

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

PART 1: GENERAL INFORMATION

Name of Manufacturer	CSPC Ouyi Pharmaceutical Co., Ltd
Site No	2 (Quality control laboratory)
Building No	8
Site address	No. 88 Yangzi Road, Economic and Technological Development Zone, Shijiazhuang, Hebei, 052160, China. FEI: 2000021110
Site No	3 (Production)
Workshop No	10 (Azithromycin API production)
Building No 15	The warehouse for in-coming materials, solvents and finished azithromycin API
Building 7-7	In-process Quality Control laboratory
Site address	No. 99 Hainan Road, High-Tech. Industry Zone, Shijiazhuang, 052165, China. FEI: 3010849184
Postal address	No. 88 Yangzi Road, Economic and Technological Development Zone, Shijiazhuang, Hebei, 052160, China.
Date of inspection	13 – 17 July 2015
Type of inspection	Initial inspection (new site)
Active Pharmaceutical Ingredient(s) included in the inspection	Azithromycin dihydrate API
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished APIs (sterile and non-sterile), freeze dried powder for injection, tablets, capsules, granules and dry suspensions

PART 2: SUMMARY
General information about the company and site

The CSPC Ouyi Pharmaceutical Co., Ltd is located in southeast of Hebei Province, and is

- 283 km south of Beijing and
- 1130 km north of Shanghai

The CSPC was founded in 1997 with four subsidiary companies including OUYI.

The CSPC OUYI was engaged in the manufacturing and marketing of the finished drug products and active pharmaceutical ingredients.

The CSPC OUYI manufactured the following APIs:

- Azithromycin
- Oxiracetam
- Tramadol Hydrochloride
- Indomethacin

and the following finished dosage forms:

- Tablets
- Capsules
- Dry Suspensions
- Oral Solutions
- Small Volume Parenterals
- Powder for Injection
- Lyophilized Powder for Injection

The site did not manufacture hormones, penicillin or cephalosporin products.

The Workshop 10 was built in 2012. The production line of azithromycin was dedicated, with independent heating, ventilation, and air conditioning system (HVAC) system and purified water distribution system.

According to the company presentation 61 staff members were involved in Quality assurance (QA) activities, 209 and Quality control (QC) activities and 1390 in production activities (site No3).

History of WHO and/or regulatory agency inspections

This was the first WHO inspection. The inspected site had been inspected by China Food and Drug Administration (CFDA) in July 2012.

Focus of the inspection

Inspection focused on the production and quality control operations related to the azithromycin API.

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. The systems for handling any deviations from the established procedures were in place and documented. Materials were released by the quality unit after satisfactory evaluation.

Responsibilities of the quality unit(s)

The main responsibilities of the Quality Department were:

- Ensure the quality system and maintain the system, review and approval procedures related to the GMP;
- Self-inspections - plan and report, corrective actions and preventive actions (CAPA);
- Batch release;
- Change control and deviations, out of specifications (OOS) investigation;
- Quality Risk management (QRM);
- Dealing with complaints, recalls and adverse drug reactions (ADR);
- Validation Master Plan (VMP) - approval and review of protocol/report;
- In process QA;
- Master production and test record control;
- Ensure that raw materials, packaging materials, intermediates, bulk products and finished products comply with the registered process and approved specifications;
- Annual product review (APR);
- GMP compliance inspections;
- Management review meetings;
- Review of stability studies;
- Review of annually training plan;
- Training implementation;
- Continuous improvements;
- Suppliers management.

The Qualified person was responsible for:

- Internal / external audits;
- Validations;

- Recalls;
- ADRs;
- Product release.

Responsibility for production activities

The main responsibilities of the Manufacturing Head were the following, but not limited:

- Quality management of production system;
- Ensure that products and manufactured and store in accordance with master batch records;
- Ensure that batch production records were reviewed and approved by QA;
- Ensure that facilities and equipment's were maintained according with the schedule;
- Ensure that validations were performed;
- Ensure that staff is trained and qualified;
- Making sure that production deviations were reported and evaluated and that critical deviations were investigated and the conclusions were recorded.

Internal audits (self-inspection)

The SOP "Self-inspection" was reviewed.

The self-inspection team leader was the QA manager. According to the SOP the following items were covered during the self-inspection:

- Quality management;
- Quality control;
- Materials;
- Production;
- Packaging and labelling;
- Facilities and premises.

The self-inspection was performed every 6 months according to the check list. After inspection the report was written and deficiencies observed during the inspections were listed. The deficiencies were classified as:

- Major
- Minor

The corrective actions and preventive actions (CAPAs) were proposed by the audited department, evaluated by the QA. Audit findings and the corrective actions were documented and reported to the management.

The self -inspection team member (supervisor – production technical department) training records were spot checked.

Product quality review (PQR)

The SOP "Product Quality review" was reviewed. The PQR plan was made on 10th December for the next year.

The regular quality reviews of the APIs were conducted and included:

- Product information
- Key starting materials
- Intermediates
- Finished
- OOS/out of trends (OOT)
- Deviations
- Change controls (CC)
- Stability
- Rejected materials
- Reprocessed materials
- Complaints
- Recalls
- Returns
- Validation
- CAPAs
- Regulatory status
- Contract manufacturing and testing
- Internal and external audits
- Critical in-process control and critical API test results
- All batches that failed to meet established specifications

The Azithromycin API was manufactured under two codes. One PQR was prepared covering the both codes. The Azithromycin API PQR for January 2014 - December 2014 was reviewed.

Quality Risk Management (QRM)

The SOP “Quality Risk Management” was checked.

The SOP was applicable for:

- New products
- Major changes
- Complaints and recalls
- Design of new facilities
- Validation
- Major deviation or OOS
- Regulatory review

The SOP listed the following QRM tools:

- Risk Filtering and ranking (RFR)
- Process Hazard analysis (PHA)
- Failure mode and effects analysis (FMEA)
- Failure mode, effects and criticality analysis (FMECA)
- Fault tree analysis (FTA)

- Hazard analysis and critical control points (HACCP)
- A hazard and operability study (HAZOP)

The FMEA was the tool which was used most frequently in practice.

Till the date of inspection 3 Risk assessments (RA) was carried out related to the

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

Good sanitation habits were observed on site. The direct contact with intermediates or APIs was avoided. The personnel were wearing clean clothing suitable for the manufacturing activity they were involved. Smoking, eating, drinking, chewing and the storage of food was restricted to certain designated areas separate from the manufacturing areas.

Training

The SOPs “Training plan & implementation”, “Training system and responsibility” and “Pre-job training” were checked.

The following training modules were provided for new employees:

- Induction training
- Department wise training
- EHS training
- On job training

The training effectiveness was evaluated by the pre-given selective questions and in some cases by the open questions. The training records for the new operator employed in Workshop 10 were checked.

The Qualified Person training records were also spot checked.

The SOP “Analysts training” was checked. After the induction training a new analyst had to perform parallel tests with experienced analyst, acceptance criterion was specified RD NMT 1%. Re-valuation of all analysts: theoretical and practical was done every year.

Consultants

One consultant was used. The consultant CV was available, consultant have sufficient education, training, and experience.

3.3 BUILDINGS AND FACILITIES

Design and construction

The 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. The 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. The laboratory areas and operations were separated from the production areas.

Utilities

Utilities were qualified and monitored. Adequate ventilation, air filtration and exhaust systems (HVAC) were provided. The HVAC systems were designed to minimize the risks of contamination and cross-contamination. The permanently installed pipework's were identified.

The Air Handling Units (AHU) consisted of two pre-filters: G4 and F6. HEPA filters H 13 were installed in the rooms. 20 % fresh air was provided for re-circulation.

Water

The purified water (PW) used in the manufacture of the APIs was suitable for its intended use, the action and alert limits were set up. The dedicated purified water distribution system was provided for the azithromycin workshop.

The new PW generation system had been installed in the workshop 10. The Performance Qualification (PQ) stage 1 and PQ stage 2 were completed and all values were well within the specification, the PQ stage 3 will last for one year which was described in the protocol, and all values relevant to the PQ will be tested and recorded accordingly. The PQ stage 3 was ongoing during the inspection. The summary (Trends) of the PW system Jan 2014 to July 2014 was reviewed.

The PW loop was routinely sanitized using 80 °C for water for 2 hours. The storage tank filter was changed every 3 months.

The dedicated purified water distribution system (loop) was provided for the Azithromycin workshop.

Containment

The highly sensitizing materials were not manufactured on site.

Lighting

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

Sewage and refuse

Not inspected.

Sanitation and maintenance

The 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

The equipment used in the manufacture of intermediates and APIs was of an appropriate design and adequately sized, and suitably located for its intended use. The major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified. Mainly closed systems were used in the production. Stainless steel or glass-line reactors were used for the production of Azithromycin API as appropriate to the process stage.

Equipment maintenance and cleaning

The schedules and procedures were established for the preventive maintenance of equipment. The equipment and utensils were cleaned according to the written procedures.

Calibration

The control, weighing, measuring, monitoring and test equipment that was critical, were calibrated according to the written procedures and an established schedule. Records of the calibrations were maintained. The current calibration status of the critical equipment was known and verifiable.

The SOP “Management of measuring instruments” and calibration plan were spot checked. This SOP was applicable for QC and production instruments. The annual calibration plan and weekly calibration plans were checked. Spot checks showed that the plan was followed.

Computerized systems

The laboratory computerized systems had sufficient controls to prevent unauthorized access or changes to the 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. The back-up system was provided.

The Computerized Process Monitoring system (SUPCON) was used to control XXXX reaction.

Maintenance

The SOP “Equipment Management” was reviewed.

The equipment were categorized as:

- A: Critical
- B: Major
- C: Minor

A and B type equipment were subjects of the preventative maintenance programme.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. The specifications were established and documented for raw material, intermediates, packaging materials and finished API. The acceptance criteria were established and documented for the in-process controls.

Master production instructions

The Master production instructions had been established and appropriately approved.

Batch production records and packaging records (BMR/BPR)

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

Laboratory control records

The standard tests methods and analytical reports were available. Some laboratory records were spot checked.

The SOP “OOS/OOT investigation” was checked.

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.

The SOP “Supplier Management” was reviewed.

The suppliers had been classified into four categories:

- A: Starting Material for APIs, APIs for Drug products, Primary Packaging Materials, Insert and card-boxes;
- B: Excipients, Desiccants, Solvents;
- C: Paper Drums, Chemicals;
- D: Outside packaging material.

The Supplier qualification procedure included:

- Sample testing;
- Trial in laboratory and small scale trial in production;
- Onsite audit or questionnaire.

The vendor qualification document for the new vendor for XXXX was reviewed.

Solvents

Seven organic solvents were used for the production of the APIs. Coupling hoses were provided by the vendor.

Receipt and quarantine

The materials were held under quarantine until they were sampled, tested and released for use.

Sampling and testing of incoming production materials

The containers from which the samples were withdrawn were marked to indicate that a sample has been taken. The sampling and dispensing of the key starting materials was carried out in the warehouse in separate room, protected from the environment. The primary packaging materials sampling plan was reviewed. The SOP “Sampling” defined primary packaging materials sampling plan according to Chinese standard GB/T2828 (identical to the “Military standard”). Sampling of the primary packing materials was carried out on the D class environment.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Production of the Azithromycin API used for manufacture of the solid dosage forms was carried out in four steps. The injectable grade API was manufactured in five steps.

In-process sampling and controls

The in-process sampling was done by the analysts; controls were carried-out in the Quality control laboratory.

Blending batches of intermediates or APIs

Blending of the batches was carried out according to the written SOP. The expiry or retest date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend.

The SOP “Final-product Batch Mix of Azithromycin” was reviewed.

Contamination control

The “SOP for clean area environmental monitoring (EM)” was checked. The SOP explained that:

- Non-viable particle size test should be performed quarterly for class D;
- Viable particle tests at rest and in operation should be performed quarterly for class D;
- T and RH every shift;
- Pressure differential every shift;
- Air volume, air change per hour and air speed – every year;
- HEPA integrity - every year.

The EM trends were spot checked and trends showed results good within specified limits.

Deviations

The SOP “Deviations” was reviewed. Deviations had been classified into the two categories:

- Minor and
- Critical

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

The primary packaging materials were stored in the warehouse in specific storage location.

Label issuance and control

The finished product labels were pre-printed labels. During the packaging operations only batch numbers and expiry/re-tests dates were manually printed.

Packaging and labeling operations

Not carried out during the inspection.

3.9 STORAGE AND DISTRIBUTION

Warehousing procedures

The inspectors visited warehouses; main warehouse and solvent farm during the inspection. The facilities were provided for the storage of all materials. The released, rejected and returned materials were stored separately. The quarantine areas were identified.

The inspected warehouse (WH) was temporary WH for storage of the starting materials, finished products and packaging materials. Starting materials were sampling in the special room, primary packaging materials were sampled in the D class, according to the Acceptable Quality Limit (AQL), and defects were defined.

Distribution procedures

APIs were released for the sale after the QA approval.

3.10 LABORATORY CONTROLS

General controls

The APIs were released for distribution to the third parties after they have been released by the quality unit.

The SOP “Product release” was checked. The batch manufacturing records (BMR) and batch packaging records (BPR) were reviewed by the workshop technician, workshop technical director – production and the QA leader. The analytical reports (AR) were reviewed by the QC deputy director and the QA authorized person for release. The audit trail review should be carried out before the product release. The “SOP for data integrity” was checked.

Testing of intermediates and APIs

The intermediates and API's, were tested to determine conformance to specifications.

Validation of analytical procedures

The method verification according to the Chinese Pharmacopeia method for Azithromycin - related substances was reviewed.

Certificates of analysis (COA)

The CoA's were signed by the QA authorized person. After the BMR/BPR, AR and CoA review, the QA person should send batch release certificate + CoA to the warehouse.

The SOP "Batch number and oddment" was checked.

Stability monitoring of APIs

The SOP "Product stability studies" was checked. The samples were stored in the following conditions:

- o 40 °C ± 2°C, 75% ± 5%
- o 30 °C ± 2°C, 65% ± 5%
- o 25 °C ± 2°C, 60% ± 5%

The window periods between withdrawal of samples and analysis were specified as well as the withdrawn samples storage conditions. One batch per year was placed for the long time stability monitoring programme.

The document "Azithromycin stability protocol" was checked. These were repeated stability studies. The stability studies were repeated because of the new supplier of the key starting material manufacturer.

The "Azithromycin stability report"- 12M was checked.

Expiry and retest dating

The SOP "Retest of materials" was reviewed.

The retest period was set-up by the Quality Department based on the stability data of APIs, excipients, raw materials and packaging materials. Generally retest frequency was specified every 2 years.

Reserve/retention samples

The SOP "Reserved samples" was checked. According to the SOP APIs with re-test dates should be retained for the period "re-test date + 1 year".

Reference standards

The Pharmacopoeia reference standards were used for impurities tests. The working standards (WS) were used for assay tests and were qualified against the Pharmacopoeia reference standards. The Azithromycin reference standards were stored in the fridge at the temperature (T) 2 °C to 8 °C. T in the fridge was recorded every 30 minutes and checked twice per day. The fridge had an alarm system, connected to the mobile phones. The WS were dispensed in the single use vials.

The SOP “Azithromycin working standard tests” was checked. All the tests according to the Azithromycin standard test method were carried out for the WS qualification.

The SOP “Standardization of WS” was checked. The WS standardization was carried out by two analysts, using different instruments. The usage of the reference standards were registered.

A number of High Performance Liquid Chromatograph’s (HPLC) were used in the QC laboratory: Waters with operational system - Empower 2 and Agilent with operational system Chemstation (Open lab). The Agilent HPLC’s were stand-alone instruments.

The HPLC columns usage was recorded. The columns were received along with the Certificate of Analysis (CoA) and upon receiving column performance was tested.

The SOP “Back-up and recovery of data” was checked. The back-ups were carried out once per month. The back-ups were done on the CDs; one set was stored in the QC office and one set in the Archive room at the site No 1.

In the Chemical laboratory only class “A” volumetric glassware was used. The glassware was calibrated every 3 years. The reagents prepared in the laboratory were properly labelled.

Microbiological laboratory

The microbial tests were carried out in 2 rooms. The separate room was used for inoculations, sterility tests (2 rooms) and LAL test. There were 3 autoclaves; one was used for the waste destruction. The liquid media’s were sterilized at 121 °C for 15 minutes. The growth promotion tests were performed for the each batch of the media and after the sterilization. The pH was checked before and after sterilization. The sterile media storage time was validated – 14 days. The environmental monitoring (EM) settle plates were exposed for 4 hours. It was said that the exposure time was validated. The APIs production rooms (D class) EM was carried out quarterly. The purified water (PW) analysis for supply and return loop sampling points were carried out weekly and for other user points monthly.

3.11 VALIDATION

Validation policy

The document Validation Master Plan (VMP) for Azithromycin” was checked.

The Operational re-qualification report for the specific Air Handling Units was checked. Re-qualification was performed on June 2015 following the ISO 14644 standard.

The following parameters were re-qualified:

- HEPA integrity;
- Air volume;
- Air exchange per hour;
- T and RH;
- Pressure differential;
- Non-viable particles;

- Recovery (clean-up) time.

The test instruments calibration certificates were presented to the inspectors.

Qualification

The qualification of critical equipment and utilities was carried out.

Approaches to process validation

The Azithromycin process validation protocol/report was spot checked. This was re-validation of the production process. The reason for re-validation was another supplier of the key starting material.

Cleaning validation

The SOP “Equipment Cleaning Validation” as well as cleaning validation protocol and report for Workshop 10 was reviewed.

3.12 CHANGE CONTROL (CC)

A formal CC system was established.

The SOP “Change Control” was reviewed. Change control had been classified in to two categories:

- Minor
- Critical

According to the SOP any changes which had a direct influence to the product quality, safety and environment should be evaluate as Critical. For the critical change a Quality Risk Management procedure should be performed before the approval.

3.13 REJECTION AND RE-USE OF MATERIALS

Rejection

The SOP “Rejected product control” and the SOP “Rejected product for Azithromycin” were checked.

Reprocessing and reworking

According to the company policy rework of the products was not allowed. Reprocessing SOPs were available for the all production steps and the reprocessing BMRs were issued by the QA.

Recovery of materials and solvents

The SOP “Hydrogenation Acetone Recovery of Azithromycin” was checked. The SOPs were available for recovery of all solvents. The recovered solvents were used in the same step of the production.

Returns

The returned APIs were identified, quarantined and stored in special place in the warehouse.

3.14 COMPLAINTS AND RECALLS

The quality-related complaints were recorded and investigated according to the written SOP. The SOP “Customer complaints” was checked. The responsible person for dealing with the complaints was from the QA. If the person was not presented, the QA manager was responsible for the investigation. The director Quality Assurance - Drugs Division General Managers Assistant – CSPC QUYI had overall responsibility for dealing with the complaints.

The complaints register January 2015 – 30 July 2015 was reviewed.

The SOP “Product recall” was checked. The responsible person for dealing with recalls was from the QA. If the person was not presented, the QA manager was responsible for the recalls. The director Quality Assurance - Drugs Division General Managers Assistant – CSPC QUYI had overall responsibility for recalls. The recalls were classified as:

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

Up to the date of the inspection there had been no recalls. Recall effectiveness was revaluated by the mock recall. The mock recall was carried out every 2 years. The last mock recall was performed on September 2014 and covered Azithromycin API for India and China market.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

N/A

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, Azithromycin dihydrate API manufactured at CSPC Ouyi Pharmaceutical Co., Ltd, site No 3, located at No. 99 Hainan Road, High-Tech. Industry Zone, Shijiazhuang, 052165, Peoples Republic of 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.