World Health Organization
20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.w

WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Hisun Pharmaceutical (Hangzhou) Co Ltd
Unit number	Line 5
Production Block	Building C06
Physical address	Xialian Village, Xukou Town, Fuyang City, Hangzhou City, Zhejiang Province, 311404, P R of China
Contact address	Same as above
Date of inspection	2 - 5 December 2014
Type of inspection	Routine Inspection and New Product (Kanamycin)
Dosage forms(s) included in the inspection	Powder for Solution for Injection
WHO product numbers covered by the inspection	Capreomycin (sulfate) Powder for solution for Injection 1g (TB261) Kanamycin (acid sulfate) Powder for solution for Injection 0.5g (TB300) Kanamycin (acid sulfate) Powder for solution for Injection 1g (TB 301)
Summary of the activities performed by the manufacturer	Production and Quality Control of Sterile Injection

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Part 2: Summary

General information about the company and site

Hisun Pharmaceutical (Hangzhou) Co. Ltd. is a 100% subsidiary of Zhejiang Hisun Pharmaceutical Co., Ltd and is located in Fuyang, Hangzhou City, Zhejiang Province, in South Eastern China.

The Injection Manufacturing workshop, building C06 was initiated in 2011. Approximately 1885 employees were employed at the site, of which 237 were in Finished Dose Form manufacture with approximately 30 operating on line 5.

The site included production of API, OSD, Lyophilized powder for injections etc. and Biological products. The site also housed a Hisun/Pfizer joint venture facility. The site currently has a wide range of multinational pharmaceutical customers.

The Capreomycin and Kanamycin powders for injection, under consideration by WHO, were manufactured on production line 5. This line was non-dedicated with up to 5 different products produced. One of the other products was being filled on the line at the time of the inspection.

History of WHO and/or regulatory agency inspections

This was the second WHO inspection. The initial WHO inspection was performed in January 2013. The site has been inspected by US FDA in July and April 2014, and CFDA in 2011 for Line 5 and 2010 for OSD. Additionally, German and Mexican regulatory authorities have inspected for APIs. A parallel CFDA inspection was performed for a different production line at the same time as the WHO inspection.

Focus of the inspection

This WHO inspection focused on the production and control of Capreomycin Powder for Solution for Injection (1g) and Kanamycin Powder for Solution for Injection (0.5g and 1g) products. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Starting Material, Packaging Components, Product Intermediates and Finished Product Warehouses, including sampling areas
- Production facilities in Building C06, particularly Line 5
- QC facilities including Analytical Chemistry and Microbiology Laboratories in building C02
- Systems for Purified Water, Water for Injection and Clean Steam Supply
- HVAC Systems associated with Building C06, Lines 5 and 4

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Key Documents reviewed

- Complaints procedure and 2014 Complaints summary list
- Recalls procedure and 2014 Mock Recall study report
- Internal Audit procedure and 2014 status list
- Change Control procedure and Capreomycin Powder for Injection associated change proposals
- Deviations Handling procedure and Deviations reports associated with line 5 or Capreomycin Powder for Injection
- Out of Specification procedure and 2014 summary lists
- Supplier Approval procedure and 2014/2015/2016 Audit Plan
- Reprocessing and Reworking Management procedure.
- CAPA Management procedure and summaries of CAPA projects in 2014 for line 5
- Batch Release procedure
- Printed Packaging Material Management procedure and drafted Export procedure
- Environmental Monitoring procedure for line 5 areas and summary Trend Analysis report of results for July-Sept 2014
- Environmental Monitoring procedure for quality water and steam systems and summary Trend Analysis report of results for July-Sept 2014
- Capreomycin Powder for Injection 2013 Product Quality Review
- Equipment Qualification Protocols and Reports for Line 5 Lyophiliser
- Validation Protocols and Reports for Autoclaves, De-Pyrogenation Tunnel, Filling and Stoppering machine, Lyophiliser and Air Handling systems
- Cleaning validation
- Cleaning validation protocol
- Training, Workshop employee training procedure
- Training for selected individuals from QC, Vial Inspection and Utilities Engineering
- Facility layouts for line 5, building C06, utilities support areas and equipment and laboratories in building C02
- Company and Site Staff Organogram
- Site Master File dated November 2014
- Company Quality Philosophy and Quality by Design statements
- Risk Management Procedure
- Risk management plan

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

- Risk assessment report of Kanamycin Powder for Solution for Injection manufacturing process
- OOS/OOT investigation procedure
- Contract testing management procedure

2.1 PHARMACEUTICAL QUALITY SYSTEM

The company exhibited a Quality by design statement and Quality Philosophy based on ICH Q8/Q9/Q10.
A system for quality assurance in general was established, with procedures covering key quality elements. The procedures reviewed were generally of a good standard with some individual minor issues observed.

The procedural system ensured that:

- Pharmaceutical products were designed and developed in a way that took account of the requirements of GMP.
- Production and control operations were clearly specified in a written form.
- Suitable arrangements were made for the manufacture, supply and use of correct starting and packaging materials
- Controls on materials, calibrations, and validations were generally performed acceptably.
- Internal Audits regularly appraised the effectiveness and applicability of the QA system and was acceptably followed.
- A Quality Risk Management (QRM) process was followed, with product Risk Assessments documented.
- Product Quality Reviews were conducted, appeared generally comprehensive and were generated in timely manner.

2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented and followed. Required staff and system resources were provided. Manufacturing processes were clearly defined and systematically reviewed. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and comprehensive records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility, with extensive hand washing required.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Clean areas were cleaned frequently in accordance with approved written programmes. Rotation of disinfectants in clean areas was established. Environmental Monitoring of microbial status of in use disinfectants was regularly undertaken. Disinfectants used in Grade A and B areas were sterilised before use.

2.4 QUALIFICATION AND VALIDATION

The company identified qualification and validation work required. The key elements of a qualification and validation programme were defined in a Validation Master Plan (VMP) and Product Validation Guideline. Documentary evidence was available that the premises, supporting utilities, equipment and processes have been designed, installed and operated in accordance with their design specifications.
During the inspection, procedures and validation documents were reviewed for:

- Media Simulation Trials
- De-Pyrogenation Tunnel
- Steam Sterilisation of Rubber Stoppers, Machine Change Parts and Garments
- Product Lyophilisation
- Cleaning validation of line 5

Media Simulation Trials:
The media fill was performed at six months interval. The activities and interventions known to occur during production based on worst-case situation were incorporated into the process simulation protocol. The media fill was considered acceptable in general. The following documents regarding line 5 were reviewed:

- Guideline of process simulation for aseptically filled products SOP
- Media fill Protocol
- List of interventions, Media fill report for revalidation performed in May 2014, and no contamination was reported. Container closure integrity test. No contamination was reported.

De-Pyrogenation Tunnel:
Revalidation of the tunnel drying oven in the injection line 5 was reviewed. The tunnel sterilizer had been appropriately revalidated.

Steam Sterilisation of Rubber stoppers/Machine Change Parts/Garments:
Re-Validation studies of Rubber Stoppers and Clean Tools sterilisation in autoclave on line 5 were reviewed and had been appropriately revalidated.

Product lyophilisation:
Equipment qualification of one of the lyophiliser units was reviewed. The units of line 5 complied with Functional Specification.
IQ was performed according to protocol and was an excellent document drafted by the supplier, but fully reviewed and acknowledged by Hisun staff.
OQ was similarly performed to protocol which again was drafted by the supplier and executed jointly by Hisun.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Process Validation of Capreomycin1g through the Lyophiliser was performed according to protocol and reported. This PQ study was comprehensive and well executed for a commercial batch size. The recipe was directly comparable to the one used for the half-size validation batches.

VHP Sterilisation:
The Steris VHP sterilizer was not reviewed during this inspection.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written procedures and the corrective actions were taken. A QA person responsible for handling complaints was designated. Complaints concerning individual product defects were recorded and investigated. Consideration was given as to whether other batches should be checked in order to determine whether they were also affected.
A series of complaints regarding re-constitution issues were reviewed. While corrective action had been taken with the complainant, preventative action in terms of enhancing re-constitution instructions had not been progressed. CAPA was made after the inspection and considered acceptable.

2.6 PRODUCT RECALLS

The Product Recall procedure was reviewed. The QA person responsible for the execution and coordination of recalls and the Recall Committee were designated.
No Injection product recalls had been required since the last WHO inspection. A Mock Recall exercise on a batch of API had been performed. Conceptually the progress of this exercise was satisfactory in general.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production of Lyophilised powders for Injection was not contracted out.
A number of local contract laboratories were used for specific or complex testing such as Arsenic, Antimony and Lead extraction, as well as coefficient of thermal expansion of vials. Technical/Quality Agreements with these laboratories were reviewed.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections/Internal Audits were performed routinely and covered basic GMP topics. Internal auditors were selected from appropriate departments and suitable training appeared to be given prior to authorizing the individual. The frequency of internal audits was stated in the procedure, but the twice yearly requirement could be relaxed. A report was made at the completion of an internal audit which in turn should generate a CAPA proposal. CAPA progress was monitored by the QA Manager.
A system of Supplier Approval was in place. Prior to approval samples of material were requested and questionnaires were completed. Supplier Audits were required to

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

be performed at a routine frequency, but printed component suppliers could be approved on the basis of questionnaires only.

2.9 PERSONNEL

Job responsibilities were recorded in written job descriptions. Personnel generally appeared aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. An organization chart was available and was appropriate.

It was noted that a number of temporary contract staff were employed in non-critical functions. The site was advised that such employment requires careful control.

2.10 TRAINING

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories. Newly recruited personnel received training appropriate to the duties assigned to them. Approved training programmes were available. Training records were filed appropriately. Training records for a QC Analyst, Utilities Engineer and Senior Vial Inspector were reviewed and appeared generally satisfactory.

2.11 PERSONAL HYGIENE

All personnel employed received initial and regular training in disciplines relevant to the correct manufacture of sterile products. Changing and washing followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The protective clothing washing and sterilization operations followed standard operating procedures. Sterile garment washing operations were validated.

Extensive hand washing was required of visitors as they entered the various areas.

2.12. PREMISES

The core clean operations suites had been constructed by Pharmaplan. The construction was of good standard, but the replaced door handles still appear awkward to use.

Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning agents and disinfectants, where used. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. The final stage of the changing room was in the at-rest state, the same grade as the area into which it leads. Changing rooms were equipped with mirrors. Airlock doors did not open simultaneously.

Storage areas

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Quality control areas
QC laboratories were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records. Separate air-handling units were provided for microbiological laboratories.

2.13 EQUIPMENT
The equipment installed was of a high standard and supplied by well known, industry recognised EU and US manufacturers. The facility was well designed and appeared to operate effectively.

The manufacturing/compounding vessel and filter system were equipped with automated CIP and SIP systems. These systems had been suitably validated.
The Filling line was designed using RABs principles and the Lyophilisers were automatically loaded and unloaded.

All fixed pipe-work was clearly labeled to indicate the contents and the direction of flow.

Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis.

Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments suited to the testing procedures undertaken.

All critical equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems were subject to planned maintenance. Planned maintenance schedules and lists were briefly reviewed and appeared generally satisfactory.

2.14 MATERIALS
Incoming materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under the appropriate conditions. Material codes had been introduced on identity labels since the last inspection.

Starting materials
Starting materials were purchased from approved suppliers. Appropriate TSE/BSE compliance statements were available for these materials. Starting materials in the storage area were appropriately labelled.
The API in bulk solution was supplied by Hisun Jiaojiang plant. Bulk containers from which samples were drawn were identified.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Packaging materials
Packaging materials were purchased from approved suppliers. Vials and Rubber stoppers were stored in separate rooms. Printed packaging materials were stored in secure conditions. Each delivery of batch of printed or primary packaging material was given a specific reference number or identification mark.

Finished products
Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer.

Rejected, recovered, reprocessed and reworked materials
Rejected materials and products were marked as such and stored separately. Finished product was not reworked, but could be reprocessed according to the procedure.

Recalled products
Recalled products were stored separately in a secure area.

Returned goods
Returned goods were stored separately in a secure area.

Reagents and culture media
Records for the receipt and preparation of reagents and culture media were available. Reagents made up in the laboratory were prepared according to written procedures and appropriately labelled. Positive and negative controls were applied to verify the suitability of culture media each time they were prepared and used.

Reference standards
Official reference standards were used as well as working reference standards prepared by the manufacturer. Reference standards were properly labeled and stored. The temperature in the reference standards storage fridge was monitored continuously.

Waste materials
Not inspected

2.15 DOCUMENTATION

In general, documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken. Some issues of detail were observed across the range of documents reviewed.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Labels
Labels applied to containers, equipment and premises were clear and unambiguous. Material approval labels exhibited a QA stamp which partially obscured the printed material item code. These codes appeared to have been universally introduced for container labeling.

Specifications and testing procedures
Testing procedures were validated and were appropriately authorized and dated in general. Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products. The company used fluorescence detector instead of electrochemical detector which is a USP pharmacopeia method for Kanamycin Acid Sulfate assay.

Master formulae
Authorized master formulae were available for both Capreomycin and Kanamycin.

Packaging instructions
Authorized packaging instructions were available.

Batch processing records
Batch manufacturing records (BMRs) were retained for each batch processed. Before any processing began, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded as part of the BMR.
Batch records were extensive with each process stage or sub-stage requiring multiple pages. Records were paper based with printouts from plc controlled equipment.

Batch packaging records
A batch packaging record (BPR) was retained for each batch processed. Before any packaging operation began, checks were made that the equipment and work station were clear of previous products, documents or materials, and that equipment was clean and suitable for use. Checks were stated to be recorded and formed part of the BPR. BPRs were not reviewed.

Standard operating procedures and records
SOPs and associated records of actions taken were available. A significant number of procedures supporting the Quality System were reviewed. A number of detail issues were observed.

Calibration Records
A number of instrument calibration records were briefly reviewed as part the review of validation documentation. Generally they were acceptably worded and filed.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Assessment of the Site Mater File
The Site Master File was made available in electronic form prior to the inspection. It was generally comprehensive, accurate and complied with the guidelines on preparation of an SMF.

2.16 GOOD PRACTICES IN PRODUCTION

A batch of another product was being filled on line 5 during the visit by the WHO team, and the overall process run appeared suitably controlled. The entire line was inspected by observation beside individual items of equipment, with filling, stoppering and vial entry to lyophiliser observed through the various windows. The operation was proceeding smoothly and operating staff appeared conscientious and skilled.
Validation batches of Capreomycin Powder for injection (1g) and three batches Kanamycin Powder for Solution for Injection (0.5g and 1g) have been processed through to after inspection. Review of substantial segments of batch records suggested that document completion was accurate and comprehensive.
Deviations from instructions or procedures were documented in accordance with the procedure. The authorization of the deviation was approved in writing by involved department and QA. Checks on yields and reconciliation of quantities were carried out. During processing, all materials, bulk containers, major items of equipment and rooms were labelled.

Manufacture of Sterile preparations
Clean areas for the manufacture of sterile products were classified according to the required characteristics of the environment. Clean rooms and clean-air devices were routinely monitored while in operation. For Grade A and B zones, particle monitoring was undertaken for the full duration of critical processing, including equipment assembly. To control the microbiological cleanliness of Grades A–D in operation, the clean areas were monitored. Appropriate alert and action limits were set for the results of particulate and microbiological monitoring. Some 5 micron particle results in the grade A/B appeared to be above allowable limit and environmental monitoring of grade D areas was infrequent

Aseptic preparation
Components after washing were handled in a Grade C environment. The preparation of solutions which were to be sterile-filtered during the process was performed in a Grade C background environment. The handling and filling of aseptically prepared products, was performed within RABs with a Grade A environment.

Aseptic processing and sterilization by filtration
Bulk Capreomycin and Kanamycin solutions were filtered through sterile filters. The integrity of the sterilizing filters was verified before use and immediately after use.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Finishing of sterile products
Containers were closed by validated methods. Crimping of the caps was performed after lyophilization. Filled containers were inspected individually. Inspection was carried out visually in a qualified and adequately maintained light inspection station, to ensure proper illumination and background of matt black and white panels. Operators doing the inspection were qualified by periodic practical testing.

Packaging operations
Before packaging operations begun, line clearance routines would be followed. This step would be recorded in BPR. The secondary packaging operation was totally fragmented with vials being excessively handled between each sub-stage.

Production records were reviewed as part of the approval process of batch release before transfer to the authorized person in QA.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel accessed production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products
Tests followed the instructions given in the relevant written test procedure. The result was checked by the QC supervisor before the material or product was released. Samples were representative of the batches of material from which they were taken. Out-of-specification results and out of trend results obtained during testing of materials or products were investigated in accordance with an approved procedure. Records were maintained.

Test requirements
Starting and packaging materials
Before releasing a starting or packaging material for use, the QC manager ensured that the materials have been tested for conformity with specifications.

In-process control
In-process control records were maintained and formed a part of the batch records.

Finished products
For each batch of medicines product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Batch record review
QC records were reviewed as part of the approval process of batch release. Retention samples from three batches of finished product for registration purpose as well as related documents were retained for one year beyond the expiry date. Finished products were stored in mock ups of their final packaging and under the recommended conditions.

Stability studies
The quality and stability of finished pharmaceutical product were evaluated. Expiry dates and shelf-life specifications were established on the basis of stability tests related to storage conditions. A written programme for ongoing stability determination was developed and implemented.
Stability and on-going stability samples were stored properly. Temperature in the incubators was continuously monitored. Incubators were equipped with alarm system.
The stability chambers were connected to a UPS system in event of a power outage

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, Hisun Pharmaceutical (Hangzhou) Co Ltd located at Xialian Village, Xukou Town, Fuyang City, Hangzhou City, Zhejiang Province, 311404, P R of China was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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 2 years, provided that the outcome of any inspection conducted during this period is positive.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int