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WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information

Name of Manufacturer	Zhejiang Hisun Pharmaceutical Co., Ltd.
Unit number	N/A
Production Block	Block 108 Block 105
Physical address	56 Binhai Road, Jiaojiang District Taizhou City, Zhejiang Province 318000 People's Republic of China
Contact person and email address.	Minxia Huang (QA Manager) mxhuang@hisunpharm.com
Date of inspection	14-17 August 2012
Type of inspection	Routine inspection (New site)
Active Pharmaceutical Ingredient(s) included in the inspection	API (Capreomycin Sulphate Concentrate Solution)
Summary of the activities performed by the manufacturer	Production and quality control of APIs

Part 2: Summary

General information about the company and site

Zhejiang Hisun Pharmaceutical Co. Ltd. was founded in 1956 and was listed as a public company in Shanghai A share Stock Exchange in 2000. It was located in Taizhou city Zhejiang Province and took three hours' drive from Hangzhou airport.

The site was divided in three parts which were separated by public roads. APIs for human drugs and veterinary products were manufactured.

At the time of the inspection the site employed approximately 5100 full time employees, 202 of which worked in Quality. The three campuses share the same QA management system.

History of WHO and/or regulatory agency inspections

The site has never been inspected by the WHO team before. Several inspections from other regulatory agencies were carried out:

34 National SFDA (including Capreomycin sulphate concentrate)
14 U.S. FDA (including Capreomycin sulphate concentrate)
4 TGA
3 MHRA
3 German Authority
3 PMDA
2 Belarus Authority
1 KFDA
1 EDQM

Focus of the inspection

The inspection focused on the production and control procedures of Capreomycin Sulphate API concentrate solution. 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

Overview of activities at site
Personnel
- Organization chart
- Job description
- Staff training

Quality Assurance and Quality Management System
- Product Quality Reviews (PQR)
- Change Control
- Deviations
- Complaints
- Recalls
- Document control
- Self-inspections
- Retention Samples
- Review of batch documents

Inspection of Production Operations & Facilities
- Production operations
- Packaging and labelling operations

Quality Control
- In-process controls
- QC Labs (physic-chemical and microbiology)
- Sampling
- Testing of the API and intermediates (IPC)
- Out of Specification investigations
- Reference substance and working standards
- Stability program

Validation
- Validation master plan
- Cleaning and cleaning validation

Production facility & equipment management
- Purified Water
- Maintenance program

2.1 QUALITY MANAGEMENT

Quality management systems were established, documented and implemented in general. The organizational structure, procedures, processes and resources were provided. Quality-related activities were defined, documented and recorded at the time they were performed. The quality unit was independent of production.

Regarding the product release process, the list of delegation for product release was reported in an official document sent by the company to the authority and other SOPs were present describing the process.

Responsibilities of the quality and production units

Responsibilities of the quality unit (personnel) and the responsibility of the production unit (personnel) activities were described and documented.

Internal audits (self-inspection)

Regular internal audits were performed once a year in accordance with an approved schedule. Audit findings and corrective actions were documented. Agreed corrective actions were completed in a timely manner.

Product quality review

Regular quality reviews of APIs were conducted per SOP on product annual quality management procedure. The results of this review were evaluated and an assessment made of whether corrective action or any re-validation should be undertaken. A SOP regarding trend analysis was in place. The PQR 2011 of Capreomycin API concentrate solution was reviewed.

2.2 PERSONNEL

Personnel qualifications

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

Training was regularly conducted by qualified individuals. Records of training were maintained.

Personnel hygiene

Good sanitation was observed on the site. Smoking, eating, drinking, chewing and the storage of food was restricted from the manufacturing areas.

2.3 BUILDINGS AND FACILITIES

Design and construction
In general buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate appropriate cleaning and maintenance. The manufacturing facilities were dedicated to the inspected API except the fermentation block. Adequate space was provided for the orderly placement of equipment and materials. The flow of materials and personnel through the building was designed to prevent mix-ups or contamination. Laboratory controls were carried out in the main QC laboratory.

Utilities
Adequate ventilation, air filtration and exhaust systems were provided and these were designed and constructed to minimize risks of contamination and cross-contamination.

Permanently installed pipework was appropriately identified.

Water
Water used in the manufacture of APIs was suitable for its intended use. Appropriate specifications were established and monitored.

Containment
The Company provided some documents referring to the evaluation of the cross-contamination especially for high activity/high toxic compounds.

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

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

2.4 PROCESS EQUIPMENT

Design and construction
Equipment used in the manufacture of intermediates and API were of appropriate design, adequate size, and suitably located for its intended use.

Equipment maintenance and cleaning
Schedules and procedures were established for the preventive maintenance of equipment. Written procedures were established for cleaning of equipment. Dedicate equipment were used for Capreomycin API production except the fermentation tankers.

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

Computerized systems
Computerized systems were not used in Capreomycin API production.

2.5 DOCUMENTATION AND RECORDS

Documentation system and specifications
Documents related to the manufacture of intermediates and Capreomycin Sulphate API concentrate solution were prepared, reviewed, approved and distributed according to SOP on drafting and management of documents. Production, control and distribution records were retained for at least one year after the expiry date of the batch. Specifications were established and documented for raw material, intermediates, capreomycin API, labeling and packaging materials. Acceptance criteria was established and documented for in-process controls.

Equipment cleaning and use record
Records of equipment use, cleaning, sanitization and maintenance were examined, observations was made.

Records of raw materials, intermediates, API labeling and packaging materials
Records of raw material, intermediates, Capreomycin API, labelling and packaging materials were maintained.

Master production instructions
Master production instructions for Capreomycin API were available, dated and signed by one person and independently checked, dated and signed by a person in the quality unit.

Batch production records
Batch production records were prepared for Capreomycin Sulphate API concentrate and included complete information relating to the production and control of each batch in general. Written procedures were established and followed for investigating critical deviations.

Laboratory control records
Laboratory control records included data derived from tests conducted to ensure compliance with established specifications and standards. Out-of-specification (OOS) investigations were performed per SOP on OOS/OOT procedure.

Batch production record review
Written procedures were established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling.

2.6 MATERIALS MANAGEMENT

General controls
Written procedures were available describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials. The system was in place for evaluating the suppliers of critical materials.

Receipt and quarantine
Upon receipt each container of materials were examined visually for correct labeling damage to containers, broken seals and evidence of tampering or contamination. Materials were held under quarantine until they were sampled, tested and released for use.

Sampling and testing of incoming production materials
Containers from which samples were withdrawn were marked to indicate that a sample has been taken. The decision on the number of containers to sample and the sample size was based upon a sampling plan. Sampling was carried out in the warehouse in the sampling room.

Storage
Materials were stored under appropriate conditions to prevent degradation, contamination and cross-contamination. Materials stored in fiber drums, bags or boxes were stored off the floor.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

The production operations of strain preparation, extraction, filling and packaging were not conducted during the inspection. Only limited production operations were carried out, e.g. some fermenters were running during the inspection.

Examination of the flow of the manufacturing process and relevant equipment was in line with the BPR examined and the process described in the submitted dossier. Some of the equipment used in different step of the process was inspected and the relevant cleaning was carried out based on the registration examined during the BPR evaluation.

Management of working and master cell bank was found acceptable and in line with the guideline.

In-process sampling and controls
The procedure and parameters for in-process controls were in place but was not carried out during the inspection.

Blending batches of intermediates or APIs
In accordance with the company policy the blending of batches of Capreomycin API was not carried out.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging and labeling materials were managed through SOP for reception, identification, g and release.

Packaging materials
Packaging materials were correspondent to those described in the currently submitted dossier for Capreomycin API.

Packaging and labelling operations
Packaging and labeling operations procedure were in place but was not carried out during the inspection.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures
Facilities were available for the storage of all materials under appropriate conditions.

Distribution procedures
The distribution responsibility has been defined in the agreement with its FPP manufacturer.

2.10 LABORATORY CONTROLS

QC had adequate laboratory facilities. Documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. The API concentrate solution was being controlled by in-house specifications based on the USP monograph. In-house test methods were being used together with other USP monograph methods, which were in compliance with those described in the currently submitted dossier.

OOS results obtained were investigated and documented according to a procedure.

Reagents and standard solutions were prepared and labeled following written procedures. Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were certified by the application of appropriate tests to ensure standardization. Reference standards were properly labeled and stored. Working standards were qualified against USP standard. Temperature in the reference standards storage fridge was monitored.

Testing of intermediates and APIs
Laboratory tests were performed for all intermediates with procedures in line with the currently submitted dossier.

Certificates of analysis
Certificates of analysis (CoA) were issued for each batch of Capreomycin API concentrate. The expiry date was provided on the label and certificate of analysis. Certificates were dated and signed by authorized personnel from the QC/QA.

Stability monitoring of APIs
A SOP on management procedure of stability study was reviewed and considered to be acceptable in general.

Reserve/retention samples
Appropriately identified reserve samples of each batch of Capreomycin API concentrate were retained for one year beyond the expiry date of the corresponding finished product. The Capreomycin API concentrate reserve sample was stored in the same packaging system in which the API concentrate was stored. Retention samples were stored under appropriate conditions.

2.11 VALIDATION

Validation policy
The company's overall validation policy was documented in SOPs.

Validation documentation
A written validation protocol specifying critical processes steps and acceptance criteria was established.

Qualification
In general appropriate qualification of critical equipment and ancillary systems were carried out.

Process validation programme
Critical process parameters were controlled and monitored during process validation studies.
The three validation batches were reviewed during inspection.

Cleaning validation
The cleaning validation protocol and report were reviewed. Some fermenters used for Capreomycin were also used for another API manufacturing process. The Company provided reports for cleaning validation of Capreomycin to mevastatin and *vice versa.*

Validation of analytical methods
Analytical methods were validated.

2.12 CHANGE CONTROL

A change control system was established. The change control regarding the fermenters was reviewed.

2.13 REJECTION AND RE-USE OF MATERIALS

Rejection
Intermediates and APIs failing to meet established specifications were rejected.

Reprocessing
The SOP for reprocessing was reviewed and the same reprocessing steps already described in the submitted dossier.

Reworking
According to the company policy when reworking was carried out process validation was considered.

Recovery of materials and solvents
According to the company policy recovery of materials and solvents was not carried out.

Returns
Returned material was managed according to a written SOP.

2.14 **COMPLAINTS AND RECALLS**

Quality-related complaints were recorded and investigated according to a written procedure SOP on complaint management procedure. Records of complaints were reviewed. The written procedure to recall products from the market was reviewed. The authorized person responsible for the execution and coordination of recalls was designated.

2.15 **CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

No contract manufacturers or laboratories were used.

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, the API (Capreomycin Sulphate concentrate solution) manufactured at Zhejiang Hisun Pharmaceutical Co., Ltd. 56 Binhai Road, Jiaojiang District, Taizhou City, Zhejiang Province, 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.