

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Hisun Pharmaceutical (Hangzhou) Co., Ltd.
Unit number	Line 5, Building 06
Production Block	Same as above
Physical address	Xialian Village, Xukou Town, Fuyang City Hangzhou City, Zhejiang Province 311404, China
Contact person and email address.	Mr. Weibing (Alex) Wang Vice President, Quality Zhejiang Hisun Pharmaceuticals Co., Ltd Email: wbwang@Hisunpharm.com
Date of inspection	14 to 17 January 2013
Type of inspection	Routine inspection (New site)
Dosage forms(s) included in the inspection	Powder for injections
WHO product categories covered by the inspection	TB
Summary of the activities performed by the manufacturer	Production and quality control

Part 2: Summary

General information about the company and site

Hisun Pharmaceutical (Hangzhou) Co., Ltd. which is 100% subsidiary of Zhejiang Hisun Pharmaceutical Co., Ltd. is located in Fuyang city Zhejiang Province, a coastal city in South Eastern China, approximately 2 hours drive from Hangzhou. The site activities included production of API (including those by cell culture and fermentation, OSD, Lyophilized powder for injections etc. The Injection Manufacturing workshop C06 under inspection was initiated in 2011. There are about 1700 employees working at the site.

Capreomycin powder for injection is manufactured in the production line 3 and line 5. WHO PQ products is produced by Line 5, the production line was not dedicated but a general purpose automated lyophilisation line. It is currently in use for the manufacture of Adenosine Powder for Injection and this was being filled at the time of the inspection.

To date there has been no commercial production sized lots produced on Line 5 other than the validation lots which were produced at half batch size.

History of WHO and/or regulatory agency inspections

The site has been inspected by US FDA for API (Daptomycin) and OSD in July 2012 and SFDA in 2012 for Line 3, 2011 for Line 5 and in 2010 for OSD. This was the first inspection of any operation on this campus by WHO PQP.

Focus of the inspection

The inspection focused on the production and control of Capreomycin Powder for injections (1.0g) 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

Warehouses including sampling areas
Production facilities – Line 5 in Building C06
QC facilities including physico-chemical lab and microbiology lab
Water station for purified water, water for injection and steam
HAVC

Document review

- Facility layouts
- Organogram
- Training
- Product Quality Reviews
- Change control
- Deviation control
- Complaints
- Recall
- OOS
- Supplier's Approval
- Release, rejection control
- Document control
- Self-inspection

Document review (production) including

- VMP
- BMR masters,
- BMR's of the inspected products
- Manufacturing process validation
- Cleaning validation
- Manufacturing equipment calibration, qualification and maintenance
- Water system
- HVAC system

Document review (QC, physico-chemical and microbiol), including

- Sample handling and testing
- Handling of reference standards
- Analytical instrument calibration, qualification, maintenance
- Recording of analytical tests, handling of raw data, reporting
- OOS handling

2.1 QUALITY ASSURANCE

A system for quality assurance in general was well established with procedures established for all key quality elements. In general the procedures reviewed were a uniformly good standard reflecting a good level of input from personnel with a good knowledge of SRA GMP requirements:

- Pharmaceutical products were designed and developed in a way that takes account of the requirements of GMP
- Production and control operations were clearly specified in a written form
- Arrangements were made for the manufacture, supply and use of the correct starting and packaging materials
- Controls on materials, calibrations, and validations were carried out
- There was a procedure for self-inspection that regularly appraises the effectiveness and applicability of the QA system
- There was a system for Quality Risk Management (QRM)
- Quality reviews were conducted
- There were procedures for deviations, investigations and CAPA

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. The necessary 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 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.

Clean areas were cleaned frequently in accordance with an approved written programme. It was the practice to rotate the disinfectants used in the critical clean rooms. Monitoring of the microbial status of in use disinfectants was included in the environmental monitoring programme and was regularly undertaken. Disinfectants used in Grade A and B areas were sterilized before use.

2.4 QUALIFICATION AND VALIDATION

The company identified what qualification and validation work was required. The key elements of a qualification and validation programme were defined in a workshop validation master plan (VMP). Documentary evidence was available that the premises, supporting utilities, equipment and processes have been designed, installed, operated in accordance with their design specifications.

During the inspection procedures and validations were reviewed for

- Media simulations
- Dry heat tunnel validation
- Validation of the sterilization of stoppers by steam
- Validation of the sterilization of equipment for machine set up
- Lyophilization
- VHP Treatment

Media simulations

Media simulation study was reviewed in detail. This involved the filling of 3 lots filled in 2011. The vials used in this study were to the same specification as those for inspected powder for injections but from a different supplier.

The media simulation study protocol provided for a reasonable set of routine and exceptional interventions and the BMRs for the media simulations reviewed were well completed and comprehensive.

The studies require repeating at defined intervals.

There have been no media fill positives to date in the studies performed however the media simulation procedure gave appropriate guidance on the actions to be taken in the event of a positive been found.

Steam Sterilization Studies

These two studies covered both stopper and equipment sterilization in the line 5 Steris sterilizer. The validations were generally acceptable and the cycle being examined involved 3 prevacuum pulses prior to steam equilibration. There was no evidence in the Inspectors' review of the data of air retention within the loads. It was noted however the loads were not particularly complex.

VHP Sterilization

The company uses a Steris VHP generator for both room and pass through sanitization. The processes have been validated and requalified on an annual basis. The validation was satisfactory in general with a satisfactory level of inactivation being found with both Chemical and Biological Indicators placed in both class A and B zones.

The hydrogen Peroxide used for the sanitization is controlled and released by QC before use as are the BIs and CIs.

VHP pass through has been used for the sanitization of microbiological monitoring plates used in the core aseptic zones. The company has yet to fully validate that there is no influence of absorbed Peroxide penetrating the overwraps but was aware this needed to be done and had already established protocols to execute.

Tunnel validation

The tunnel sterilizer had been appropriately validated and shown to achieve at least a 4 log reduction in endotoxin titre with a standard 3 log limit set.

Performance qualification of Lyophilisers

The initial PQ performed in May and June 2011 was reviewed. This validation had been performed for the original Line 5 product Adenosine.

There was adequate information regarding the cleaning and sterilization systems in place and these appeared to perform satisfactorily.

Shelf uniformity tests had been performed and were satisfactory.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written procedures and the corrective actions were taken. A person responsible for handling the complaints and deciding the measures to be taken was designated.

Complaints concerning a product defect were recorded and investigated. Consideration was given to whether other batches should be checked in order to determine whether they were also affected.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was reviewed. The authorized person responsible for the execution and coordination of recalls was designated.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production or quality control operations were not contracted out.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were performed routinely. Self inspection covered basic GMP topics. The frequency at which self-inspections were conducted was stated in the procedure. A report was made at the completion of a self-inspection.

The system was in place for approving suppliers. Before suppliers were approved and included in the approved supplier's list they were evaluated. Critical materials suppliers' assessments had been performed but not all by site audit.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were 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.

There was a roster in place to ensure that the appropriate staff had been covered by media fills.

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 kept. A procedure for Analyst qualification and periodic proficiency verification was in place.

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 closing washing and sterilization operations followed standard operating procedures. Sterile garment washing operations were validated.

2.12 PREMISES

The core clean operations had been constructed by Pharmaplan and the construction techniques were of the usual high standard.

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 opened simultaneously.

The fill lines are designed using RABs principles and the lyophilisers are automatically loaded and unloaded.

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.

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 mainly supplied by well-known US and EU manufacturers. The facility was well designed and the equipment appeared to be running well except for a continuing issue with the stopper bowl feed that was requiring an excessive number of interventions due to frequent blockages due to what appeared to be doubled stoppers.

The manufacturing vessels and filter systems were designed to be CIP and SIP. The design was automated.

All fixed pipework was clearly labelled 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.

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

Starting materials

Starting materials were purchased from approved suppliers. Starting materials in the storage area were appropriately labelled.

The API in bulk solution was supplied by Hisun Taizhou plant. Bulk containers from which samples were drawn were identified.

Packaging materials

Packaging materials were purchased from approved suppliers. 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 and 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 well designed, comprehensive, and 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.

Labels

Labels applied to containers, equipment and premises were clear and unambiguous.

Specifications and testing procedures

Testing procedures were validated and were appropriately authorized and dated. Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products.

Master formulae

Authorized master formula was available.

Packaging instructions

Authorized packaging instructions existed.

Batch processing records

Batch manufacturing records (BMRs) were kept for each batch processed. Before any processing begins, 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 and were part of the BMR.

Batch packaging records

A batch packaging record (BPR) was kept for each batch processed. Before any packaging operation begins, 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 recorded and were part of the BPR.

Standard operating procedures and records

SOPs and associated records of actions taken were available.

Assessment of the Site Master File

The Site Master File was available in electronic form before the visit was made to the manufacturing site. In general it complied with the guidelines on preparation of the SMF.

2.16 GOOD PRACTICES IN PRODUCTION

There was a trial batch of Capreomycin lyophilised powder for injection scheduled during the visit by the WHO team, because it has not yet commercialized for line 5. The filling step was inspected.

Deviations from instructions or procedures were done in accordance with an approved procedure. The authorization of the deviation was approved in writing. Checks on yields and reconciliation of quantities were carried out. During processing, all materials, bulk containers, major items of equipment and rooms were labeled. The three batches validated for registration purpose were reviewed.

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.

Aseptic preparation

Components after washing were handled in a Grade D or better environment. The preparation of solutions which were to be sterile-filtered during the process was carried out in a Grade C or better environment, such as Grade A with C background. The handling and filling of aseptically prepared products, was carried out within an isolator with Grade A environment.

Aseptic processing and sterilization by filtration

Capreomycin solution was filtered through a sterile filter of 0.22 micron into a previously sterilized container. A second filtration through a further sterilized microorganism-retaining filter prior to filling was carried out. The final sterile filtration was carried out close to the filling point. The integrity of the sterilized filter was verified before use and immediately after use.

Examination of the records including the monthly trend reports for the grade A and B zones were acceptable and appropriate limits were in place.

The results of WFI monitoring were also noted to be satisfactory with no significant trends present.

Finishing of sterile products

Containers were closed by validated methods. Crimping of the caps was performed after lyophilisation. 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, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. The line clearance was performed and recorded in BPR. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

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 had access to 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.

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 kept for one year after the expiry date. Finished products were kept in their final packaging and stored 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.

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., Xialian Village, Xukou Town, Fuyang City, Hangzhou City, Zhejiang Province 311404, 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 3 years, provided that the outcome of any inspection conducted during this period is positive.