices (including for ancillary equipment, such as addition vessels) and a lack of evidence to support the cleaning approach being used for major equipment.

The calibration department was inspected along with the procedures in place, records of certain key in-process measuring devices and were found to be adequate. Traceability to standards was well maintained.



## **2.5 DOCUMENTATION AND RECORDS**

The executed batch records (production and analytical) were adequately detailed and covered all operations. The logbooks in the different workshops were well maintained, as well as the calibration status of different measurement devices.

Deficiencies were noted with regards to the batch numbering system, which could potentially lead to confusion between products and different intermediates. This was subsequently addressed.

Issues were also noted with regards to the specifications for acetone and nitrogen, a processing aid but these were addressed through the company's corrective and prevention actions.

## **2.6 MATERIALS MANAGEMENT**

Materials management was found to be satisfactory except for some minor deficiencies related to supplier qualification and to the packaging of one starting material, which were addressed in the company's corrective and preventive actions.

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

Production operations and in-process controls were well managed and designed. The in-process sampling practices were considered to be acceptable, as well as the blending practices which were used for the APIs.

The measures in place to avoid contamination and cross-contamination seemed to be acceptable throughout the units inspected except for the handling of the drying trays. This issue was corrected by the company.

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

The packaging operations of final API's were designed in order to minimize the risk of contact with the environment and personnel.

The labelling system was found to be deficient for intermediates but was corrected by the company.



## **2.9 STORAGE AND DISTRIBUTION**

The warehousing and distribution practices and procedures were adequate in general. The maintenance and monitoring of the storage conditions was well performed.

## **2.10 LABORATORY CONTROLS**

The quality control laboratory was good. The equipment was very well maintained. Training and qualifications of the staff were found to be relevant and very well recorded. The stability facilities and reserve/retention samples ensured that materials were stored under appropriate conditions at all times.

## **2.11 VALIDATION**

Process and cleaning validation was acceptable. Nevertheless, some minor issues were raised which were addressed by the company. Analytical validation was not covered.

## **2.12 CHANGE CONTROL**

The general procedure managing change control was found adequate. Nevertheless, one change control which was examined showed a deficiency in their system. The company corrected this issue.

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

The only recovered material was isopropanol. An issue was raised on this process and was corrected by the company.

## **2.14 COMPLAINTS AND RECALLS**

Only minor complaints and few returns were noted. There was no recall recorded up to the date of this inspection.

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

The contract (dated 9.11.2007) for the outsourcing of X-ray testing was examined and was found to be acceptable. The outsourcing of some calibration activities was not examined.



### **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, *Zhejiang Medicine Co. Ltd.*, located at 98 East Dadao Road, Xinchang, 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.