

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

Part 1: General information about the inspection

Name of manufacturer	Zhejiang Starry Pharmaceutical Co
Physical address: Manufacturing facility and factory office:	No1 Starry Road, Xianju Modern Industrial Centralization Zone, Xianju city Zhejiang province, Peoples Republic of China
Inspected Unit(s)	Workshop No 2 Workshop No 7 Workshop No 14
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of: • Levofloxacin starting material, intermediates, and Levofloxacin hemihydrate API • Contrast media (In Vitro Diagnostics)
Active Pharmaceutical Ingredient(s) included in the inspection	API under Prequalification APIMF 260 Levofloxacin hemihydrate
Scope and type of inspection	Routine inspection
Date of inspection:	09 – 12 November 2015
Project (if any):	Prequalification Team

Part 2: Summary***General information about the company and site******Background information***

Zhejiang Starry Pharmaceutical Co (further in the text Starry) was founded in 2008. Inspected manufacturing facilities were in operation from 2008.

In total 5 products / APIs were manufactured in 18 workshops.

The total number of employees engaged on the site for Production, Engineering, QC/QA, Stores and Distribution were 850 employees.

Production	632
Quality Control (QC)	34
Quality Assurance (QA)	19

The workshops, and QC laboratory were operational seven days, in three shifts. The office and administration operated 5 days a week.

History of WHO or regulatory agencies inspections

The site was previously inspected by the WHO team on January 12 – 15, 2015.

The site was inspected by SFDA:

- in August 2009 and GMP certificate for Levofloxacin API was issued
- in February 2013 and GMP certificate for Levofloxacin hydrochloride API was issued
- in January 2015 and GMP certificate for Lopamidol API was issued

The site was also inspected by various customers, Pharmaceutical and Medical devices Agency Japan (PMDA), Korean FDA, and the Mexican Health authority.

Focus of the inspection

The inspection focused on implementation of corrective actions and preventive actions (CAPA) from the first WHO inspection and the production and control procedures of

- APIMF 260 Levofloxacin hemihydrate.

Inspected Areas

The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients:

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management

WHO Public Inspection report:
Zhejiang Starry Pharmaceutical Co API
November 2015

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- Production and in-process controls
- Packaging and identification labelling of APIs and intermediates
- 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 (QM)

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

Responsibilities – job descriptions

Quality Units responsibilities were specified in the following documents:

- Job description for Quality unit – Quality assurance (QA)
- Job description for Quality control (QC)
- Job description of the Vice General Manager, Quality
- QC responsibilities

The following responsibilities were described in the QA Unit, QC Unit and Vice General Manager Job descriptions:

- Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company
- Establishing a system to release or reject raw materials, intermediates
- Packaging and labelling materials
- Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution
- Making sure that critical deviations are investigated and resolved
- Approving all specifications and master production instructions
- Approving all procedures impacting the quality of intermediates or APIs
- Making sure that internal audits (self-inspections) are performed.
- Approving of starting material
- Approving changes that potentially impact quality of intermediates or APIs.
- Reviewing and approving validation protocols and reports
- Making sure that quality-related complaints are investigated and resolved

WHO Public Inspection report:
Zhejiang Starry Pharmaceutical Co API
November 2015

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- Making sure that effective systems are used for maintaining and calibrating critical equipment
- Making sure that materials are appropriately tested and the results are reported
- Making sure that there are stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate
- Performing product quality reviews

The SOP “Job description for production unit” specified the following responsibilities:

- Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures
- Producing APIs and, when appropriate, intermediates according to preapproved instructions
- Reviewing all production batch records and ensuring that these are completed and signed
- Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded
- Making sure that production facilities are clean and when appropriate disinfected
- Making sure that the necessary calibrations are performed and records kept.
- Making sure that the premises and equipment are maintained and records kept.
- Making sure that validation protocols and reports are reviewed and approved
- Evaluating proposed changes in product, process or equipment.
- Making sure that new and, when appropriate, modified facilities and equipment are qualified.

Management review (MR)

Not available. The Company had considered internal audits as management reviews.

Internal audits (self-inspection)

The SOP “Management procedure for self-inspection” was discussed. According to the SOP, self-inspection should be carried out every 6 months. Last self inspection was carried out in December 2014. The internal audit team leader was the deputy general manager. According to the SOP, audits should be performed by a team consisting of personnel from cross-functional areas.

Product quality review (PQR)

The SOP “Annual Product quality annual review” was discussed. The SOP content covered product, varieties, yield, batch numbers, quantity of the raw material especially from the new supplier, process parameters, control of intermediate or intermediates and test results of the finished products, review of utilities e.g. water, environmental, investing out of specifications (OOS) and out of trend (OOT), handling of rejected unqualified products, such as reprocessing of rejected API, corrective measures for all major deviation and all relevant measures and efficiency of preventive actions, investigation of stability and trends, change control, review of validation, complaints,

recalls and investigation if caused by quality, review of research, implementation of CAPA, suggestions from quality reports from previous year, annual evaluation and suggestion, review of the product quality and working procedures.

Quality Risk Management (QRM)

The SOP “Quality Risk Management” was discussed.

The following tools were listed for risk assessment (RA) to be applicable on site:

- Simplified risk management method
- Informal risk management method
- Failure mode effect analysis (FMEA)
- Failure mode effect and criticality analysis (FMECA)
- Fault tree analysis (FTA)
- Hazard analysis and critical control points (HACCP)
- Hazard operability analysis (HAZOP)
- Preliminary hazard analysis (PHA)
- Risk ranking and filtering

Guidance was available for applying FMEA.

3.2 PERSONNEL

Personnel qualifications

Adequate number of qualified personnel by appropriate education, training and experience were available on site to perform and supervise the manufacture of intermediates and APIs.

Personnel hygiene

The SOP “Personnel Hygiene management procedure for the general production area” and SOP “Personnel Hygiene management procedure for clean area” were discussed during the first WHO inspection, January 2015 – no changes. Direct contact with intermediates or APIs was avoided, smoking, eating, drinking, chewing and the storage of food was restricted, personnel with an infectious disease or who have open lesions on the exposed surface of the body were not engage in activities that could result in compromising the quality of APIs.

There were very good instructions on the walls of the clean room change, illustrated with clear photographs, and the senior personnel were careful to explain in detail the procedures for changing to the visitors.

Consultants

It was stated by the company that they did not use consultants.

Training

The SOP “Personnel training management procedure” was reviewed during the first WHO inspection, January 2015 – no changes.

WHO Public Inspection report:
Zhejiang Starry Pharmaceutical Co API
November 2015

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According to the SOP there were the following types of training:

- Induction training for newly employed staff. This training included:
 - o GMP training
 - o Safety
 - o Enterprise culture and company regulations
 - o Intellectual property rights
 - o On job training
- Continuous training
 - o Annual external training for managers
 - o General staff - SOPs training, production, GMP training and basic knowledge of chemistry
 - o Personnel working in clean areas annual training – personnel hygiene, microbiological knowledge and clean room operations

Training effectiveness was evaluated by written examinations – multiple choice questions and explanatory answers. Scoring system was used to evaluate effectiveness of the training. Minimum score to pass the test was specified 80.

The following training records for newly recruited analysts were discussed during the first WHO inspection, January 2015.

- QC analyst SOP training
- QC analyst technical (practical) assessment. Analysis were performed in parallel with experienced analysts and results compared
- Operator in “clean area”

Training schedule for 2015 was presented to the inspectors.

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.

Utilities

Heating, ventilation and air-conditioning system (HVAC)

For the clean zone of Workshop 14 one air handling unit (AHU) was serving the air to the production rooms. Air was recirculated, fresh air intake was 60%.

After the previous WHO inspection, large “inspection windows” had been installed to all filter sections of the AHU. AHU was well maintained.

Pre-filters were cleaned in a separate room using potable water and dried naturally.

High efficiency particulate air filters (HEPA filters) were installed in the ceilings of the production rooms. HEPA filters integrity/leak test was carried out every year.

Re-qualification of AHU and clean rooms was carried out once in two years.

SOPs for qualification/re-qualification tests were discussed. Results presented during the inspection were within specified limits.

Purified Water system (PW)

The PW production workshop produced PW for Workshop 13 and 14. There were two separate loops from 2 separate PW storage tanks. PW was only used for equipment washing; it was not used in the final product. PW was produced from incoming potable water from the city supply line and stored in a storage tank, before multimedia filtration and activated carbon treatment. It was then purified in a 2 stage reverse osmosis (RO) to make PW to the USP specifications. From the RO it was stored in storage tanks with vent filters. Storage tank and loop for Workshop 14 was discussed. A 0,22 µm membrane filter had been installed after the storage tank; through that filter PW was pumped in a continuous loop to user points. The PW contact surfaces were 316 L stainless steel. There was a monthly re-passivation of the tank and loop and a monthly sanitisation using hot water produced by the in-line heat exchanger, at 85-90 °C for 2 hours. On-line total organic carbon (TOC) and conductivity analysers were installed.

PW trends were reported in annual summaries. Trends for 2014 were discussed. Results seen were within specified limits.

Gases

Nitrogen gas and compressed air used in production were manufactured on site. Nitrogen tests and compressed air tests were performed quarterly for every sampling point. Nitrogen gas and compressed air were filtered via 3 µm → 1 µm → 0.1 µm filters. Production of Nitrogen gas and compressed air was not inspected.

Containment

In general appropriate measures were established and implemented to prevent cross-contamination, e.g. from personnel or materials, moving from one dedicated area to another.

Lighting

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

Sewage and refuse

The SOP “Waste management” was discussed during the first WHO inspection, January 2015 – no changes. Waste management was contracted out.

Sanitation and maintenance

Buildings used in the manufacture of intermediates and APIs were properly maintained and repaired. Written procedures were established for equipment and facilities cleaning. Written procedures were established for pest control, flying insects and rodents.

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

Written procedures were established for cleaning of equipment. Cleaning labels were attached to the equipment, and cleaning certificates, approved by QA, were attached to batch processing records.

The SOP “Testing instruments management procedure” was discussed; the SOP was applicable for laboratory instruments. Preventive maintenance (PM) schedule for laboratory equipment was not available. It was noted that PM was recorded in equipment log books.

The SOP “Equipment usage, maintenance and repair” was discussed; the SOP was applicable for production equipment and utilities. Production equipment PM schedule for 2015 was presented to the inspector. Spot checks showed that PM schedule was followed. PM was carried out according to equipment-specific check lists.

Calibration

Control, weighing, measuring, monitoring and testing of critical equipment was performed according to written procedures and an established schedule. Records of calibrations were maintained. The current calibration status of critical equipment was known and verifiable.

Analytical balance No XX (range 0.01mg – 81 g) daily and monthly calibration was discussed. Daily calibration was carried out using the following standard weights:

- 10 mg
- 100 mg
- 1 g
- 5 g

The calibration certificates of all standard weights were available.

The SOP “Testing instruments calibration” was discussed. The SOP was applicable for laboratory and production testing instruments. Testing instruments calibration schedule for 2015 was presented to the inspectors.

T mapping of the vacuum tray drier was discussed. T mapping was carried out for empty chamber and full load chamber. T was recorded every two minutes. T mapping studies appeared to be well documented. T sensors calibration certificates were attached to the T mapping report.

Computerized systems

Computerized systems were not used in production.

Laboratory instruments

The following softwares were used:

- High performance liquid chromatograph (HPLC) and gas chromatograph (GC)
 - o LabSolutions
 - o OpenLab ChemStation
 - o OpenLab control panel
- Ultra violet spectrophotometer (UV)
 - o LabSolutions UV probe
- Infra red spectrophotometer (IR)
 - o LabSolutions
- GC
 - o LabSolutions

During the inspection, operation of LabSolutions version 6.40 SP1 and OpenLab ChemStation revision C.01.05 SP1 (50) were discussed.

Audit trails were enabled for all instruments. The new procedure was introduced in October 2015 which required printed audit trails to be added to analytical test reports.

Analytical results for Levofloxacin hemihydrate batch No XXXX on paper were compared to the electronic data.

Access levels were defined.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

The SOP “Management procedure for classification and code of document was discussed during the first WHO inspection, January 2015 – no changes. SOP specified the structure and numbering system of documents.

WHO Public Inspection report:
Zhejiang Starry Pharmaceutical Co API
November 2015

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The SOP “Management procedure for preparing, reviewing, approving, effective date of document” 4 was discussed during the first WHO inspection, January 2015 – no changes. Documents should be reviewed every three years.

The SOP “Management procedure for printing, issuance, use, withdrawal of document” was discussed during the first WHO inspection, January 2015 – no changes. Printed document copies were distributed to the relevant department. Distribution was controlled by the documents distribution register. New or revised documents were in force after appropriate training.

Specifications were available for:

- Raw materials
- Intermediates
- Crude materials
- Recovered solvents
- Finished APIs
- Packaging materials and labels

Equipment cleaning and use records

List of production equipment was maintained for each step of production. Labels with cleaning status were attached to the equipment. Equipment cleaning certificate was attached to Batch Production Records (BPR).

Records of raw materials, intermediates, API labelling and packaging materials

Records of raw materials, intermediates, and packaging materials were maintained and contained the required information, for example:

- Name of the manufacturer
- Identity and quantity of each shipment of materials
- Name of the supplier
- The number allocated on receipt; and the date of receipt, etc.

Master production instructions (MPI)

Master production instructions for each intermediate and API were available.

Batch production records (BPR)

Batch production records were prepared for each intermediate and API and included information relating to the production and control of each batch.

Batch numbering system

The SOP “Management procedure for the batch numbering system” was discussed. Batch numbering system was explained for raw materials, intermediates, recovered materials and finished APIs.

In case tailings were blended, a new batch number was assigned.

Laboratory records

Testing results for Levofloxacin hemihydrate batch No XXXX were discussed and found to match with the specification. Analytical control report was traceable.

Batch production record review

Batch production records were discussed during the plant tour and generally found to be filled appropriately.

3.6 MATERIALS MANAGEMENT

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

Supplier approval

The SOP “Quality evaluation procedure for supplier of main material” was discussed during the first WHO inspection, January 2015 – no changes. The SOP was applicable for starting materials, packaging materials and labels suppliers. General material suppliers e.g. solvents (chloroform) and imported materials suppliers were approved based on questionnaires and sample assessments. Critical material suppliers were approved based on questionnaires, samples assessments and site audits. Critical material suppliers audit schedule for 2015 was available and presented to the inspectors.

During the previous inspection the critical material XX supplier audit report was available for inspection and was discussed. Audit was performed according to the check list. After audit report was written, observations were classified as critical and major. Audited suppliers were requested to submit CAPAs. CAPAs were assessed and reviewed by QA.

Qualification of the new supplier of the raw material XX was discussed. The supplier profile file seemed to be informative.

Approved list of suppliers of general, imported and critical materials was presented to the inspectors.

Solvents

Solvents were delivered in dedicated tankers; tankers cleaning certificates were provided. Samples of the delivered solvents were taken from the tankers. After QC release, solvents were mixed with existing stock, analysed and a new batch number was assigned. Solvents’ hose pipes (couplings) belonged to the solvents delivery company. It was discussed that it would be good practice to protect the solvent farm connections from rain and snow.

Solvents in drums were stored in separate warehouses

Receipt and quarantine

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

Sampling and testing of incoming production materials

The incoming materials were inspected for batch number, approved vendor status, appearance, condition of the container, lot number, expiry date and Certificate of Analysis. A status label was attached to each container.

The containers were sampled according the “Raw materials, intermediates and finished products sampling”. The sampling plan was following:

After sampling each container that had been sampled had a sampled label attached to it, with information on product name, batch or lot number, sampler, date, etc.

Sampling of packaging materials and labels was carried out according to the “Packaging materials and labels sampling”. Sampling was based on the Chinese standard GB/T2828.1 – 2003/ISO 2859-1:1999 “Sampling procedures for inspection by attributes - Part I: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection.

Storage

With regards to liquid raw materials, the Company stated that these were not dispensed in warehouses; full containers were issued to production. It was also stated that there was no practice to return materials from production to warehouses.

Temperature (T) limit was “below 30 °C” and relative humidity (RH) below “75%”. T and RH in the intermediates and finished products warehouses were monitored twice per day.

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.

In-process sampling and controls (IPC)

pH (using paper indicator) IPC tests were performed in the workshops by operators. Samples for Loss on Drying (LOD) for the first three production steps were taken by the operators, for the last step by the QC personnel. LOD tests were carried out in production

workshops (final API after drying) or in Quality Control Laboratory (QCL) using express method.

Blending batches of intermediates or APIs

The SOP “Product tailing management procedure” was discussed. In case of blending the new Batch Manufacturing Record (BMR) and Batch Packaging Record (BPR) were issued and used for blending operations.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging materials

Packaging materials: drums, low density polyethylene (LDPE) bags were stored in specific warehouse.

Label issuance and control

The SOP “Intermediates and export products labelling” was discussed. According to the procedure, customers should send the required label template to the Company’s sales department. Sales department created an electronic template, printed out the sample, filled label printing notification form and submitted for QA review/approval. After QA approval, QA and sales department signed the label printing notification form. Labels were printed by the sales person; the label printer was located in the sales department. After printing, the printing record was filled in. One extra label was printed and attached to the batch packaging record; the same was applicable if the batch was labelled in several sub-parts, label change record was filled in. During the inspection it was explained that in the nearest future the label printer will be located in the QA department and printing of final labels will be carried out by the QA personnel.

Packaging and labelling operations

Packaging operations were carried out in Workshop 14, in Class D clean room conditions. Labelling of the finished API was carried out in the warehouse by the production personnel.

3.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Facilities were provided for the storage of all materials. In general quarantine areas were identified.

Distribution procedures

When the final destination and customer were known, API would be labelled with the details that the customer requires. The API was packed in a fibre drum, inside a double polyethylene bag. Stability testing was conducted using equivalent packing materials.

After QC disposition, each container was labelled with a release label with lot, expiry date, analytical report number, analyst, etc.

The SOP SMP09-002 “Finished product release and review management procedure” was discussed. APIs were released for sale after QA approval. Deputy General Manager and quality management representative were responsible persons for product release. According to the SOP, BPRs and analytical reports were discussed according to the check list.

3.10 LABORATORY CONTROLS

Instrumental analysis was inspected, focusing on data reliability and integrity in HPLC analysis. The SOP “Agilent OpenLab ChemStation ECM operation procedure” and the SOP “LabSolutions CS operation procedure” were discussed. After the previous WHO inspection – January 2015 the requirement was established to print out audit trails and add the print outs to analytical worksheets to be reviewed along with other data related to the analysis.

In the chemical laboratory class “A” volumetric glassware was used, re-calibration was carried out every three years.

The document “QC laboratory HPLC and GC classic chromatograms” and the SOP “Data back-up management” were discussed. The SOP was applicable to equipments connected to the server and to stand-alone equipments.

Reference standards

Pharmacopoeia reference standards (RS) and working standards (WS) were stored in a locked refrigerator. Usage of RS and WS was recorded. WS for assay test of Levofloxacin hemihydrate were qualified against the USP RS, traceability to the USP standards was ensured. Two analysts and two different equipment were involved for WS standardization. WS standards were dispensed in 20 vials, each vial contained 1 g of the WS. After opening, WS should be used within one month. WS expiry time was 1 year according to the stability studies.

Reagents

Reagents prepared in the laboratory were properly labelled. Solvents / dry chemicals expiry dates were set up by the QCL:

- Solvents - 1 year from the date of opening
- Dry reagents – 3 years from the date of opening

Out of specification (OOS) results

The OOS procedure and the form attached were discussed. The SOP included also out of trends (OOT).

A unique number was assigned to each OOS or OOT.

OOS/OOT logbook/register was discussed.

The Company explained that if errors or deviations are observed during a test, these incidents were handled as laboratory deviations and the SOP “Deviation handling procedure” would apply.

The laboratory used an appropriate checklist for the OOS investigation to check 27 potential issues, for example:

- Current approved version of the Method of analysis
- Correctness of calculations
- Data integrity and correctness of raw data
- Correct potency and preparation of standard reference material,
- Sample and dilution
- Equipment calibration status

Microbiological Testing

Microbiological laboratory was visited during the first WHO inspection – January 2015. Microbial tests were carried out only for environmental monitoring, PW and cleaning validation studies. Starting materials, intermediates and finished APIs were not subjected to microbial testing. Due to time constraints a very brief visit was made to microbiology laboratory. Growth promotion tests were performed for all batches of dry media and after media sterilisation. Sterile media expiry time was stated to be 21 days. During the current inspection it was explained that the laboratory had purchased R2A media for PW analysis and the testing method was under validation.

Testing of intermediates and APIs

Laboratory tests procedures and specifications were available and tests were performed for all intermediates and APIs. Impurity profiles were established and tested.

Certificates of analysis (CoA)

CoA were issued for starting materials, intermediates and finished APIs. CoAs were approved by the QC Manager.

Stability monitoring of APIs

The stability chambers were temperature mapped as part of incoming qualification. The qualification report showed the equipment complied with the requirement for temperature maximum, minimum and average. T and RH in the chambers were monitored daily. T sensors were connected to the data logger that recorded the T every 15 minutes. Print outs were discussed daily. Stability chambers were equipped with alarm system connected to cell phones. The company stated that alarm systems were challenged. One stand-by stability chamber was available and was calibrated for:

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

The stability testing SOP was discussed. Samples were stored under the following conditions:

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

According the SOP at least one batch of finished API should be placed on on-going stability studies every year.

Expiry and retest dating

APIs and intermediates expiry/retest dates were based on an evaluation of data derived from stability studies.

Reserve/retention samples

Retentions samples of Levofloxacin hemihydrate were retained for a period of 1 year past the 2-year “expiry date” or “re-test date” (as per the customer’s order). Retention samples were stored in a separate room under controlled conditions, in the QC building. Packaging was equivalent to the marketed packages.

3.11 VALIDATION

Validation Policy

Validation policy was explained in the Validation Master Plan (VMP). VMP for 2015 was discussed. VMP explained the general approach to validation.

The SOP “Verification and Validation management procedure” was discussed during the previous WHO inspection – January 2015, no changes. SOP explained the approach to facilities lay out, HVAC system, water system, equipment (including design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ), process and cleaning validation. According to the SOP, HEPA filters integrity/leak tests should be carried out annually, HVAC system re-qualification and PW system verification should be carried out every two years. Process and cleaning re-validation should be carried out every two years.

The cleaning validation report for Milling machine XX was discussed during the previous WHO inspection – January 2015.

Validation documentation

Written validation protocols and reports were established and specified how activities will be conducted. The protocols and reports were reviewed and approved by the Vice General Manager QA and reviewed by the Director, manufacturing department and Vice Director QA.

Qualification

The Levofloxacin centrifuges XX and ZZ qualification report VR1-02-0920 was discussed during the first WHO inspection – January 2015. The DQ, IQ and OQ report was approved the Vice General Manager QA.

The PQ of centrifuges XX and ZZ in relation to Levofloxacin hemihydrate (code YY) had been scheduled for July 2015, but was not conducted because till the date of inspection no batches of Levofloxacin hemihydrate (code YY) had been produced in 2015.

Approaches to process validation

The Levofloxacin hemihydrate process re-validation protocol/report No XX was reviewed during the previous WHO inspection – January 2015.

Re-validation covered all production steps. Critical and important process parameters and test parameters and acceptance criteria were specified and validated for intermediate, crude, purified crude and finished API. Validation report contained starting material, intermediates, and finished API specifications. API specifications and test method was according to the USP requirements.

Process validation programme

For concurrent validation three consecutive production batches were used.

Periodic review of validated systems

Validated systems were periodically reviewed and were part of the PQR.

Cleaning validation

Cleaning validation was mentioned in the VMP, and there were protocols produced for each cleaning validation exercise.

Validation of analytical methods

It was explained that analytical methods were validated during product development procedure. Analytical method validations were not discussed during the course of inspection.

3.12 CHANGE CONTROL

Change control (CC)

SOP “Change Control” was discussed. The SOP was applicable to:

- Manufacturing operations
- Specifications
- Materials
- Suppliers
- Facilities
- Equipment
- Software

WHO Public Inspection report:
Zhejiang Starry Pharmaceutical Co API
November 2015

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- Key personnel

The changes were classified as:

- Critical
- Major
- Minor

According to the SOP, in case of critical changes customers and authorities should be informed.

Deviations

SOP “Deviation Handling Regulation” was discussed during the previous WHO inspection – January 2015, no changes. The deviation SOP had sections for changes due to expected deviation, and unexpected deviations. The SOP stated that a register should be established according to the form XX. Deviation register since the start of 2015 (on paper) was discussed. Deviations were classified as “minor” or “major”. The register used product codes to indicate the material.

The deviation event No XX was discussed.

Corrective actions and preventive actions (CAPA)

SOP “Corrective actions and preventive actions” was discussed during the previous WHO inspection – January 2015, no changes. The CAPA procedure had sections for verifying effectiveness of the CAPA. The SOP was applicable to:

- Self-inspection and external audits
- Deviations
- OOS/OOT
- Change controls
- Complaints, recalls and returned products

Contamination control/Environmental monitoring

The SOP “Clean rooms environmental monitoring (EM)” was discussed during the first WHO inspection, January 2015 – no changes. EM monitoring was performed by two methods – active air sampling and sedimental settle plates. Acceptance criteria were as mentioned above. Active air sample size was 28.3 L/ minute. Sedimental settle plates were exposed for 4 hours. The Company explained that exposure time 4 hours was validated, however validation protocol/report was not discussed. Alert and action limits were specified. Airborne particles EM for all clean rooms and all change rooms was carried out every quarter, microbiology settle plates EM was carried out monthly. T and RH were monitored twice per day. Pressure differentials were monitored once per shift.

EM records were discussed for Workshop 14. EM monitoring results were also presented as trends in annual summaries. EM trends for 2015 were discussed. Results seen were

within specified limits.

3.13 REJECTION AND RE-USE OF MATERIALS

Rejection

The SOP “Rejected products management procedure” was discussed during the previous WHO inspection – January 2015, no changes. Intermediates and APIs failing to meet established specifications were rejected. Rejected products were stored in dedicated warehouse for rejected products. After investigation QA decision was made either to destroy, re-work, re-process, use with limited conditions or return to the supplier. Use with limited conditions was applicable only for intermediate products. Rejected products register was maintained and presented to the inspector. Rejected products registers were maintained product wise.

Reprocessing and reworking

The SOP “Re-processing management procedure for rejected product” was discussed during the last WHO inspection – January 2015, no changes. The SOP defined re-process as introducing an intermediate or unpacked API that does not conform to standards or specifications, back into the validated process. The SOP defined re-work as reworking intermediate or unpacked API that does not conform to standards or specifications using different process from approved.

Re-processed and re-worked products registers were maintained.

Recovery of materials and solvents

The SOP “Management procedure for recovery and use of solvent” was discussed during the previous WHO inspection – January 2015, no changes. It was stated by the company that for manufacturing process of Levofloxacin only re-covered solvents were used, mother liquor was stated not to be used. According to the SOP re-covered solvents could be used only for the manufacture of the same product previous steps. Re-covered solvents were tested and should comply with specifications for re-covered solvents. How many times solvents could be re-covered was specified in the SOP. Recovery of solvents was documented in the relevant product BMR.

Returns

The SOP “Handling procedure for returned products” was discussed. Returned products were stored in returned products warehouse. Returned products were discussed by QC personnel and sales person. According to the SOP in case if the conditions under which returned intermediates or APIs have been stored or shipped before or during their return, or the condition of their containers casts doubt on their quality, the returned intermediates or APIs were reprocessed, reworked or destroyed, as appropriate. If the checks showed that the returned product’s inner/primary packaging was intact, the product could be sold to customers. Separate registers were maintained product wise.

3.14 COMPLAINTS AND RECALLS

The SOP “Management procedure for consumer's complaints of quality” was discussed. According to the SOP the sales department was in charge of collecting the Customer complaints, which were recorded on a form XX, registered, and then handed to the Quality Management (QA) who assigned a unique number to each complaint, and then investigated.

Complaint No XX was discussed.

The SOP “Management procedure for recalling of the product” was discussed. Recall was the responsibility of the Quality Unit, and the Vice President in charge of QA was responsible for any recall. The effectiveness of the arrangements for recalls was tested and evaluated every 3 years by mock recall.

The last mock recall was executed in April 2015 for domestic market and covered Levofloxacin hydrochloride API.

There were 4 levels of recalls:

- Level I - recall within 24 hours
- Level II - recall within 48 hours
- Level III and IV – recall within 72 hours

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Not applicable.

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, APIMF 260 Levofloxacin hemihydrate manufactured at Zhejiang Starry Pharmaceutical Co, located at No1 Starry Road, Xianju Modern Industrial Centralization Zone Xianju city Zhejiang province, 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.