

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

Name of Manufacturer	Shangyu Jingxin Pharmaceutical Co., Ltd.
Unit number	N/A
Production Block	515, 518
Physical address	No 31, Weisan Road, Zhejiang Hangzhou Bay Shangyu Industrial Area, Shangyu City, Zhejiang Province, P.R.China-312369
Contact person and email address.	Mr. Fan Wang Shangyu Jingxin Pharmaceutical Co., Ltd. Email: zxp@jingxinpharm.com
Dates of inspection	18 to 21 August 2015
Type of inspection	Re-inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Levofloxacin hemihydrate (APIMF 245)
Summary of the activities performed by the manufacturer	Production and quality control of APIs

## **Part 2: Summary**

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

Shangyu Jingxin Pharmaceutical Co., Ltd. was founded in December 2004 and wholly owned by Zhejiang Jingxin Pharmaceutical Co., Ltd. It is a market listed company. Zhejiang Jingxin Pharmaceutical Co., Ltd. has five manufacturing sites located in Xinchang, Shangyu, Jiangxi, Inner Mongolia and Guangdong for dosage form, APIs, intermediates and traditional Chinese medicines respectively. The API products manufactured routinely on the inspected API site included Ciprofloxacin HCl\Lactate, Levofloxacin HCl\Lactate\Hemihydrate, Simvastatin, Rosuvastatin calcium, Ofloxacin, Cisapride, Loratadine, Sertraline HCl, Gatifloxacin Base\Mesylate, Amfebutamone HCl and Pitavastatin Calcium. No penicillin and Cephalosporin were manufactured on this site.

The workshops inspected were:

Workshop 515: for Levofloxacin carboxylic acid

Workshop 518: for Levofloxacin Hemihydrate\HCl\Lactate

The Levofloxacin Hemihydrate API was produced with two different processes and different grades by coding system.

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

This was the second WHO GMP inspection at this site. The Levofloxacin API facilities have previously been inspected by the WHO Prequalification of Medicines Programme in August 2014. The site had been inspected by EDQM in 2012, 2013 and 2015. However the inspection scope in terms of facilities and products did not fully overlap the WHO inspection.

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

The inspection focused on the production and control of Levofloxacin API. The inspection covered all the sections of WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

### ***Inspected Areas***

Day 1 started with an opening meeting. During the opening meeting the tentative inspection plan was discussed and confirmed. The company made a presentation about the site to be inspected. These presentations highlighted the company profile, the description of the site, a summary of manufacturing capacities, location of production of the various APIs and the site inspection history. The inspection covered the following areas according to an inspection plan sent to the company in advance and modified as necessary:

Facility tour:

- Warehouses: solid and liquid raw materials finished APIs, packaging materials.
- Workshop 515 Production of intermediate
- Workshop 518 Production including finishing and packaging
- QC Laboratory: Chemical and Physical Lab - specifications and test methods, SOPs, logbooks, records, worksheets and test reports, stability program, OOS results,

evaluation of results, release and rejection procedures, reference standards, retention samples, equipment, instruments and devices

Document review:

- Quality management
- Product Quality Reviews (PQR)
- Quality risk management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- 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**

#### **Principles**

A quality management system that included the required elements had been established, documented and implemented. As shown in the organograms reviewed, QA/QC departments were separate from the production departments. The persons authorized to release APIs were specified.

#### Responsibilities

Responsibilities for the quality units and for production activities were described in job descriptions and in SOPs. The sample of these documents reviewed during the inspection indicated that key quality and production responsibilities had been adequately described.

#### Product Quality Review (PQR)

A SOP “Management procedure for product quality annual review” was reviewed. According to the SOP PQR plan should be prepared in December each year and PQR should be completed within the first quarter of the year.

One PQR was prepared for all product codes.

The PQR of the Levofloxacin Hemihydrate 2014 was reviewed.

The following was covered by the PQR:

- Follow up of CAPAs

- Follow up of previous year PQR
- Review of test results of finished products
- Review of test results of intermediates
- Review of critical process parameters
- Review of starting materials
- Review of Stability
- Review of OOS/OOT
- Review of rejected batches
- Review of deviations
- Review of reprocessed batches
- Review of blended batches
- Corrective actions and preventive actions (CAPA) review
- Review of complaints
- Review of returns
- Review of recalls
- Review of change control
- Review of validation/qualification
- Review of regulatory affairs
- Assessment and proposal.

#### Quality Risk Management

A SOP “Quality Risk Management procedure” was reviewed and the SOP was applicable for whole life of API:

- Development
- Manufacturing
- Sales

Fish bone diagram and FMEA was mainly used as a tools for risk assessment (RA). A 12 score system was used for FMEA. FMEA was specified as priority tool. Addition tools what could be used for the RA was specified HACCP, FMECA and Fish bone diagram. Explanation how to use listed tools was available.

Risk analysis (RA) register for 2015 was presented to the inspector. Till August 2015 seven risk analysis have been performed. A RA of “Electronic data integrity RA for QC instruments used for analysis” was reviewed.

RA team consisted of:

- QA Manager
- Assistant QA Manager
- QC Vice Manager
- QC Administration Supervisor
- HPLC Supervisor
- QA persons responsible for QC activities
- IT Manager
- Equipment Supervisor (engineering department)
- Engineering department staff member

RA was carried out using FMEA. The RA was reviewed together with the SOP D-QC “Operating and maintenance procedure for the Agilent Open LAB data system”. The SOP specified the following access levels:

- Administrator (IT)
- Administrator 1 (QC Manager)
- Administrator 2 (QC Supervisor and two QA staff members responsible for QC)
- Level 4 (user)

RA conclusion was the following:

- GC and HPLC instrument risks are low risks and current measures in place are acceptable:
- IR, UV and particle size analyser - high risks are identified and additional actions should be taken.

Additional actions (for example: software and hardware update, access levels etc.) were identified, and partly implemented (for example: access levels and security passwords) till the August, 2015. Software and hardware update dates were specified in RA.

#### Corrective actions and preventive actions (CAPA)

A SOP “CAPA procedure” was reviewed. According to the SOP CAPAs should be implemented within 30 days and QA should follow up effectiveness of CAPA.

The SOP was applicable to:

- Any non-compliance, including potential non-compliance
- Quality failures
- Complaints
- Returns
- Deviations
- Rejections
- Recalls
- Self-inspection and external inspections
- Analysis of process performance and trends

CAPAs were classified as:

- Major
- Other

CAPA register for 2014 was checked and CAPAs were recorded. A CAPA related to the complaint was reviewed.

A SOP “Root cause analysis tools” was reviewed. The tools specified were:

- Fish bone diagram
- 5 Why`s
- Tree diagram
- Relationship diagram

#### Management review

A SOP “Quality system periodic review (QSPR)” has not been changed since the previous WHO inspection. QSPR should be completed by the end of December each year.

#### Out of specifications (OOS)

The general OOS procedure, 2015 OOS log book and OOS records were reviewed. Examples included an OOS for a batch regarding single impurity, where the root cause was attributed to impurity of the starting material.

#### Internal Audit (self-inspection)

Internal audits were performed according to a SOP with responsibility for this activity stated as being the Quality Department Manager. Checklists were used regarding comply/non-comply required for each item reviewed. After each internal audit a non-compliance report was required to be issued and the action required handled through the CAPA system.

The internal audit was performed once a year for a comprehensive internal audit and twice a year for selected department.

### **3.2 PERSONNEL**

#### Personnel qualifications

Key personnel’s qualification including the QP, QA manager and production manager were reviewed and acceptable in general.

#### Training

Training was conducted according to a written procedure. As an example of training and the records maintained, the job description and record of newly appointed QP were reviewed. The acceptance criterion for assessing training effectiveness was specified for GMP related subject by written test.

#### Personnel Hygiene

Requirements for entry to manufacturing areas were documented with the level and type of protective clothing required dependent on the nature of the API and step of manufacture. Adequate change rooms were provided for entry into Grade D manufacturing areas with hand washing facilities provided.

### **3.3 BUILDINGS AND FACILITIES**

#### Design and construction

Buildings and facilities used in the manufacture of the API were dedicated to the Levofloxacin APIs. Levofloxacin carboxylic acid was manufactured in Workshop 515. Levofloxacin Hemihydrate, Levofloxacin HCl and Levofloxacin lactate were manufactured in the workshop 518.

They were designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. There was adequate space for the orderly placement of equipment and materials to prevent mix-ups and

contamination. However, piper working was not always clearly labeled. QC areas and operations were separated from production areas. Entry to manufacturing and packaging areas was through appropriate change rooms.

### Utilities

HVAC system was installed in 2005. There was one AHU serving all “classified areas”. AHU consisted of pre-filter, secondary filter and terminal HEPA filters.

Air was directly exhausted from the following rooms:

- Crystallization room
- Drying room
- Milling room
- Blending room

AHU was operated on 30 % recirculated air. Air for recirculation was taken from the rooms where non explosive substances were exposed.

The SOP “Monitoring and maintenance procedure for classified areas” and the SOP “HVAC system operation procedure for classified areas” were reviewed.

According to the SOP “HVAC system operation procedure for classified areas” primary and secondary filters should be replaced every 6 months, or if the pressure difference is out of limits. Filters replacement log book for 2014 was presented to the inspectors.

AHU KZ-10001 re-qualification protocol/report was checked. Re-qualification was carried out on 26<sup>th</sup> February 2015. The following parameters were re-qualified:

- Air velocity
- Air changes per hour
- Pressure differential (at rest)
- T & RH
- HEPA filter integrity (contracted out)
- Clean up time
- Particle counts (non-viable particles)
- Airborne particle counts

Environmental monitoring (EM) trends were checked along with the re-qualification report. All results were within specified limits. EM monitoring was carried out regularly for all “clean rooms”.

### Water

Purified water (PW) was produced by double RO system. Distribution was through a stainless steel loop at ambient temperature. Monthly sanitization was performed at 80°C. Water tank filter was replaced once per year. Before replacement the new filter integrity checks were carried out. There were 78 PW sampling points. PW flow rate and T was monitored on-line at the returned loops from the WS. Conductivity and pH were monitored on-line. TOC tests were carried out in QCL. Trends for the samplings points were reviewed. All microbial results were within specified limits. Average  $\pm 3$  sigma was used as a statistical tool to monitor the trends.

#### Containment

Levofloxacin API was manufactured in dedicated facilities. The only concern was the design of the drying area where there were two dryers processing different batches of Levofloxacin API at the same time without physical segregation or adequate procedures in place to prevent the possibility of batch mix-up.

#### Lighting

Lighting in all areas visited was acceptable.

#### Sanitisation and maintenance

All manufacturing areas visited appeared to be well maintained and clean in general.

### **3.4 PROCESS EQUIPMENT**

#### Design and construction

Equipment used for the APIs within the scope of the inspection was generally of good standard and suitable for intended use. The workshop and equipment for manufacturing Levofloxacin hemihydrate was dedicated.

#### Equipment maintenance and cleaning

A SOP "Equipment maintenance procedure" was reviewed. The SOP was applicable to production equipment. There were following maintenance procedures specified in the SOP.

According to the SOP preventive maintenance (PM) schedule should be prepared annually (December & January). PM plans for centrifuges, V blender and driers were cross checked with equipment PM records. Checks showed that PM schedule was followed. PM was carried out according to the equipment PM check lists.

#### Calibration

As an example for equipment calibration PW flow meter was selected.

The SOP "Calibration frequency procedure" was checked. Equipment was classified as Class A, B and C. Calibration frequency was depending on equipment classification. The SOP "Measuring equipment classification procedure for calibration" was checked.

PW flow meter was classified as class measuring equipment. According to SOP class measuring equipment should be calibrated annually. Equipment calibration schedule for 2015 was presented to the inspectors. According to the schedule PW flow meter should be calibrated on 28<sup>th</sup> August 2015. PW flow meter calibration was performed on 15<sup>th</sup> May 2015. PW flow meter calibration record and SOP "PW flow meter calibration procedure" were checked. Portable ultrasonic flow rate meter was used for calibration; instrument calibration certificate was presented to the inspectors. Portable ultrasonic flow rate meter sensor was attached to the pipeline surface and readings of in-built flow rate meter and portable flow rate meter were compared.

#### Computerized systems

No computerized systems were used in the production of Levofloxacin API. The HPLC and GC were networked with the Open Lab in computer system.



### 3.5 DOCUMENTATION AND RECORDS

The company had a defined system for managing documentation according to a SOP. SOPs had been properly authorized and had been kept up to date. Each SOP included a version number and a brief record of the reason for any change. Record was managed by a SOP and required to be maintained were also available and were generally satisfactory.

Batch numbering procedure was available and reviewed.

Equipment cleaning and use record

SOPs for major equipment use and cleaning were available, and cleaning records were available. Equipment SOPs, records and logbooks were generally acceptable.

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

Records of the receipt, quarantine, sampling and release of raw materials, intermediate, labels and packaging materials had been maintained.

Master production instructions (master production and control records)

The master production instruction was available and did the spot check.

Batch production records (batch production and control records)

The approved master formula of the Levofloxacin Hemihydrate were checked and compared to the ones used in practice. The in-process BMRs and the completed BMRs reviewed were acceptable.

Laboratory control records

The QC records of the working reference of Levofloxacin and the completed QC records reviewed had been reviewed.

### 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.

Inspectors visited:

- Solvent farm
- Class B liquid warehouse
- Solid materials warehouse.
- Class A liquids warehouse

Sampling of starting materials, including solvents and packaging materials was conducted at defined locations by procedures designed to prevent contamination of the material sampled and contamination of other materials. Containers from which samples were withdrawn were marked to indicate that a sample has been taken.

Finished products were stored in temperature controlled warehouse. Labelling of the finished products was carried out in the shipment area. Labels were issued and controlled by the QA.

Solvents were delivered in dedicated tankers; certificates of analysis were checked before sampling. Samples from tankers were taken by the QC staff. Before incoming solvents were mixed with existing stocks they were tested and released.

The SOP “Sampling (testing) procedure for packaging materials” was reviewed. Primary packaging materials sampling was done according to the sampling plan.

The SOPs of “Low density polybags (LDPE) testing procedure” and the SOP “Management procedure for materials in the storage tanks” were reviewed.

The SOP “Equipment maintenance procedure” and Annex “Equipment maintenance list” was checked focusing on solvents storage tanks maintenance. According to the annex solvent storage tanks maintenance should be carried out every 3 months. Thickness of the walls should be checked every 6 months. Maintenance was carried out according to the check list. Performed solvents storage tanks maintenance schedule was cross checked with the maintenance records. Cross checks showed that the maintenance schedule was followed.

Cleaning of the solvents storage tanks were carried out once per year, cleaning records were presented to the inspectors.

#### Supplier’s qualification

Suppliers of materials were required to be approved according to a SOP. The approval process included a questionnaire, a sample for trial and analysis, and an audit of critical suppliers. Critical suppliers were required to be re-evaluated on every 2 years. An audit report for a Key Starting Material (KSM) for Levofloxacin and the quality agreement with this supplier were reviewed.

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

#### Production operations

There was no other toxic or hazardous substances (including  $\beta$  lactams) handled on the site.

#### Production operations

Production operations were carried out in two workshops (WS) - 515 and 518. Starting from crystallization step production was carried out in classified rooms (class D).

#### Deviations

Deviations were documented, explained and investigated.

A SOP “Deviation management” and flow chart were reviewed. According to the SOP deviations should be closed within 30 days.

Deviations were classified as:

- Critical (major)
- Other

Deviations register for 2014 and 2015 was presented to the inspector. Deviation investigation reports regarding Levofloxacin HCl API “QC tests confirmed OOS for individual impurity was reviewed.

The SOP D-PC011-R04 “Production process management procedure” was checked.

#### Production operations

Production operations in workshop 515 and 518 were reviewed and generally found acceptable. Levofloxacin hemihydrate: Batch size 525kg ~ 595kg, shelf life: 24 months

#### Time limits

As applicable, time limits for each processing step were included in the BMR.

The holding time study report of intermediates was available for review. The holding time of Levofloxacin wet material was six month as specified.

#### In-process sampling and controls

Requirements for in-process sampling were described in the BMRs and acceptance criteria included. In-process sampling and testing appeared to be appropriately conducted and recorded.

#### Blending batches of intermediates or APIs

The blending operation was regulated by SOPs. A BMR of batch blended was reviewed and to be acceptable in general.

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

#### Packaging materials

Low density polybags (LDPE) were used for packaging of the Levofloxacin Hemihydrate API. LDPE were stored in separate warehouse and sampled in dedicated place.

#### Label issuance and control

The SOP “Label and release tag control procedure” and the SOP “Labelling procedure” were checked. QA was responsible for printing required information to the labels. Label printer was located in the QA room.

Finished API label printing and use logbook was used for the reconciliation of the printed labels.

A SOP “Packaging materials receiving and distribution procedure” was reviewed. According to the SOP in case pre-printed labels were received in several consignments, for each consignment unique batch number should be assigned. Labels were received in the warehouse and afterwards transferred to the QA labels storage room. Finished APIs labelling was performed by QA staff. Labels in the QA labels storage rooms were stored in the locked cupboards. Levofloxacin Hemihydrate labels were cut, self-adhesive labels.

### 3.9 STORAGE AND DISTRIBUTION

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

The environmental conditions for the storage of Levofloxacin APIs were specified and appropriately monitored. Records of monitoring were maintained and both temperature and humidity appeared to be consistently within the specified limits.

APIs were only released for distribution to third parties after they have been released by the quality assurance according to a procedure.

### 3.10 LABORATORY CONTROLS

#### General controls

The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments.

#### Testing of intermediates and APIs

QC testing was conducted as specified in the relevant specification and according to documented test methods.

HPLC was used for assay and related substance (RS) testing of the Levofloxacin Hemihydrate. Working reference standards were characterised against USP reference substance.

The computer access control, authorization of the functions and testing method validation were checked during the inspection.

#### Stability monitoring of APIs

A SOP “Stability studies management” was checked. Stability samples were stored at the following conditions:

- 40°C ± 2°C and 75 ± 5% RH (accelerated)
- 30°C ± 2°C and 65 ± 5% RH (zone III)
- 30°C ± 2°C and 75 ± 5% RH (zone IV)
- 25°C ± 2°C and 60 ± 5% RH (zone I and II)

The SOP “Retention sample procedure” was checked. According to the SOP the reserve samples should be stored in the same packaging system in which the APIs were stored or in more protective packaging system than the marketed packaging system. Quantities retained were at least for three full analyses. APIs and intermediates retention samples were kept at least for 5 years.

SOPs “Levofloxacin impurity B working standard (WS) qualification procedure”, “Reference standards control procedure” and “Levofloxacin impurity B working standard ZF-1406B173 qualification report” were spot checked. Impurities WSs were qualified against Reference standards. WS’s were dispensed in balance room.

Reference standards were used only for WS qualification. For all tests e.g. assay impurities and identity tests only WS were used. The qualification of the WS record was reviewed.

A analytical balance calibration was checked. Balance was calibrated daily and monthly. Date and time function was locked.

#### Expiry and retest dating

The shelf life for Levofloxacin Hemihydrate was 24 months. The shelf life for the retest date was discussed at the time of inspection.

#### Reserve/retention samples

There was a designated temperature controlled area (15 to 25°C) for storage of retention samples. Access to this area was restricted. Retention samples were stored in container systems that were comprised of the same materials as those used for the final intermediate. The retention sample log book was checked.

### **3.11 VALIDATION**

#### Validation policy

The company's validation policy was described in a SOP on Validation. This document required validation for production equipment, utilities, systems, processes and procedures, validation to be verified at periodic intervals, and re-validation frequency of the different aspects was specified.

#### Qualification

Requirements for the qualification of equipment and utilities were included in the abovementioned Validation Master Plan. Periodic requalification was required depending on criticality. An equipment qualification up to date list was available and considered acceptable in general. Equipment IQ, OQ and PQ, HVAC and PW system qualification was performed in December 2012.

The OQ and PQ of a crystallization tank were reviewed.

#### Process validation programme

Process validation (PV) was performed according to a SOP on process validation. The protocol and report for Levofloxacin hemihydrate were reviewed. The review is summarized below.

The validation protocol and report for Levofloxacin Carboxylic acid manufactured at 515 and Levofloxacin Hemihydrate at 518 were reviewed. The specification of the finished Levofloxacin Hemihydrate was checked.

#### Periodic review of validated systems

Periodic review of validated systems was required by the above mentioned Validation SOP.

#### Cleaning validation

Cleaning validation was not reviewed during this inspection. Note that separate facilities and equipment were dedicated to the production of Levofloxacin APIs.

#### Validation of analytical methods

The USP compendia method was used for testing of the Levofloxacin Hemihydrate, residue solvents was additional testing. The analytical method was validated according to a SOP. The validation report for analytical method of residue solvents was reviewed and discussed.

#### Computer validation

The open lab used in the QC lab for networking of HPLC and GC was validated by the Agilent. The change control regarding the installation of the software was reviewed.

### **3.12 CHANGE CONTROL (CC)**

A SOP “Change control management” and flow chart were reviewed. CCs were classified as:

- Major
- Other

The SOP was applicable to the following changes:

- Process
- Quality specifications
- Analytical methods
- Personnel
- Raw materials
- Packaging materials
- Equipment and facilities
- etc.

CC register for 2015 was presented to the inspector. Till 18<sup>th</sup> of August 2015 there were 24 CC registered. Four CC were classified as “Major”. Two CC were related to the equipment change. Levofloxacin Hemihydrate product code change from D21 to D25 was covered by the CC and reflected in the PQR.

As an example “Glass line crystallization reactors replacement in workshop 518 with the same capacity and material reactors” was reviewed.

A CC of “Change of Qualified person (QP)” was spot checked. Change of the QP was approved by SFDA.

A process change was also reviewed. Conclusion of the validation report was: The process change is capable to manufacture product meeting the specifications. Product quality before and after changes is comparable. Validation protocol/report was approved on 17<sup>th</sup> July 2015. Till 19<sup>th</sup> August 2015 relevant CC was not initiated. The batches after process validation were manufactured in accordance to the “old” version of the Master BMR.

### 3.13 REJECTION AND RE-USE OF MATERIALS

#### Rejection

The rejected material was handling according to a written SOP.

#### Reprocessing

Reprocessing was performed according to a written SOP. The log book for reprocessed batches was available and reviewed. There were two batches of levofloxacin reprocessed in 2014 but were not successful and finally rejected. There was no batch reprocessed in 2015.

#### Reworking

No reworking was allowed by the company procedure.

#### Recovery of materials and solvents

Solvent and material recoveries were performed according to SOPs. The principle was the early stage recovered was not allowed to be used in the latter processing stage.

### 3.14 COMPLAINTS AND RECALLS

A SOP "Procedure for complaints" was reviewed. QA Manager together with QA complaint staff was responsible for complaints investigation. Complaints were categorized as:

- Quality related
- Customer related
- Analysis related
- Labelling related
- Others

Product related complaints were trended in the PQRs. All complaints were trended once per year using PARETO chart.

Complaint register for 2014 was checked. In 2014 there were 12 complaints. A complaint investigation was reviewed. The batch under the complaint was returned and reprocessed.

A SOP "Product recall and return management" has not been changed since the last WHO inspection. QA dedicated staff member was responsible for dealing with recalls. Till the date of inspection there was not recalls. Recalls were classified as:

- Class I (critical) - should be initiated within 24 hours, clients, sales agents and authorities national/international
- Class II (major) - should be initiated within 48 hours
- Class III (minor) - should be initiated within 72 hours

Mock recall should be performed once per year. Last mock recall was performed on August 2014 and covered Chinese market.

Returned products were stored in the return goods area in the warehouse. Information was requested form the customer regarding storage and transportation of the returned products.

Returns registers for 2014 and 2015 were presented to the inspector. There were 7 returns registered in 2014 and 2 returns registered in 2015.

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

No contract manufacturers or laboratories were used for the inspected API.

#### **Part 3: Conclusion**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, Levofloxacin hemihydrate (APIMF 245) manufactured at Shangyu Jingxin Pharmaceutical Co., Ltd., No 31, Weisan Road, Zhejiang Hangzhou Bay Shangyu Industrial Area, Shangyu City, Zhejiang Province, P.R.China-312369 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.