

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

Name of Manufacturer	Chongqing Holley Wuling Mountain Pharmaceutical Co Ltd
Unit number	N/A
Production Block	Buildings 1 and 2
Physical address	No 108, Southern Jinyuan Road, Banxi Light Industrial Area, Youyang City, Chongqing, 409800, PR of China
Contact person and email address.	Mr.YU Ning (Michael) YU Ning (Michael): michael.yu@holley.cn
Date of inspection	8 - 11 December 2014
Type of inspection	Follow up Inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Dihydroartemisinin (APIMF239) Artemether (APIMF268).
Summary of the activities performed by the manufacturer	Manufacture and control of APIs.

Part 2: Summary

General information about the company and site

Chongqing Holley Wuling Mountain Pharmaceutical Co., Ltd was established in 1986. A new site was built at No.108 Southern Jinyuan Road, Banxi Light Industrial Area of Youyang City and construction started in May 2011. This site is 15km away from the original old site which was located in Zhongduo County, Youyang City, Chongqing, China. The site specialises in the manufacture and control of a range of APIs derived from Artemisinin. The company supplies a number of major pharmaceutical companies with Artemisinin or its derivatives.

The company also manufactures a Chinese Herbal cough syrup on site, but this was not part of the WHO inspection.

Chongqing Holley is a member of the Pharmaceutical Division of the Holley Group of companies. This group comprised a number of companies, some of which used unofficial names in documents.

History of WHO and/or regulatory agency inspections

This was the second WHO inspection of the new site and was a follow up inspection to the April 2014 inspection. This new site was licensed and inspected by the local FDA in December 2013. It has not yet been inspected by another foreign drug regulatory authority. The old site had been inspected by WHO in 2005 and 2010.

Focus of the inspection

The inspection focused on the production and control of Dihydroartemisinin (APIMF239: DHA) and Artemether (APIMF268) APIs. The inspection covered all 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

Review of Site Master File

Review of Significant Changes since April 2014 Inspection

Review of progress against CAPA Plan from April 2014 Inspection

Quality Management: Recalls/Complaint Handling/Deviations/CAPA/Change Control/Supplier Qualification/Internal Audit/OOS and OOT/Rework and Reprocessing/Product Release/Label Control/Training Policy/Definition of Critical Process Parameters

Technical Agreement with Material Supplier

Warehouses: Warehouses 2/3/4 Artemisia leaf storage

Warehouse 1/Solvent storage – drums and bulk tanks

Production: Buildings 1 & 2 –Artemisinin and Dihydroartemisinin (DHA) and

	Artemether uncontrolled and controlled areas
Utilities:	Purified Water system/ Air handling units in Building 2
Validation:	DHA and Artemether Process Validation/Site Validation Master, Plan/Analytical Methods Validation, Cleaning validation
QC Laboratory:	Chemical and Physical Lab - Sampling and sample handling, work allocation, specifications and test methods, SOPs, logbooks, records, worksheets and test reports, stability program, evaluation of results, release and rejection procedures, chemicals and reagents, reference standards, retention samples, equipment, instruments and devices, Stability Chambers
	Microbiology Lab – Facility, media preparation, test procedures and results
Equipment	Qualification/Calibration
Quality management	Product Quality Review/Environmental Monitoring

2.1 QUALITY MANAGEMENT

General

The quality management system was established, documented and implemented. The site organizational structure was reviewed and was acceptable in general. A Quality Manual was supported by Quality Policies which in turn were supported by SOPs. The Manual and Policies contained general statements concerning quality matters. Site Master Files (March 2014 and November 2014) were presented and reviewed. The Organisation Chart of the company was available and reviewed. The Quality Assurance department was independent from the production department, but staff numbers were relatively small. The production and quality control procedures were defined and were generally followed.

Responsibilities of Quality department

Job responsibilities of the Quality Unit were discussed and reviewed.

Responsibilities of Production department

Job responsibilities for the Production Manager and the Manager of Artemisinin Extraction, Building 1, were briefly reviewed.

Internal Audits

Internal audit requirements were described in a SOP. Audits were required to be performed annually. The schedule for 2015 was briefly reviewed. A CAPA had been developed after the inspection and was considered acceptable.

Product Quality Review (PQR)

PQRs were conducted on an annual basis according to the SOP. PQRs for DHA and Artemether for 2013 were reviewed. There were no product recalls, no complaints, no returns, no OOS results and no reprocess and reworking batches were reported. In this annual PQR, two deviations and one change control related to an upgrade of the BMR were recorded. The stability study was performed according to the established procedure.

The DHA annual product quality review of 2014 was reviewed. There were no deviation, no recalls, no complaints, no reprocess or reworking, no change controls and no returns. In this annual PQR, a stability study showed the quality was within specification for the 2 year shelf life.

Deviation Management

Deviations were handled according to a SOP. Deviations were classified as critical, major and minor. The 2014 deviation log book was reviewed and discussed with the company during the inspection.

CAPA management

The procedure for CAPAs was described in the written SOP. However the procedure was not always followed. CAPAs to this observation were made and considered acceptable.

Quality risk management

There was a SOP which described the procedure for quality risk management. Process failure mode and effect analysis (Process FEMA) was used for risk assessment of DHA and Artemether manufacturing. The reports were reviewed and considered acceptable in general.

2.2 PERSONNEL

Personnel qualifications

According to the SMF, key personnel were suitably qualified with appropriate tertiary qualifications and experience in the manufacture of API products.

Training

Training requirements were described in a SOP. This SOP applied to all employees. The training curriculum template contained a comprehensive list of training topics. Department managers would select relevant topics for each of the members of their departments to attend. Training was assessed by a written test. Observed operation assessment required to be 100% compliant. A training file was reviewed; the training method was initial training. There were no details describing if this had been done by

way of lectures, self-learning or observed operation. There had been no change to the training procedure since the last inspection.

The training plan for 2014 was reviewed. All employees were required to attend topics on the Annual Training Plan performed for ICHQ7a training.

Personnel Hygiene

Overshoes, gowning and hand washing were required in areas where product was exposed. Direct contact with intermediates or APIs was avoided.

2.3 BUILDINGS AND FACILITIES

Design and construction

Buildings were constructed of masonry with finishes appropriate to the activities carried out. There were four API production buildings, three Artemisia dry leaves warehouses, one comprehensive warehouse, two solvent storage areas, one office building and other auxiliary structures. Buildings and facilities used in the manufacture of the API were essentially dedicated to the APIs inspected.

Production buildings 1 and 2 were designed, and constructed to facilitate cleaning, maintenance and operations and were generally appropriate to the type and stage of manufacture.

There was adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. QC areas and operations were separated from production areas.

Utilities

Areas for the final processing and packaging of Artemisinin, DHA and Artemether were provided with filtered air to achieve a Grade D standard. Recent air quality results were reviewed and achievement of grade D was confirmed.

An AHU for the Artemether controlled area was inspected. Readings on Magnahelix gauges installed across the filters were recorded every three hours, following an SOP. The filters in the AHU were confirmed as G3 and F7. HEPA filters of 0.5 micron were installed above the ceiling of each room.

Water

The Purified Water System which supplied Building 2 was inspected. IQ and OQ documents were available and were generally satisfactory.

PQ studies now included a Phase 3, started in July 2014 after the last WHO Inspection.

Lighting

Lighting levels were minimally adequate in most areas.

Sewage and Refuse

Handling of waste appeared adequate. No uncontrolled waste was observed. This subject was only briefly mentioned during the inspection.

Sanitation and Maintenance

The areas visited were clean and well maintained in general. Cleaning and sanitization were performed according to documented procedures using materials approved by QA.

2.4 PROCESS EQUIPMENT**Design and Construction**

Equipment used for the APIs within the scope of the inspection was generally of a good standard and suitable for intended use. Where necessary to prevent cross-contamination, equipment for manufacturing DHA and Artemether were dedicated. Material of product contact was 304 grade stainless steel. Some equipment had been transferred from the old factory, but appeared to be acceptably maintained. IQ and OQ documents for transfer of a DHA centrifuge were reviewed and suitable equipment checks were noted.

Equipment Maintenance and Cleaning

There was a general SOP for equipment maintenance “Maintenance Plan for Equipment”. In addition, there were specific SOPs for each type of equipment such as 1000 litre reactor vessels. Reactors were on a three-month preventative maintenance schedule which appeared to be generally achieved. Tasks included checking the rotation of the agitator and the level of oil in the agitator drive gearbox. Equipment cleaning was with solvent and water with no other cleaning agents used. Visual examination was supported by use of rinse and swab samples for cleaning validation. The cleaning procedure for containers was reviewed and found acceptable.

Calibration

The list of all instruments calibrated was reviewed and appeared extensive. There were three classes. Class A was on a 6-month schedule, Class B on an annual schedule and Class C were not routinely calibrated. Classes A & B were calibrated according to State requirements by Chongqing Chenyang Measuring Quality Analysis Centre. Records for an Analytical Balance, a Pressure Gauge and a Temperature gauge were reviewed and were generally satisfactory.

Computerized Systems

No computer systems were used in the warehouse and in production. All steps were manually operated and recorded. There was no central computer system in QC although individual pieces of equipment, such as the HPLC had their own dedicated recording and calculating systems.

2.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

The preparation, approval and control of documents were via the SOP “GMP Management Procedure”. Activities were generally documented in SOPs. These were approved versions and were reviewed on a three year cycle. Provisions regarding the computer generated data and chromatograms had been added to control those data.

Product specifications were generally according to the International Pharmacopoeia or to an in house/customer standard.

There were an extensive number of controlled equipment drawings and utilities schematics available.

Batch production records (batch production and control records)

The in-process BMRs and the completed BMRs reviewed had been properly completed and were acceptable. BMR and BPR for Artemether were reviewed and were acceptable.

Equipment cleaning and use record

Equipment was required to be cleaned according to SOPs specific to the type of equipment. All items of equipment were dedicated to specific products so procedures were concerned with batch-to-batch cleaning.

Records of major equipment use and cleaning showed the date, time and product processed with the equipment. These details were recorded in log books, controlled by production and followed the appropriate SOP.

Laboratory Control Records

Testing records consisted of hand written sheets of paper each individually numbered. Test methods were laboriously transcribed onto these sheets and the opportunity for errors was observed and discussed.

2.6 MATERIALS MANAGEMENT

General controls

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available.

The Supplier Qualification Procedure was reviewed, and found acceptable in general, with only minor issues noted. Approved vendor lists for general raw materials, key raw materials and packaging materials were available, but were only updated on a 6 months cycle.

Solid starting raw materials were received in Warehouse 1. A room was dedicated for sampling materials, but this room had no air protection for sampling of solid raw materials and opened directly onto a “dirty” warehouse corridor. Packaging materials, such as bags for product, did however receive clean air protection. Finished products were stored in allocated storage rooms. For example, Artemether was stored in a cool store controlled below 20°C/75% RH. This room had been temperature mapped, but some abnormal temperature “cycling” was observed. Separate rooms were allocated for recalled materials, returned materials and rejected materials. All were kept locked and all were empty at the time of the inspection.

Artemisia leaves were received into Warehouses 2, 3 and 4. Only warehouse 2 contained a stock of leaves at the time of the inspection. Some issues of kilogram quantity and bag numbers on the few labels present on the stacks of bags were observed and discussed.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Chongqing Holley Wuling Mountain Pharm manufactures both Artemisinin and its derivatives: DHA, Artemether and Artesunate on the site. There were no toxic or hazardous substances (including β lactams) handled on the site.

Production operations

Production operations in Building 1 and Building 2 were reviewed and generally found acceptable. Reactors were appropriately labeled with the batch in progress and the associated batch documentation was up to date.

Time limits

Time limits were specified in the BMR where necessary and appeared to be followed without variation. Holding time studies for API and intermediates at isolation stages were reviewed and considered to be generally acceptable. The company was in the process of validating an extended holding time for crude DHA.

In-Process Controls

In-process controls were conducted on the second floor of Building 2. Tests were conducted by production personnel after they had been trained by QC staff.

Blending of batches of Intermediates

The company blended different lots of delivered leaves to achieve a claimed standard potency. Resulting crude Artemesinin lots were blended to make up weights for processing onto finished material.

Contamination Control

Processing operations were performed in closed vessels, but many loading and unloading operations were performed manually through open vessel hatches. There was no thought to use of localised extraction, but the risk was small because of space between vessels and the API products were essentially all derivatives from the same source starting material. Grade D air was supplied to all API finishing areas.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging materials

Packaging materials were purchased from approved suppliers and placed in quarantine before sampling, testing and release by QC. The storage and labeling of these materials was acceptable. Aluminium laminate or polyethylene bags were the primary contact material with the API.

Packaging and labeling operations

Packaging and labeling was performed in areas dedicated for this purpose. These areas were appropriately designed and classified, and routinely monitored.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures

The company had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Appropriate hand written records for stock and distribution were maintained.

The final products of DHA and Artemether were stored in a controlled room under conditions which did not exceed 20°C and RH 75%. This room had been temperature mapped since the last inspection. The intermediate DHA and Artemether were stored in a cold storage room under the temperature 2 to 8⁰C.

Distribution procedures

Finished APIs were packed in sealed laminate or polythene bags and distributed to customers in standard plastic containers. Distribution processes and routes were not discussed in this inspection.

2.10 LABORATORY CONTROLS

General controls

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

There were dedicated rooms for activities like sample receipt, wet chemistry, instrumentation, hot areas etc. The labs were clean and well maintained. There were adequate pieces of equipment with up to date calibration status.

Testing of intermediates and APIs

Sample receiving and distribution were inspected. The sample receiving procedure was acceptable in general. QC testing was conducted as specified in the relevant specification and according to documented test methods. Samples for testing were kept in a designated area. Analytical worksheets were page numbered, but not sequential and could be subject to unauthorised replacement. All details on worksheets were laboriously hand written including details of test methods.

The access control and data security of HPLC software was briefly reviewed. It was stated that manual integration and re-integration were not required and no procedure was available.

The Chinese Pharmacopoeial reference standard of Artemether was used as primary reference substance to prepare the working standards according to the written documents. International Pharmacopeia Reference substances were now available for DHA and Artemether, but only a minority of official Reference Standards for Related Substances were available. It appeared that limited effort had been made to obtain these latter Related Substances.

Stability monitoring of APIs

The long term stability samples were taken according to the defined program/protocol and stored in long-term conditions of 25°C/60% RH. The records for DHA and Artemether batches in the stability chamber were briefly reviewed. The chambers were stated to be connected to emergency generators for possible power outages.

The stability study protocol for crude DHA was reviewed. The three validation batches of Artemether were under study.

Reserve/retention samples

There was a designated temperature controlled room for storage of retention samples. Access to this area was restricted. A sample of each batch of API manufactured was kept there. Retention samples were stored in container systems that were comprised of the same materials as those used for the final API.

Handling of out of specification (OOS) results

An OOS handling procedure was available. The OOS log book 2014 was available for inspection. An OOS regarding the clarity testing was reviewed and discussed.

Microbiology Lab

The media preparation process was reviewed and issues regarding location and autoclaving were noted. The autoclave for media sterilization and destruction was not equipped with suitable cycle recording systems and thus achievement of sterilization was questionable. The microbiological limit testing procedure for purified water was reviewed.

2.11 VALIDATION**Validation Policy**

The company's validation policy was described in a Validation Master Plan and a Product Validation Guideline document. These documents appeared to partially duplicate each other and rationalisation was suggested. This document required validation for new facilities, production equipment, utilities, systems, processes etc. Requirements for the qualification of equipment and utilities were included in the abovementioned Validation Master Plan. Re-validation was to be performed at 3 yearly intervals.

Process Validation

Process validation for the production of DHA and Artemether had been performed in July 2014. The process validation report was reviewed and had been generally conducted according to Protocol. The conclusion was based on a summary report of the three batches included and had been approved by all relevant personnel. The critical parameters of each manufacturing process had been specified and monitored.

DHA: (material code C002)

The Process Validation Protocol and a report concerned with DHA Crude and DHA were reviewed.

Artemether: (material code C003)

The Process Validation Protocol and the Report were reviewed. The validation was conducted in November 2012.

Cleaning Validation

Cleaning validation was performed according to a generic cleaning validation protocol, using solvents and water only. The equipment was dedicated. Acceptance criteria were defined for residues from any previous batch of the product. Cleaning validation for Artemether was performed in 2012. The cleaning validation protocol and the report were reviewed.

Equipment Qualification

Qualification of the DHA centrifuge (IQP and OQ) transferred from the old factory and the Purified water system were reviewed. Despite the age of the centrifuge, the IQ and OQ exercises had been generally well conducted and documented.

The URS, IQ, OQ and PQ protocols and reports for the Purified Water system were reviewed.

Validation of analytical methods

The testing methods for DHA and Artemether followed the International Pharmacopeia monograph. The method verification protocol and Analytical validation report for quantification of Artemether and the analytical method validation for determination of levels of DHA impurity were briefly reviewed. The testing data of the validation batch of Artemether were also reviewed.

2.12 CHANGE CONTROL

Change control was handled according to the SOP. Changes were classified as major and minor. The need to notify regulatory authorities was included in the procedure. As a CAPA to the previous finding, the process validation of DHA and Artemether had been performed in July 2014 after the production transferred from the old site to this new site and used its own Artesimisinin as starting material.

2.13 REJECTION AND RE-USE OF MATERIALS

Rejection of Raw Materials

Handling of rejected raw materials was adequately controlled by the SOP “Reception and management procedure for raw materials and packing materials”.

Reworking and Reprocessing

The SOP “Reworking and Reprocessing APIs” described reprocessing and reworking in different clauses. Reprocessed batches were identified by a suffix “a” to the batch number and were added to the long-term and accelerated stability programmes. Reprocess of returned APIs were assigned a new batch number.

Reworked batches were included in a concurrent validation study and new test methods developed as required. It was stated verbally that there were no reprocessed and reworked batches for the APIs within inspection scope.

Solvent Recovery

Management of Solvent Recovery was described in a SOP. For derivatives/finished API, e.g. materials made in Building 2, no recovered solvents were used.

For the extraction process each batch of recovered solvent was tested against the specification for new solvents. Solvents were recovered on a semi-continuous system and retesting was conducted at regular time interval.

Returns

The handling of returned materials was not reviewed at this inspection.

It should be noted that following QA evaluation, it was possible that returned products would be permitted to be reprocessed.

2.14 COMPLAINTS AND RECALLS

Product complaints were handled as per the written procedure SOP. The log book of 2013 was reviewed. There were no complaints since the last inspection.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

No contract manufacturers or laboratories were used for the inspected APIs by the company.

Calibration services were provided by the Chongqing branch of the State Meteorological agency. Calibration generally appeared to be achieved to schedule.

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, APIs manufactured at Chongqing Holley Wuling Mountain Pharmaceutical Co., Ltd located at No.108 Southern Jinyuan Road, Banxi Light Industry Area, Youyang City, Chongqing, 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 2 years, provided that the outcome of any inspection conducted during this period is positive.