



**World Health
Organization**

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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	Yantou campus
Production Block	Y58, Y55, Y66, Y31, Y22
Physical address	56 Binhai Road, Jiaojiang District Taizhou City, Zhejiang Province 318000 People's Republic of China
Contact person and email address.	Mr. Weibing(Alex) Wang Email: wbwang@Hisunpharm.com
Date of inspection	12 to 13 September 2014
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Capreomycin sulphate concentrate(APIMF169) Moxifloxacin Monohydrochloride(APIMF238) Linezolid(APIMF252)
Summary of the activities performed by the manufacturer	Production and quality control of Non-sterile APIs

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WHO Public Inspection Report
Zhejiang Hisun 12 - 13 September 2014



Part 2: Summary

General information about the company and site

Zhejiang Hisun Pharmaceutical Co. Ltd. (hereafter referred to as Zhejiang Hisun Pharmaceutical) was founded in 1956 and was listed as a public company on the Shanghai (A share) Stock Exchange in 2000. Zhejiang Hisun Pharmaceutical Co. Ltd. is located in Taizhou City Zhejiang Province and was a three hours' drive from Hangzhou airport.

The Zhejiang Hisun Pharmaceutical operations in Taizhou city cover a very large area and can be divided into three parts (The company calls these the Yantou campus; Waisha Campus; and East Factory) which were separated by public roads. APIs for both human drugs and veterinary products were manufactured. Each campus has multiple separate workshops and buildings making it very important to clearly define the exact identification of the inspected facilities as well as any facility of interest to the user of this WHOPIR.

The blocks used for the APIs inspected (including warehouses) and their production were in the Yantou campus and located in different buildings. QC Labs and corporate QA operations associated with these APIs were located on the Waisha campus.

In addition to the APIs of relevance to this WHO inspection several high activity/high toxic compounds including a number of cytotoxic and cytotoxic compounds were also manufactured on the Yantou campus. These included: Daunorubicin; Mitomycin, Bleomycin; Idarubicin; Pirarubicin; Gemcitabine; Cladribine; Fludarabine. The blocks for production of these compounds were relatively close to the blocks where Capreomycin Sulphate concentrate was manufactured but were adequately physically and administratively segregated.

History of WHO and/or regulatory agency inspections

This was the second WHO inspection to the site. The first inspection was performed in August 2012 and related to the fermentation and purification of Capreomycin.



The company as a whole has a rich inspection history by SRAs. As well as several FPP inspections by US FDA, UK MHRA, Australian TGA, and German Länder Inspectorates, various API workshops across the Taizhou operations had been inspected by several national drug regulatory authorities including U.S. FDA, TGA, EDQM, German Länder Authority, Japan PMDA and the local Chinese Provincial FDA.

Focus of the inspection

The inspection focused primarily on the processes for the manufacture and control of several newly submitted APIs but also followed up and reviewed the production and control procedures of the APIs; Capreomycin Sulphate concentrate, Moxifloxacin Monohydrochloride and Linezolid. The inspection covered most of 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. The primary focus was with the review of the newer APIs with that for approved Capreomycin process being primarily restricted to the verification of CAPA from the previous inspection and spot checks commensurate with the risks associated with the use of this product as a low bioburden concentrate for later formulation, aseptic filtration and lyophilization at the Hisun FPP facility inspected previously by WHO in Hangzhou.

Inspected areas

The inspection commenced with:

- Introductions and the opening meeting, the company made a brief presentation about the overall activities of the corporation.
- Confirmation of scope of inspection and inspection plan for the various production blocks to be covered (Y58, Y55, Y66, Y31, Y22)
- More detailed company presentations with an overview of activities in the relevant blocks and high level description of manufacturing steps of the product range in focus

Documentation was reviewed as listed below (but not limited) to:

- Organization charts and job descriptions of key individuals (production, QA)
- QRM assessment report for Yantou Campus

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- Product list and assessments of risks of cross contamination for the site
- Relevant product annual quality reviews and their management including:
- o PQR of Capreomycin API concentrate 2013
 - o PQR of Linezolid 2013
 - o PQR of Moxifloxacin 2013
- Computerized system and data management procedures in API QC and in-process labs, including integration and processing method for chromatogram's
 - Cleaning procedure for multiuse plant and pipelines

All areas of production relevant to the APIs of interest in the various production blocks to (Y58, Y55, Y66, Y31, and Y22) were covered during on-site inspection.

2.1 QUALITY MANAGEMENT

In general, all required quality management systems and elements were established, documented and implemented. The company operates a three tier documented Corporate QMS with Corporate Policies issued and controlled by Head Quarters. The QMS is generally mature with a strong corporate element.

The organizational structure, procedures, processes and resources provided were generally satisfactory. Quality-related activities were defined, documented and were seen to be recorded at the time they were performed.

The company operates on the basis of risk and compliance based approaches supported by process and science based knowledge. The general principles of ICH Q8, Q9, and Q10 are the implemented within QMS in various degrees of maturity. Level 2 documents (Local SOPs, Validation plans and reports, Specifications, BMRs etc and Level 3 (Records) being controlled at the Hisun local site level.

All key QMS procedures requested for review were in place and the majority of SOPs and systems were well developed reflecting the combination of corporate oversight and commitment together experience of working in joint ventures with a number of leading major multi-national companies and the extensive exposure to many SRA inspections over the years.



Responsibilities of the quality and production units

Responsibilities of the quality unit (personnel) and the responsibility of the production unit (personnel) activities were available for inspection. The responsibilities of the quality Unit are independent of production Unit. Appropriate job descriptions and role definitions were documented.

Internal audits (self-inspection)

The company has procedures and a programme in place. In view of the nature and number of the observations made during this inspection and the CAPA implementation plan to these observations, it was considered the company was had a good level of GMP understanding and the self-inspection programme appeared to be effective. In view of this indirect evidence the programme was not covered in further detail by this inspection.

Product quality review

Regular quality reviews of APIs were conducted per SOP on product annual quality management procedure No.H3-SOP-71006. The results of this review were evaluated and an assessment made of whether corrective action or any re-validation should be undertaken.

The PQRs for 2013 of Capreomycin API concentrate, Moxifloxacin and Linezolid were reviewed. These were generally satisfactory and provided most of the key elements expected in the GMP guideline. They contained a full discussion of the majority of the indicators identified by the company and confirmed by the inspectors, and identified elements that could be considered for further study and possible improvement. The company has subsequently further improved the review process with the addition of addition data for certain API starting materials as part of their corrective action plan.

2.2 PERSONNEL

Personnel qualifications

There had been no change in key staff since the last inspection.



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 documented in written job descriptions.

As a whole the Taizhou site employs approximately 4000 staff with approximately 2000 of these being involved in API operations across the various campuses. Manufacturing and QC-IPC work three shifts and the others a one shift operation.

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

Personnel hygiene

Sanitation was at an acceptable level in general on the site. Smoking, eating, drinking, chewing and the storage of food was restricted from the manufacturing areas. The gowning areas were fit for purpose and under good levels of control. General gowning levels and procedures were appropriate to the production activities and the discipline of compliance was being maintained.

Consultants

Not applicable.

2.3 BUILDINGS AND FACILITIES

Design and construction

In general the 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 not dedicated to the inspected APIs except that for the extraction of Capreomycin which was dedicated.

Utilities

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

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Permanently installed pipework was generally appropriately identified. Opportunities for enhanced procedure for certain shared transfer pipework to improve the reliability of cleaning were identified during the inspection and appropriate re-engineering performed as part of the company's CAPA to these observations.

Following observations made during the inspection the company has implemented improved integrity testing schedules for glass lined reactors particularly those used in the final crystallization process areas.

Water

Water used in the manufacture of APIs was suitable for its intended use. Appropriate specifications were established and monitored. The water generation plants reviewed were of good design generally and being well maintained.

Containment

As discussed below, the company does manufacture a number of high potency and sensitizing molecules within the overall Taizhou operations. The location and separation of these facilities were reviewed as were the procedures for organisational and administrative control of personnel and services both at the routine level and in the case of unintended emergency situations. The Company provided relevant procedures and reports providing the evaluation of specific cross-contamination risks especially for high activity/high toxic compounds. These were quite comprehensive however overall a facility-wide risk assessment master report consolidating these contamination studies was recommended as an improvement, and the commitment made to prepare a more comprehensive master list of studies for the overall site made in the company CAPA.

The inspectors were however satisfied as to the effective segregation of the higher risk materials from those of interest to the PQ programme.

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 generally well maintained, in a good state of repair and being maintained in a clean condition. Classification of the areas was appropriate to the operations being performed.

2.4 PROCESS EQUIPMENT

Design and construction

Equipment used in the manufacture of intermediates and API in focus 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 and were available where requested for review.

Calibration

Control, weighing, measuring, monitoring and test equipment were calibrated according to written procedures and an established schedule was in place. The current calibration status of critical equipment was known and was verifiable. Those instruments chosen for review were appropriately handled and documented according to their status and risk for the process.

Computerized systems

Computerized systems were not used in the inspected API production operations and the company was relying heavily on a somewhat complex manual documentation system.



2.5 DOCUMENTATION AND RECORDS

Documentation system and specifications

Documents related to the manufacture of APIs were sampled and reviewed throughout the inspection and were found to have been prepared, reviewed, approved and distributed according to SOP and effectively handled. 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, finished APIs etc.

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

Records of raw material, intermediates, APIs, labelling and packaging materials were maintained and when requested made promptly available to the inspection team.

Batch production records

The most recent batch production records were reviewed for Capreomycin Sulphate API concentrate. These in general, included all relevant and complete information relating to the production and control of each batch. Written procedures were established and followed for investigating critical deviations. The records and reports of deviations and investigations reviewed were generally satisfactory. There appeared to be reasonable risk based emphasis on root cause identification and CAPA rather than symptomatic correction depending upon risk classification.

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.

The policies and procedures in place for assuring good data management in the laboratory were reviewed. The company had policies and procedures for the assurance of laboratory data integrity. These had been in place for some time however there were a number of updates over the last year. QA staff stated that it had been actively following recent issues highlighted by USFDA and other SRA Inspectorates and wished to ensure that it had robust systems in place to meet current expectations and trends.

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In this respect it was noted that the chromatographic software versions in use were relatively recent and had appropriate access controls and audit trails implemented and in use. At the time of the inspection current SOPs had no requirement for the system audit trails to be reviewed at the time of batch release of the product. (It was however accepted that there was a system for monthly review audit of this information). The system has been further strengthened as part of the company's CAPA to the observations made in this inspection.

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.

Assessment of the Site Master File

The Site Master File was available in electronic form before the visit was made to the manufacturing site. Although the SMF covered all yes areas it was noted that in some areas the data provided was somewhat limited especially as it related to APIs manufactured that were outside the scope of the immediate WHO PQ programme. For example it was noted that the products of workshop Y63 were named as “anti-infection” products without any further detail of the manufactured molecules and there was a note that it was now “not in use”.

Although the information was made promptly available on site during the inspection, it was recommended that further information be provided in the SMF to allow the Inspection Team to obtain a full picture of cross contamination risks given that there were workshops where products normally requiring dedicated facilities located on some of the Taizhou campuses.

2.6 MATERIALS MANAGEMENT

General controls

Procedures for the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were inspected. The finished APIs' log book and



the traceability were checked. The material code management was discussed with the company during the inspection.

There was a rather complex system of log books in the warehouse that documented movements between the storage and production units and there was some confusion as to their status as GMP and financial records, and the retention times for such detailed logs after the annual financial audit. Material movement between the stores and the workshops for dispensing against orders was manually controlled using a variety of logs and records of transactions.

Although the system was somewhat complex and difficult to follow, the records when finally fully assembled appeared to reconcile and provided a full history. The weakness inherent in the manual system complexity has been adequately strengthened within the short term CAPA proposals and in the medium term should be eliminated as the company rolls out its new ERP system.

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

Examination of the flow of the manufacturing process and relevant equipment was in line with the BPR examined in general compliance with the details in the submissions to WHO PQT. That equipment used in different step of the manufacturing process that was inspected was satisfactory. Majority of the equipment used for production of the APIs in focus were not dedicated other than the purification equipment for Capreomycin.

Production flows were generally well laid out and logical. The production areas were in good condition and appropriate to their application.



Certain of the APIs in focus are crystallized in glass line vessels. The potential for damage of linings and checking for reactor linings was discussed and subsequently improved checks implemented to enhance the measures already in place at the time of the inspection.

In-process sampling and controls

The procedure and parameters for in-process controls were in place and carried out during the inspection.

Blending batches of intermediates or APIs

In accordance with the company policy the blending of batches of APIs inspected was not allowed by procedure and there was no evidence that it had been carried out for any market.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

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

Packaging and labelling operations

Packaging and labeling operations procedure and records were in place but unfortunately these process steps were not being carried out during the inspection. The premises and equipment appeared satisfactory but they could not be confirmed in an operational state.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Facilities were available for the storage of all materials and those observed were under appropriately controlled and monitored conditions.



Distribution procedures

The receiving and distribution of the finished API products were inspected and found satisfactory. It was noted that there was no coding of different grades of the API and intermediate. These grades are not fully interchangeable and a coding system for GMP as well as ERP purposes is in the process of implementation.

2.10 LABORATORY CONTROLS

The API QC laboratory was situated on the Waisha Campus. The premises, facilities and utilities were separate from production. There were dedicated rooms for activities like sample receipt and storage, wet chemistry, hot areas and instrumentation. There were adequate pieces of equipment with up to date calibration status.

The following functions of the QC laboratories and relevant SOPs and associated records were reviewed:

Records of sample receipt and allocation of analysis

Sampling plan and sample register

Batch testing report

Computerized system management procedure in API QC lab

Integration and processing method for chromatograms

Capreomycin specification

Stability monitoring of APIs

A SOP on management procedure of stability studies was available. The facilities for the storage and monitoring of stability samples is of a good standard. There were cabinets available for all relevant storage conditions.

Reserve/retention samples

Retention samples were available and stored under appropriate conditions.



2.11 VALIDATION

Validation policy

The company's overall validation policy had not been changed since last inspection. The system is comprehensive and adequate.

Validation documentation

Written validation protocols specifying critical processes steps and acceptance criteria were established and available where requested.

Qualification

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

Process validation (PV) programme

Critical process parameters were controlled and monitored during process validation studies.

The PV of Linezolid was performed in 2013. It is a synthetic product and with only one manufacturing process/synthesis route irrespective of the end market. The company claimed that no recovered solvents and mother liquid were used for production.

The PV of Moxifloxacin HCl was performed in 2012. There were different grades but all made by one manufacturing process with the differences being in specification and test method rather than processing.

Cleaning validation

The cleaning validation was performed with worst case approach. Records and performance of the studies reviewed were satisfactory.



2.12 CHANGE CONTROL

A change control system was established. The system is comprehensive and according to corporate guidance. The same QA system is used across both API and FPP operations. The change control was covered under the FPP report of this inspection.

2.13 REJECTION AND RE-USE OF MATERIALS

Rejection

SPOs required intermediates and APIs failing to meet established specifications to be rejected. There was adequate space available for the segregation of rejected material prior to disposal.

Reprocessing

There has no change in procedures and processes since last inspection. Systems were considered satisfactory.

Reworking

According to the company policy when reworking was carried out process validation was considered and regulatory approval would be sought. There were no cases of reworking of the APIs in focus having occurred.

Recovery of materials and solvents

According to the company policy recovery of materials and solvents was not carried out for the PQ product.

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. The written procedure SOP to

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recall products from the market was reviewed. The SOP was adequate. 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 for the PQ product.

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 capreomycin sulphate concentrate (APIMF169), Moxifloxacin Monohydrochloride (APIMF238) and Linezolid (APIMF252) manufactured at Yantou campus, Zhejiang Hisun Pharmaceutical Co., Ltd. located in 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.