

**Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient (API) Manufacturer**

PART 1: GENERAL INFORMATION

Name of Manufacturer	KPC Pharmaceuticals, Inc.
Unit	Phytochemistry Plant No.4 (PCP4) dedicated to Artemether
Physical address	No.141Chunyu Road, Wuhua Zone, Kunming, Yunnan Province, P.R.China
Date of inspection	16-18 November 2015
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Artemether - APIMF125
Production Lines	Chemical Synthesis
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished non-sterile APIs. No toxic or hazardous substances were handled or manufactured

PART 2

General information about the company and site

The KPC Pharmaceuticals, Inc. (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 3300 staff members.

The artemether API was manufactured in No. 4 Phytochemistry Plant (hereafter is abbreviated as “PCP4”), which was first commissioned in 2005. PCP4 is a dedicated plant for production of Artemether API (all process steps).

According to the company Site Master File (SMF) total number of employees involved in PCP4 operations was 185:

- 25 employees were involved in the Quality Management (QM) activities
- 62 employees were involved in the Quality Control (QC) activities
- 30 employees were involved in the production activities

History of WHO and/or regulatory agency inspections

The site was previously inspected by the WHO team in 2004 (PCP1), 2009 (PCP4 for artemether API) and in 2012 (PCP4 for artemether API).

Focus of the inspection

Inspection focused on the production and quality control operations related to the artemether - APIMF125.

Inspected Areas

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls
- Contract manufacturers (including laboratories)

PART 3: INSPECTION OUTCOME

3.1 QUALITY MANAGEMENT

Principles

In general, a system for managing quality was established, documented and implemented. The quality unit was independent of the production department. The person responsible for release of intermediates and APIs was specified. Materials were released by the quality unit after satisfactory evaluation.

The site consisted of several plants/workshops; “Plant QA person” was appointed in each plant.

The Director of Quality was also Qualified Person (QP). The job description of Director of Quality was discussed. According to the job description Director of Quality was responsible for:

- Approval of documents/SOPs
- Approval of standard test procedures (STP)
- Approval of quality specifications and any other related quality documents
- Approval of change controls (CC)
- Approval of suppliers
- Approval of 3rd party tests
- Approval of contract manufacturers
- Make sure that raw materials, packaging materials and intermediates confirm quality standards
- Make sure that finished product batch production records (BPRs) are discussed before product release
- Supervise facilities and equipment maintenance
- Make sure that validations and qualifications are carried out on time, approval of validation /qualification schedules and reports
- Make sure that internal audits are carried out
- Make sure that analytical tests are carried out according to the STP
- Make sure that complaints are investigated and CAPAs implemented
- Make sure that stability testing is carried out
- Make sure that PQR is prepared on time
- Make sure that deviations, out of specifications (OOS) and out of expectations (OOE) are investigated and CAPAs implemented
- Make sure that QA and QC personnel are appropriately trained
- Responsible for finished product release
- Responsible for recalls

Delegations of the QP responsibilities were not specified in the job description; however delegations were specified in the Quality Assurance (QA) Manager job description.

The QA manager job description (responsibilities) was discussed. According to the job description QA Manager was responsible for:

- Raw materials, intermediates and finished product release on behalf of the QP
- Make sure that raw materials, intermediates and finished products confirm the specifications
- Make sure that BPRs contains all information
- Organize QA monitoring of the production process
- Make sure that quality system documents are updated
- Make sure that validation and qualification are carried out on time
- Supplier audit and assessment
- Contract production and quality audits
- CC and deviation investigation
- PQRs
- Internal audits
- Complaints and adverse drug reactions (ADR) investigations
- QA staff training
- Product recalls

Job description of Head API plant was discussed. According to the job description Head API plant was responsible for:

- Production planning
- Make sure that production operations are carried out following GMP
- Make sure that Product quality is confirmed
- Make sure that approved production and storage procedures are followed
- Make sure that BPR/BPP are complete and discussed
- Equipment maintenance
- Qualifications and validations
- Training and continuous training
- Improving production process
- Safety

Internal audits (self-inspection)

The document “GMP: self-inspection” was discussed.

The internal audit team was defined by the QA manager for individual internal audits. Teams were cross functional. According to the SOP the following items were covered during the internal audits:

- Personnel
- Facilities
- Equipment
- Materials including packaging and labelling
- Production
- Qualification and validation
- Document management
- Production

- Quality control
- Quality assurance
- Contract production/testing

Internal audit was performed at least every 6 months according to a check list. After the audit report was written and deficiencies observed during the audit were listed. Deficiencies observed were recorded in the report section “Conclusion”. Deficiencies were listed in the corrective action and preventive action (CAPA) plan by the team, afterwards CAPAs were proposed by audited department, evaluated by QA Manager and approved by the QP. Audit findings and corrective actions were documented and reported to the top management.

Product quality review (PQR)

The SOP “Annual Product Quality review” was discussed. The PQR covered January – December. According to the SOP, PQR should be finished by the first quarter of the next year. Separate PQRs were prepared for different product codes.

The following items were included in the PQRs:

- Product information
- Key starting materials (KSM)
- Intermediates
- Finished API
- Deviations
- Change controls (CC)
- Stability
- Complaints
- Recalls
- Returns
- Validation
- CAPAs
- Regulatory status
- Contract manufacturing and testing
- External audits
- Critical in-process control and critical API test results
- Batches that failed to meet established specifications

PQR 2014 for artemether code XX was discussed:

Quality Risk Management (QRM)

The SOP “Quality Risk Management” was discussed. The SOP was applicable for:

- Facilities
- Production
- Equipment
- Qualification/validation
- Rework / reprocess

- Process parameters
- Changes / deviations (if required)

According to the SOP, Failure mode and effects analysis (FMEA) was used as risk assessment (RA) tool. 1 to 5 scoring system was applied to assign risk priority numbers.

The RA No XX “Artemether API quality risk assessment” was discussed. RA was carried out on 20 March 2015. FMEA was not used for this RA. The RA covered production steps from Step 3 recrystallization.

The RA No YY “Heating, ventilation and air-conditioning system quality risk assessment” was discussed, FMEA was applied.

Corrective actions and preventive actions (CAPA)

The SOP “Corrective actions and preventive actions” was discussed. This SOP was applicable to all departments and covered:

- Materials receipt, sampling and storage
- Production process
- Testing
- Out of specifications (OOS) / out of expectations (OOE) / out of trends (OOT)
- Audits and self-inspection
- Environmental monitoring (EM) and purified water (PW) monitoring
- Facilities, equipment and measuring instruments
- Validation
- PQR
- Complaints / recalls
- RA
- Any other management process

As an example, document “Self-inspection CAPAs plan” was discussed. The scope of the self-inspection was QA and QC departments. CAPA follow up report No XX was discussed. CAPAs implementation was checked and approved by QA.

3.2 PERSONNEL

Personnel qualifications

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

Personnel hygiene

The SOP “Personal hygiene” was discussed. Smoking, eating, drinking, chewing and the storage of food and personal medicines and wearing jewellery were restricted to certain designated areas separate from the manufacturing areas and laboratories. Personnel with an infectious disease or who have open lesions on the exposed surface of the body were not allowed to be in direct contact with the product. Good sanitation habits were observed on site.

Direct contact with intermediates or APIs was avoided. Personnel were wearing clean clothing suitable for the manufacturing activity they were involved in.

Training

Training programme 2015 for PCP4 production personnel was discussed. Trainings were planned either for the whole staff (incl. housekeeping personnel in the „general“ production area) or for defined groups. Lists were available, assigning people to groups. Individual files and training-specific records were maintained.

The SOP describing organisation of training specifically for the QC personnel was available. The SOP described practical assessment of new analysts. Comparative testing was applied (new analyst, experienced analyst); SOP established tolerance limits for comparative assay tests. Assessment form was filled for analysts; the form also indicated methods for which the analyst was approved for independent work. Records for a new analyst were discussed and found to be adequate.

According to the SOP, 2 months off work triggered recertification. Analysts were assessed for operations annually (not comparative testing).

Consultants

N/A

3.3 BUILDINGS AND FACILITIES

Design and construction

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Buildings and facilities had adequate space for the orderly placement of equipment and materials. The flow of materials and personnel through the buildings and facilities were designed to prevent mix-ups or contamination. Laboratory areas and operations were separated from production areas.

PCP4 did not have its own QC laboratory (apart from in-process controls); testing was performed in the QC laboratories common for the whole site.

Label storage room and key starting material (artemisinin) dispensing room were separated from the PCP4 production areas. Some production aids were also stored in the label storage room; the labels however were kept in a locked cabinet.

Utilities

Utilities were qualified and monitored. Adequate HVAC systems were provided. HVAC systems were designed to minimize risks of contamination and cross-contamination. Permanently installed pipework's were identified.

Heating, ventilation and air-conditioning system (HVAC)

One air handling unit (AHU) was serving the air to the clean rooms. Air was recirculated, fresh air intake was 20 - 30%.

HEPA filters were installed in the clean rooms. Pressure differentials were monitored on the filters. Filters were cleaned in a dedicated room by potable water and then dried. Spare filters were available and stored in a separate room. AHU was observed to be well maintained. HVAC system re-qualification was carried out every year. AHU was equipped with alarm system and AHU performance (T, RH and pressure differentials) was continuously monitored by the computer system.

HEPA filter leak tests were outsourced; the Company had adequate information about the testings. Pre-filters were monitored by the Company, pressure drop records were maintained by HVAC units.

Water

Purified water (PW) was produced by RO (pre-treatment prior to RO and UV treatment after RO). PW production room was inspected and found to be orderly. Adequate sampling points were provided and identified in the system. The Company stated that weekly ozone treatment was applied and covered the PW collection tank and loop (automatic process with ozone concentration monitor).

Nitrogen

Nitrogen gas was used in the direct contact with the product. The SOP “Quality management of liquid nitrogen used in artemether production” was discussed. Liquid nitrogen was delivered in dedicated tankers. Sample of the delivered nitrogen was taken from the tanker. After QC release, nitrogen was transferred to the liquid nitrogen storage tank; afterwards liquid nitrogen was converted to the gas phase and transferred to the gas nitrogen storage tank. Gas nitrogen was tested for oxygen %, QC released and CoA issued. Gas nitrogen was filtered via 0.45 µm filter and 0.22 µm. 0.22 µm filters were located close to the user points.

Containment

Highly sensitizing materials were not manufactured on site.

Lighting

Adequate lighting was provided in to facilitate cleaning, maintenance and proper operations.

Sewage and refuse

Not inspected

Sanitation and maintenance

Buildings used in the manufacture of intermediates and APIs were properly maintained and repaired and kept in a clean condition.

3.4 PROCESS EQUIPMENT

Design and construction

Equipment used in the manufacture of intermediates and APIs were of appropriate design and adequate size, and suitably located for the intended use. Equipment surfaces in contact

with raw materials, intermediates and APIs were made of materials that did not alter the quality of the intermediates and APIs. Major equipment were appropriately identified.

Equipment maintenance and cleaning

Preventive maintenance of production equipment was organised in a systematic manner. Schedules and procedures were established. Preventive maintenance of equipment system for synthesis step III was discussed. It was recorded on equipment-specific templates with relevant check-lists.

Equipment and utensils were cleaned according to written procedures.

Some SOPs for „daily“ cleaning and master records for „periodic“ cleaning were discussed. SOPs were in a more general wording, master records gave more detailed instructions for conducting the cleaning.

Calibration

Analytical balance No XX (range 14.49 mg – 220 g) verification/calibration was discussed. Date and time function on analytical balances was locked.

Computerized systems

Laboratory computerized systems had sufficient controls to prevent unauthorized access or changes to data. The records were available of any data change made, the previous entry, the person who made the change and when the change was made. Back-up system was provided.

Computerized systems were not used in production.

Maintenance

Production equipment preventive maintenance (PM) was organised in a systematic manner. PM schedule was available. PM was carried out according to equipment-specific check lists.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

Documents related to the manufacture of intermediates and APIs were prepared, discussed, and approved. Specifications were established and documented for raw materials, intermediates, packaging materials and finished API. Acceptance criteria were established and documented for in-process controls.

Master production instructions

Master production instructions had been established and appropriately approved.

Batch manufacturing records and packaging records (BMR/BPR)

BMR/BPR were prepared for each intermediate and API. Issuance of the BMR/BPR was controlled by QA. BMR/BPR were numbered with a unique batch number, dated and signed.

Laboratory control records

Standard test methods and analytical reports were available. Some laboratory records were discussed. The standard test method for low density polyethylene bags was discussed. The specification for “Artemether API” was discussed.

Out of specification

The SOP “OOS/OOE/OOT investigations” was discussed and was applicable to all tests, including raw materials and on-going stability tests.

3.6 MATERIALS MANAGEMENT

General controls

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. In the warehouse, materials were managed manually (no software).

The SOP “Supplier management” was discussed.

Suppliers had been classified into the following categories:

- Critical materials suppliers – level I
- Major materials suppliers – level II
- Minor materials suppliers – level III

The company used scoring system (1 to 5) to assess criticality of the suppliers.

The SOP “Supplier qualification” was discussed.

The Supplier qualification procedure included:

- Purchasing department informed about the new supplier
- Three sample testing
- Small scale trial in production
- Stability testing
- On-site audit or questionnaire, depending on materials

The following supplier qualification documents for the new supplier of artemisinin were discussed:

- New supplier approval form
- Six batches of artemisinin were received and tested
- Process validation using three batches was carried out in July 2014.
The Company explained acceptance criteria for new supplier validation as following: process parameters and quality testing results had to be within the routine limits.
- Stability studies were initiated on 10 August 2014.

The site audit was carried out in 2015 by the QA and chemist from PCP4. The following GMP topics were covered during the audit:

- Quality management system
- Training
- Facilities and equipment
- Production management
- Materials management

After the audit, the report was discussed by the QA head and approved by QP. Deficiencies were listed and the audited site submitted CAPAs; subsequently the new supplier was approved.

Solvents

Methanol (MetOH) was delivered in dedicated tankers. Sample of the delivered MetOH was taken from the tankers. After QC release, the solvent was transferred into one of the three storage tanks; the Company stated that deliveries were not mixed; new delivery was pumped into the empty storage tank. The Company refined MetOH prior to using it in the synthesis. Separate storage tanks were installed for the refined solvent

Solvents hose pipes (couplings) were dedicated and stored in a separate storage place in drums.

Receipt and quarantine

Materials were held under quarantine until they were sampled, tested and released for use. Approved suppliers list was available in the warehouse.

Sampling and testing of incoming production materials

Containers from which samples were withdrawn were labelled to indicate that a sample had been taken. Sampling of the key starting material (artemisinin) was carried out in the raw materials warehouse within a mobile laminar air flow box (LAF). Artemisinin under quarantine was stored in room No XX, released was stored in room No YY and rejected in room No ZZ. 100 % sampling was carried out for artemisinin; identity tests were carried out for all individual containers. T and RH requirements for the artemisinin warehouse were specified: T below 20 °C and RH below 75 %. T and RH were monitored and recorded twice per day.

Packaging materials warehouse had separate areas for quarantine, released and rejected materials. Primary packaging materials sampling was carried out the warehouse within a mobile LAF.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Raw materials for manufacturing of intermediates and APIs were weighed and measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices were of suitable accuracy for the intended use. Deviations were documented and explained. The processing status of major units of equipment was indicated.

Dispensing of artemisinin was carried out in PCP4 building, in a separate room.

Intermediate materials – dihydroartemisinin (DHA) and crude artemether – could be put on storage before subsequent processing; adequate storage rooms were provided in PCP4.

Blending batches of intermediates or APIs

The Company stated that blending was not applied to artemether code XX batches.

Contamination control/Environmental monitoring

The SOP “Monitoring of the clean room” was discussed. Environmental monitoring (EM) was performed by three methods – active air sampling, sedimental settle plates and contact plates. Sedimental settle plates were exposed for 4 hours. Alert and action limits were specified. Airborne particles (active air sampling) EM for all clean rooms and all change rooms and microbiology settle plates EM was carried out quarterly. T / RH and pressure differentials were monitored three times per day (once in each shift).

EM results were presented as trends. EM trends for 2014 were discussed for the artemether API packaging room. EM results were also presented as trends in annual summaries, prepared once per year.

Deviations

The SOP “Deviations” was applicable to all departments. Deviations were classified: critical, major or minor. Initial classification was assigned by the department where the deviation occurred, QA discussed the classification and confirmed the final classification.

Registers/logs were maintained separately for deviations related to QC, QA, PCP4, etc. QA issued deviation report forms to departments, maintained the registers and assigned sequence numbers to events.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

General

There were written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.

Packaging materials

Primary packaging materials were stored in the the general packaging materials warehouse. Primary packaging materials (low density polyethylene LDPE bags) were delivered in carton boxes. The SOP “Artemether dedicated packaging materials sampling procedure” was discussed.

Label issuance and control

Labels, including labels for intermediates, were obtained from printing houses as material/API-specific templates. Label templates were issued by a warehouse person upon working order from the production unit; working order had to include the in-house batch number assigned to the labels. During packaging operations the following batch-specific data were handwritten on the labels by operators:

- Product name
- Batch number
- Gross weight

- Net weight
- Tara weight
- Re-test date

Release labels were attached to the finished artemether API drums by QA personnel in the finished artemether API cold storage warehouse. QA personnel had the duty to check the product labels when attaching release labels.

Packaging and labelling operations

Packaging and labelling operations were not carried out during the inspection. The SOP “Packaging of artemether API” was discussed. Product labels were issued by the responsible person from the production. Product labels were attached to the drums by production operator and discussed by another operator. According to the SOP QA personnel should be presented during the packaging process. According to the SOP, one label was attached to the BPR.

3.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. The storage areas for incoming raw materials, starting materials and intermediate materials were inspected. Bin card system was used for materials reconciliation.

Distribution procedures

APIs were released for sale after QA approval.

Transportation of the finished API

The SOP “Material transportation” was discussed. Artemether API was used only for KPC own production operations:

- artemether solution for injection
- and transported within the KPC territory.

At the end of production in PCP4 artemether workshop, according to the SOP, transportation should be carried out within 30 minutes from the production to the artemether API cold warehouse. Transportation was recorded in “Transportation form” which specified batch number, time when API was placed on the transportation truck and time when the API was placed in the cold warehouse.

Finished products storage

Artemether API code XX for on-site use (as well as for distribution from the Company) was stored in a cold storage warehouse at T 2 °C – 8 °C. Temperature in the warehouse was monitored twice per day; records were made manually. Back-up power supply was provided. Temperature mapping study report No XX for the cold warehouse was discussed.

3.10 LABORATORY CONTROLS

General controls

Quality department was independent from the production department. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available.

Laboratory instruments

All the following laboratory instruments were stand-alone (not connected to server(s)): high performance liquid chromatographs (HPLC), gas chromatographs (GC), ultraviolet spectrophotometer (UV) and infrared spectrophotometer (IR).

Audit trails were enabled for all instruments.

Log books were available for all laboratory instruments.

Testing of intermediates and APIs

Intermediates and the finished artemether API were tested to determine conformance to specifications.

Validation of analytical procedures

The SOP “Validation and verification of analytical methods” was discussed. For the Pharmacopoeia methods the following tests methods were verified:

- Assay
- Related substances

The following parameters were verified for the analytical methods verification:

- Repeatability
- Intermediate precision
- Specificity (for RS)
- Robustness

The following parameters were verified for the analytical methods validation:

- Accuracy
- Precision
- Specificity
- Limit of detection
- Limit of quantification
- Linearity
- Range
- Robustness

Product release

The SOP “Arthemeter intermediate and finished API release procedure” was discussed. According to the SOP, QA should review BMRs and certificates of analysis for dihydroartemisinin, arthemeter crude and arthemeter API.

Certificate of analysis (CoA)

The SOP “Batch analytical records management” was discussed. According to the SOP, a person was appointed in the QA who was responsible for review of analytical test records. Review was carried out according to the check list. Checking of electronic raw data, including audit trails was part of the check list.

CoA`s were signed by QA and approved by the QP.

Batch numbering system

The SOP “Batch numbering system” was discussed.

Stability monitoring of APIs

The SOP “Artemether API stability studies” was discussed. Samples were stored at the following conditions:

- o 25 °C ± 2°C, 60% ± 5% (accelerated)
- o 5 °C ± 3°C (long term)
- o 5 °C ± 3°C (on-going)

Window periods between withdrawal of samples and analysis were specified ±5 days for long term and on-going stability studies. Window period for accelerated stability samples was specified not more than 2 days after the schedule.

One batch per year was placed for on-going stability monitoring programme.

Expiry and retest dating

The SOP “Retest of materials” was discussed. The retest period was established by QA based on the stability data for intermediates and APIs.

Reserve/retention samples

The SOP “Retention sample” was discussed. According to the SOP retention samples should be stored in simulated marketing packaging. API retention samples were stored in the refrigerator (2 °C – 8 °C) located in the QC laboratory.

According to the SOP APIs retention samples should be retained for 6 years and intermediates retention samples should be retained for 5 years. Artemether API and related intermediates retention samples storage was discussed during the inspection. Retention samples were stored in simulated packaging.

Good chromatographic practice

The SOP “Good chromatographic practice” was discussed. The SOP was applicable for the HPLC and GC tests. Before manual integration was applied, analyst should inform QC manager, QC manager should inform QA. Only after approval by the QA, manual integration could be applied.

Access rights were defined on equipment&software-specific forms (three user levels as a rule).

The SOP “Management of workstations of analytical instruments” required audit trails to be enabled. The Company stated that once audit trails were enabled, even the administrator level could not disable the function; this was not discussed during the inspection. The SOP specified that IT department had the highest access rights.

Reference standards (RS)

The SOP “Management of reference standards” was discussed. Separate room was provided for storage of RSs. Dispensing log was maintained.
Working standards were not used.

In the chemical laboratory only class A volumetric glassware was used. Glassware was received along with calibration certificates and calibrated upon receipt; re-calibration was carried on site after three years from the receipt.

Reagents prepared in the laboratory were properly labelled.

Back-up of electronic data

The SOP “Back-up pf electronic data” was discussed. The SOP covered data management for the whole site. Responsibilities were assigned to departments. In each department a person was appointed with general responsibility for the department. The site had its own IT department, responsible for overall security measures.

The QC department had a separate QC-level SOP which described organisation of back-up and storage of back-up copies of laboratory data. In the IT department, a person was appointed with specific responsibility for QC data.

Register/log was maintained on back-up operations conducted in QC.

Microbiological laboratory

Microbial limit tests were carried out in LAF cabinets.

Separate room was used for positive controls, microbial identification tests and sterility test. Endotoxin test (LAL test) was carried out in the Pharmacological laboratory (separate building at the site, under the same address).

The SOP “PW control in PCP4” was discussed. According to the SOP samples for chemical and microbiological monitoring should be taken and tested at least once per month. Samples from PCP4 were taken on Wednesday. PW trends were seen for 2014. Nutrient agar media and Rose Bengal agar II media instead of R2A media was used for PW analysis. The Company explained that R2A media will be required to be used for PW analysis when the new edition of the Chinese Pharmacopeia will come into force on December 1st 2015. The Company stated that R2A media had already been purchased and test method validation was completed.

3.11 **VALIDATION**

Validation policy

Validation master plan (VMP) was approved for each year. Spot checks, critical systems were covered.

Qualification

Qualification of production equipment was organised in a systematic manner. Schedules and procedures were established

The SOP „Qualification“ was discussed. The SOP covered equipment in all departments of the site.

Qualification Master Plans for the year were drawn separately for departments (e.g. site QC, PCP4 etc). PCP4 plan/schedule for 2015 was discussed.

For most equipment, regular (operational) qualification was conducted with 2 year intervals. Regular operation qualifications (OQ) of equipment system for step III was discussed. It had been done according to the schedule and recorded on equipment-specific templates incl. check-lists where relevant.

With regards to laboratory instruments, qualification reports of two HPLCs were discussed. Qualifications had been conducted by an outside company who was a local representative of the equipment provider. On spot checks, standard qualification tests had been performed.

Approaches to process validation

Validation report submitted to inspectors related to concurrent validation in 2012. It included all production steps. The Company explained acceptance criteria as following: process parameters and quality testing results had to be within the routine ranges and limits. It was noted though that a separate risk analysis had been conducted and reported in 2002 which included experimental data to justify the process parameters applied in routine production. On spot checks, no discrepancies were found between current parameters and 2002 data.

In 2014 a “validation for new supplier of the starting material” had been conducted. On spot checks with regards to production stage III, the process parameters for batch No XX matched with validation report from 2012 (crystallisation and drying time and temperature). The Company stated that processes had to be revalidated with 4 year intervals.

Cleaning validation

Clean equipment hold time study (microbiological) was conducted in 2015. Chemical validation was planned for 2016.

3.12 CHANGE CONTROL (CC)

The SOP “Change control” was discussed. Changes were classified: critical, major, minor. The recent SOP version established a new format for requesting and managing changes; need for validations and qualifications were clearly indicated.

3.13 REJECTION AND RE-USE OF MATERIALS

Rejection

The SOP “Dealing with unqualified products” was discussed. The SOP was applicable for rejection and reprocessing of dihydroartemisinin, artemether crude and finished artemether API. According to the SOP rejected materials should be labelled with red labels and stored in locked room under the QA control. Reprocessing was allowed for dihydroartemisinin, artemether crude and finished artemether API. According to the SOP, reprocessing was allowed to be conducted twice.

Reworking

The SOP “Artemether API reworking process” was discussed. According to the SOP, artemether API rework was allowed in case turbidity of solution was more than standard solution turbidity. In case of rework, a deviation should be opened, process validation performed and stability studies initiated. Till the date of inspection artemether API had not been reworked.

Recovery of materials and solvents

The Company stated that only fresh solvents were used in artemether production, and that processed solvents from PCP4 were not further used in other production units of the Company.

Returns

Returned APIs were identified, quarantined and stored in a defined place in the warehouse.

3.14 COMPLAINTS AND RECALLS

Quality-related complaints were recorded and investigated according to the written SOP. The SOP “Customer consultation and quality complaints” was discussed. A person from QA was appointed for dealing with complaints on a daily basis. QP had an overall responsibility for dealing with complaints.

Complaints register for 2014 and January 2015 – 30 October 2015 was discussed. Till the date of inspection from 2014 there were no complaints registered regarding artemether API.

The SOP “Product recall” was discussed. A person from QA was appointed for dealing with recalls. QP had overall responsibility for dealing with recalls. Recalls were classified as:

- Class I - recall within 24 hours
- Class II – recall within 48 hours
- Class III – recall within 72 hours

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Manufacturing operations were not contracted out.

Crystal modification test was contracted out to the XX. Quality test agreement between KPC and the XX was discussed. Contract defined responsibilities of parties. The agreement permitted the contract giver to audit the contract acceptor's facilities. The agreement specified that subcontracting of the work entrusted under the contract was not allowed without the contract giver's prior evaluation and approval of the arrangements.

The quality agreement with YY was discussed. The agreement specified responsibilities of the parties. The agreement permitted the contract giver to audit the contract acceptor's facilities.

PART 4: CONCLUSION

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, Artemether - APIMF125 manufactured at KPC Pharmaceuticals, Inc., Phytochemistry Plant No.4 (PCP4), located at No.141 Chunyu Road, Wuhua Zone, Kunming, Yunnan Province, P. R. China, 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.