WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information

Name of Manufacturer	Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd
Unit number	N/A
Production Block	Workshop No. 2 (Levofloxacin) & 3 (Ofloxacin)
Physical address	333 Jiangnan Road of Hengdian Town, Dongyang, 322118, Zhejiang, P.R.C
Contact person and email address.	Dr.Chen Yifu Regulatory Affairs Manager Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd. certification@kangyupharma.com
Dates of inspection	27 – 30 January 2015
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Levofloxacin hemihydrate (APIMF 099) Ofloxacin (API for FPP)
Summary of the activities performed by the manufacturer	• Production, quality control of non-β-lactam APIs. • Manufacturer of Cephalosporin API and FPP in separate blocks on the site (not inspected)

Part 2: Summary

General information about the company and site

Zhejiang Apeloa Kangyu Pharmaceutical Co. Ltd. was established in 1993 and is a member of the Hengdian Group. The site inspected is located in Dongyang, Hengdian, P.R.C. and started operation in 1995. Key intermediates, APIs and some finished pharmaceutical products are manufactured at this site.

The company has been licensed by the SFDA for the manufacturing of Active Pharmaceutical Ingredients (APIs) as well as Finished Pharmaceutical Products (FPP).

The number of personnel at the time of the inspection was approximately 1391 (QA/QC: 113, Production: 717, RD: 85, Sales: 116, Warehouse: 26, Administration: 166, Other: 168).

Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd. has two manufacturing sites. One is located at 333 Jiangnan Road, Hengdian Town and another is located at 333 Second Jiangnan Road, Hengdian Town. The distance between two manufacturing sites is approximately 2.5km.

Only the 333 Jiangnan Road, Hengdian Town site was inspected. At this site Levofloxacin hemihydrate is manufactured in Synthesis Workshop No. 3 and Ofloxacin is manufactured in Synthesis Workshop No.2. These workshops are dedicated to Levofloxacin (various salts) and Ofloxacin, respectively. This site occupies a total land area of 319,000m2; of which 134,000m2 is used as pharmaceutical manufacturing facilities. Cephalosporin API and FPP manufacturing also occurs in separate blocks on the site.

A related company (also a member of the Hengdian Group), Apeloa Kangyu Bio-Pharmaceutical Co. Ltd., Geshan Industrial Zone, Dongyang, manufactures biopharmaceutical products under separate management and a separate Quality Management System.

History of WHO and/or regulatory agency inspections

This was the third WHO inspection with previous inspections by the WHO performed on 20 - 22 March 2012 and 11 - 14 October 2011.

The site had inspected by US FDA in 2007, 2010 and 2012, but the inspection scope in terms of facilities and products was different to the WHO inspections.

Focus of the inspection

The inspection focused on the production and control of Ofloxacin and Levofloxacin hemihydrate. The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients and was conducted, with modification as necessary, according to a tentative inspection plan sent to the company in advance.

Inspected Areas

Opening meeting
- Introduction, attendance Record
- Brief company overview and presentation
- Summary of manufacturing processes and product range
- Changes since last inspection

Personnel
- Organization Chart
- Job descriptions for key personnel
- Training procedures and records

Quality Management
- Product Quality Review
- Quality Risk Management
- Deviation control and change control
- Complaints and Recalls
- OOS and investigation
- Supplier approval
- Product release
- Rejection and reuse of materials
- Contract agreements
- Document Control
- Self-inspection

Buildings and Facilities
- Site layout
- Design and construction
- Utilities

Warehouse(s)
- Storage – quarantine, release, reject
- Materials
- Receipt, handling and storage
- Identification
- Sampling
- Status Control
- Temperature (and humidity) monitoring
- Packaging materials

Production (Documentation and site visit)
- Batch document preparation
- Production area
- IPC sampling and testing
- Contamination Control
- Reprocessing and Reworking
- Packaging
- Cleaning
- API testing and release
- Batch record review

Validation and qualification:
- Validation Master Plan
- Validation and qualification status (matrix) and schedule

- Equipment qualification
- Process validation

Quality Control Laboratory (documentation and site visit)

- Quality management system
- Premises
- Sampling and sample handling
- Work allocation
- Documentation:
- Specifications and test methods
- SOPs, logbooks, records
- Worksheets and test reports
- Contract testing
- Stability program
- OOS results
- Analytical method validation
- Evaluation of results, release and rejection procedures
- Trending of results
- Traceability
- Materials
- Chemicals and reagents
- Reference standards
- Retention samples
- Equipment, instruments and devices

Purified water system

- Design & construction including documentation
- Operation and maintenance
- IQ/OQ/PQ
- Monitoring and testing

Engineering & Services:

- SOPs, registers and records including:
- Preventive Maintenance
- Calibration

Closing meeting with company representatives

2. QUALITY MANAGEMENT

The quality management system was generally well established, documented and implemented. The company was also ISO 9001 certified.

The site organizational structure was presented and was generally acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified.

The company manufactured a number of grades of Levofloxacin hemihydrate and Ofloxacin. It was a major concern that the Quality Management System was unable to adequately ensure that these APIs would always be manufactured in compliance with the details submitted in the APIMFs submitted to WHO PQ. Corrective actions have been implemented and were considered acceptable for this issue.

Internal (self) audits
The SOP for self-audits was reviewed. Self-audits were performed at least every 12 months. QA had overall responsibility for the self-audit program and the composition of audit teams was defined. Team members were not permitted to audit their own work areas. Self-audits were performed as per a pre-scheduled plan and elements were verified in accordance with a checklist. Any findings requiring correction were entered into the CAPA system for action and follow-up of effectiveness. Although specific details of self-audits were not reviewed, the records reviewed were acceptable.

Product quality review (PQR)
The SOP for PQR was reviewed. The 2014 PQRs for Levofloxacin hemihydrate and Ofloxacin were reviewed and were generally acceptable. Although the way that individual results had been trended and reviewed could be improved, both PQRs indicated that processes were consistently able to produce API's that met specifications.

Quality Risk Management
Quality risk management and risk assessment was handled and performed according to a documented procedure. The SOP required a QRM Group to be established and chaired by the Vice GM Quality. Various approaches to risk assessment were allowed, but the focus was on a quantitative FMEA model with descriptions of 5 levels for probability, severity and detectability, and RPN calculated from this.

The report on risk assessment performed for Levofloxacin in August 2014 was reviewed and generally found acceptable.

Out of specifications (OOS)
The general OOS procedure SOP, the 2014 OOS log book and OOS records were available for review.

Deviations
Deviations were handled according to SMP. An example of a deviation regarding a lab testing OOS was reviewed.

3. PERSONNEL

Personnel qualifications
There was adequate number of personnel suitably qualified by education and training to perform and supervise the manufacture of APIs. The personnel met during the inspection were experienced and appeared to be knowledgeable about GMP.

An organization chart was available. Key personnel responsibilities were specified in job descriptions and a sample of these were selected for review.

Training
Training was required to be conducted on an initial and ongoing basis. A training plan for 2015 was available. The effectiveness of training was evaluated by means of written assessments with a required pass-mark specified.

A selected sample of training records was reviewed and found acceptable.

Personnel Hygiene
Personnel hygiene requirements were documented in a SOP. The requirements for entry into the Grade D cleanrooms were well documented, including by approved photographs on change room walls. Staff observed in these areas wore appropriate protective clothing.

4. BUILDINGS AND FACILITIES

Design and construction
The workshops for the production and packaging of Levofloxacin and Ofloxacin were dedicated to these APIs and were generally located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture of the APIs.

Adequate space was provided for production and QC activities. Contamination during the final stages of production, including packaging, was minimized by these activities taking place in a suitably controlled Grade D environment.

Utilities
Adequate ventilation, air filtration and exhaust systems were provided. The HVAC system providing filtered air to the Grade D cleanrooms was reviewed and found acceptable. Compressed air was appropriately filtered and monitored.

Purified Water
Purified water was produced from mains drinking water by RO followed by EDI. The general design appeared to be good and the system appeared to be well maintained. Distribution was at ambient temperature. The distribution system included a UV unit and entry to the storage tank was via spray-ball. The distribution loop was sanitized weekly. Microbiological and TOC sampling and testing was reviewed and found satisfactory.

Containment
Levofloxacin (various salts) and Ofloxacin were produced in dedicated facilities thereby minimizing the risk of cross-contamination.

Lighting
Lighting was considered to be adequate in all areas visited during the inspection.

Sanitation and maintenance
All areas visited appeared to be clean. Cleaning procedures were available and records maintained. There was evidence of suitable pest control measures throughout the premises.

5. PROCESS EQUIPMENT

Design and construction
Other than the equipment was also used to manufacture different salts of levofloxacin, the equipment used to manufacture Ofloxacin and Levofloxacin hemihydrate were dedicated to specific steps of each process. The equipment viewed generally appeared to be of suitable design and construction for the allocated process.

Equipment maintenance and cleaning
The equipment viewed during the inspection appeared to have been suitably maintained and in good condition. Although documented procedures and records were available for equipment preventive maintenance some minor points were noted. CAPA has been made and considered acceptable.

Cleaning procedures and records were available for each item of equipment and those reviewed were satisfactory. The time frame for cleaning of equipment and its subsequent release for use in the manufacture of the API was specified in the equipment cleaning procedure and was stated on the equipment status labels.

Calibration
Calibration of devices (temperature, pressure etc.) was conducted according to an established program. Measuring equipment was labelled with a calibration status label and all viewed were within recalibration date.

Computerized systems
Computerized systems were not used in the warehouse or in production.

There was no LIMS in the QC laboratory and individual pieces of equipment, such as the HPLC, FTIR and UV spectrophotometers, and GC equipment, had their own dedicated standard “off-the-shelf” computer system.

6. DOCUMENTATION AND RECORDS

Documentation system and specifications
Documentation was controlled according to a documented procedure which was reviewed during the inspection. The scope of this procedure covered all types of documents, including specifications and records, and specified responsibilities for approving different types of documents. Changes to documents were handled though the change control procedure. There was concern about the way that temporary changes were made. The CAPAs had been made and found acceptable.

Equipment cleaning and use record
Equipment was cleaned according to written procedures and records were maintained. Log books were kept for each major piece of equipment and showed the usage of the equipment.

Records of raw materials, intermediates, API labeling and packaging materials
Manual systems were used for records of raw materials, intermediates, API labels and packaging material. The sample of records of material receipt, quarantine, release and status labelling reviewed were satisfactory. There were also systems (including requirements for record keeping) for reject materials and API returns.

Master production instruction (master production and control records)
Approved master batch production and packaging records were available for Levofloxacin hemihydrate and Ofloxacin APIs.

Batch production records (batch production and control records)
Approved Master BMRs were issued to each applicable workshop and copied for use as batch production records by workshop staff without direct QA control.

Several in-process batch records were inspected during the visits to the workshops and all were up to date and had been properly filled in.

Laboratory control records
The in-process QC records and the completed QC records were available for review.

Batch production record review
Completed batch production records were reviewed by the relevant Workshop Director before being reviewed by QA according to a checklist. Final batch release was by the QP.

7. MATERIALS MANAGEMENT

General controls
The receipt, identification, quarantine, storage, sampling, testing and approval or rejection was conducted according to approved documented procedures. The review of a sample of materials and associated records showed that they were generally acceptable.

A key starting material for Levofloxacin was changed from in-house manufacture to out sourced supply. The Suppliers approval was via change control procedure. Non-compliances observed during the inspection that was listed in the full report regarding the regulatory update to WHO and informing the FPP manufacturers, were addressed by the manufacturer to an acceptable level.

Receipt and quarantine
Materials were checked for correct labelling and the supplier was checked against the approved supplier list on receipt. They were then placed in quarantine by using yellow tape to segregate the material until sampled and approved by QC. Status labels were used for status identification.

Sampling and testing of incoming production materials
Incoming production materials and packaging materials were sampled by QA with labels used to identify the containers sampled. The samples were tested by the QC laboratory before being released or rejected. If released, another status label to reflect this was applied to each container and the yellow tape removed. If rejected, the

material was required to be status labelled accordingly and moved to a secure reject area.

Storage
There were separate warehouses for the storage of liquid raw materials, solid raw materials, packaging materials and finished APIs. These areas were included in the inspection and generally found to be acceptable. Storage conditions were specific in a SOP and where necessary were monitored with records maintained.

Re-evaluation
Raw material status labels included a re-test date at which time the material was re-quarantined before re-testing. A new retest date or shelf life would be assigned after retesting or reprocessing according to the company procedure. This was discussed with the company during the inspection.

8. PRODUCTION AND IN-PROCESS CONTROLS

Production operations
The production of Levofloxacin hemihydrate and Ofloxacin took place in several steps, each consisting of a number of sub-steps. Raw materials were weighed on mechanical balances in the production area. Weighing was required to be witnessed and this was recorded in the BMR.

Processing took place according to the instructions in the BMR. The steps reviewed indicated that the BMR had been kept up to date. Each major piece of equipment was appropriately labelled with a status label.

Time limits
As applicable, time limits for each processing step were included in the BMR. For the records reviewed, no deviations were noted.

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.

Contamination control
Levofloxacin (various salts) and Ofloxacin APIs were produced in dedicated workshops and production operations were generally considered to be conducted in a manner that minimises the possibility of contamination.

Cephalosporin APIs and FPPs were also manufactured on the site in separate dedicated workshops. These facilities were separated by a distance of around 200m from the Levofloxacin and Ofloxacin workshops. The potential for cross-contamination from this source was assessed and discussed during the previous inspection.

9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging materials
Packaging and labelling materials were received, quarantined, sampled, tested and approved according to a documented procedure. Packaging materials were stored in a dedicated warehouse for this purpose with printed API labels kept in a locked area with restricted access.

Packaging and labeling operations
A specified number of labels were required to be issued and this number was required to be reconciled after completion of packaging activities. Labels were not returned to the store and one label was retained in the BMR.

Packaging and labelling took place in designated Grade D packing areas for Levofloxacin and Ofloxacin respectively. Only one batch of one product was permitted to be packaged at a time and there were adequate other controls, such as line clearance checks, to prevent mix-ups. In-process QC checks were included. Packaging and labelling activities appeared to be satisfactorily documented.

10. 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 Ofloxacin and 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.

11. 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. The sample receiving and distribution log book was checked. Samples for testing were kept in a designated area.

Primary pharmacopoeial reference standards were available and secondary reference standards were prepared against the primary reference standards.

HPLC was used for assay and RS testing of the Levofloxacin APIs. Non-compliances observed during the inspection that were listed in the full report regarding the computer access control and authorization of the functions were addressed by the manufacturer to an acceptable level.

Stability monitoring of APIs
A range of stability chambers were available. Following initial stability studies to determine re-test date; at least one batch of API per year was required to be placed on on-going stability study.

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

Handling of out of specification (OOS) results
The OOS/OOT handling procedure was reviewed and discussed. Non-compliances observed during the inspection that was listed in the full report regarding OOS procedure were addressed by the manufacturer to a satisfactory level.

12. VALIDATION

Validation policy
The company's overall validation policy was adequately described in a documented SOP that described how validation requirements will be met, including frequency of re-validation. This document cross-referenced validation protocols for each API.

Qualification
Major equipment was qualified according to documented protocols and records maintained. Requalification of the purified water system was reviewed and the report indicated that this had been done to a satisfactory standard.

Process validation programme
The company's validation programme was described in a Validation Master Plan which was updated annually. The VMP included the dates of the last process validations for Levofloxacin and Ofloxacin and if re-validation was due in the current year, the scheduled dates for re-validation. The VMP also cross referenced the report numbers for the last process validation of each API.

The report for the last process validation for Ofloxacin was reviewed and generally found acceptable.

Periodic review of validated systems
The status of validated systems was reviewed annually at the time that the VMP was updated and also annually though the product quality review process.

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

13. CHANGE CONTROL

There was a procedure for change control. A change control register and records were maintained. The definition of major change in the procedure was reviewed and discussed at the time of the inspection. CAPA has been made regarding the observation and found satisfactory.

14. REJECTION AND RE-USE OF MATERIALS

Recovery of solvents and materials at different stages (e.g. crude API from mother liquor) of synthesis was done according to documented instructions and were tested to meet predefined specifications. Solvent recovery was done on site. An SOP on the reprocessing, rework and recovery was available.

15. COMPLAINTS AND RECALLS

Complaints were handled according to a documented procedure which was reviewed. It was the responsibility of QA to investigate complaints and instigate CAPA if necessary. A specified form was used to record complaints and their resolution.

During 2014 there had been no recorded complaints regarding Levofloxacin and two regarding Ofloxacin. The records for these and their associated CAPAs were reviewed and they appeared to have been handled appropriately.

Recalls were handled according to a documented procedure and this was reviewed. The SOP defined that a Recall Group was responsible for classifying recalls according to 3 specified levels, with notifications times according to local regulations. There had been no recalls for Levofloxacin or Ofloxacin. A mock recall had been conducted in 2009 and one for FPP in 2012.

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

No manufacture or routine QC testing was contracted out. Contracts with suppliers of key starting materials were available.

Part 3: Conclusion
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, APIs of Levofloxacin hemihydrate and Ofloxacin manufactured at Zhejiang Apeloa Kangyu Pharmaceutical Co. Ltd. located at 333 Jiangnan Road of Hengdian Town, Dongyang, 322118, Zhejiang, China were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.