



**Prequalification Team
WHO PUBLIC INSPECTION REPORT
Finished Product Manufacturer**

Part 1: General information

Name of Manufacturer	NCPC New Preparation Branch Factory
Production Block	Workshop 201
Physical address	No.115 Hainan Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China
Contact Address	Same as above
Date of inspection	20 to 24 October 2014
Type of inspection	Routine inspection (New site)
Dosage forms(s) included in the inspection	Powder for injection
WHO product numbers covered by the inspection	Streptomycin for injection (TB296) 1g
Summary of the activities performed by the manufacturer	Production and quality control of the FPP including the sterile.

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

WHO Public Inspection Report
NCPC New Preparation Branch Factory
Shijiazhuang, Hebei, China
20 to 24 October 2014

Part 2: Summary

General information about the company and site

NCPC New Preparation Branch Factory located at No.115 Hainan Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China was established in 2011. It is an affiliated of North China Pharmaceutical Co., Ltd. (NCPC). The total land area is 225,400 square meters. The factory manufactures preparations and health-care products, including lyophilized powder for injection, powder for injection, small volume injection, eye drops, capsules, tablets, granules, and oral solutions.

There were 706 people employed at the time of inspection. The company claims that there is no toxin or hazardous substances manufactured in this factory.

History of WHO and/or regulatory agency inspections

This was the first WHO inspection. The plant was inspected and licenced by the local drug authority.

Focus of the inspection

The inspection focused on the production and control of Streptomycin Powder for Injection 1.0g (TB296). 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

Production and QC labs including:

- Receiving areas (raw materials and packaging materials)
- Storage areas for starting, packaging materials
- Sampling and dispensing areas
- Production areas related to the WHO product, including support areas such as vial washing and sterilization, vial filling, vial crimping, labeling and inspection, and finished product storage
- Quality control laboratory (chemical, stability testing, microbiological laboratory, printed material QC laboratory)
- Quality assurance and documentation
- HVAC, water system

Documents reviewed included but were not limited to:

- Facility layouts
- Quality risk management
- Training
- Change control

- Deviation control
- OOS procedure
- Specifications and testing procedure
- Supplier's Approval
- Water monitoring
- Complaints and recall
- PQ of tunnel sterilizer and steam sterilizer
- Protocol and report of media fill "
- Protocol and report of process validation
- BMRs
- Microbiological data of environment monitoring
- Technical agreement with API manufacturer

2.1 PHARMACEUTICAL QUALITY SYSTEM

Product quality review

Annual product quality review was performed according to a documented procedure. The product quality review for streptomycin had not yet been done as the process validation was performed in July 2014. A 2013 product quality review for a similarly manufactured product was reviewed as an example of the implementation of the procedure.

2.2 GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were implemented. Necessary resources were generally provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls. Qualification and validation were performed. Manufacturing steps were recorded in batch manufacturing and packaging records. Manufacturing processes were defined and reviewed. Product was released by the authorized persons.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at a satisfied 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. 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 general. Documentary evidence was available that the 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
- Steam sterilization

Media simulations

Media simulation study was reviewed in detail. The validation SOP requires that more than 5000 vials filled for 3 consecutive runs of the actual presentation and then this is followed with routine revalidations on a 6 monthly basis with worst case presentations.

The most recent validation to support the manufacturing configuration of Streptomycin injection was the filling of 3 runs of media solution. The vials used in this study were to the same specification as those for the injection product.

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.

Overall, the media simulation of the aseptic filling operation was considered acceptable.

Tunnel sterilizer validation

The SOP on operation of the vial washing machine and tunnel operation was reviewed in detail. The tunnel sterilizer had been appropriately validated and considered to be acceptable. Testing of the tunnel HEPAs were reviewed and risk of particulate matter problems were considered during the qualification.

The following documents have been reviewed,

- Injection production line A washing and sterilization process
- Powder for injection production line filling machine components cleaning SOP
- Testing of the tunnel HEPAs

Steam sterilizer

The protocols and reports for the qualification of this autoclave which was used to sterilize equipment were reviewed. Requirements had been based on checklists provided by the supplier and acceptance criteria were included.

The following documents were reviewed:

- IQ – report was considered acceptable with no deviations reported.
- OQ – report was generally considered acceptable.
- PQ – report had been done for maximum and minimum loads with no deviations noted. This was considered acceptable.

Computerized system validation

The company had implemented a computerized Warehouse Management System that included material status control using barcoded labels and automated finished goods conveyor transport system to an automated high-rise warehouse. A specialist company had been engaged to configure and install the system and another specialist company had been engaged to assist with the validation of the system.

The overall approach to validation of this system was documented and with reference of GAMP. Other documents reviewed included the User Requirement Specification and Functional Specification (FS). The FS included a reference to a risk assessment that had been done to determine which elements of the URS were GxP relevant. Detailed specific functional specifications for GxP relevant requirements had then been documented. For example, FS for control of material release by QC and FS for material rejection by QC. A limited sample of validation test scripts and the recorded results were reviewed and found satisfactory.

A small number of deviations had been handled as described in the protocol and included in the final report with information on correction. The final validation report had been approved by all nominated personnel and accepted.

2.5 COMPLAINTS

Procedure for handling product complaints was available for review. Responsibilities were described and an appointed person in QA was responsible for coordinating complaint handling. The form used to record complaints could be used to record written, verbal or electronically submitted complaints.

Complaints were classified as quality, medical or counterfeit and severity as 1 to 4. Similar or related complaints were required to be checked during the investigation and there was a cross-reference to the CAPA procedure. Complaints were required to be

summarized monthly and reported to the Quality Manager. They were also summarized and reported to top management annually.

The quality complaint log for 2014 was reviewed and there were none relating to a powder for injection product.

2.6 PRODUCT RECALLS

Recalls were handled according to SOP. The SOP described requirements for 3 levels of recall and included appropriate timelines for each. A mock recall was required to be performed annually and the last had been done in April 2014. There had been no recall for the inspected products.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production or quality control operations for Streptomycin injection were generally not contracted out.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self- inspection

Self-inspections were done according to SOP. Every Department/Workshop was required to be inspected at least once per year. Criteria for personnel conducting self-inspections were included in the SOP and a list of those approved was available.

A schedule of self-inspection to be done during 2014 was available and reviewed. It appeared that all had been done as per the schedule. Detailed self-inspection records were not reviewed, but the system was considered to be acceptable.

Quality audit and supplier's approval

Supplier evaluation and approval management procedure and Supplier audit management procedure were reviewed. Site audit to critical materials suppliers were performed once a year.

The audit report to the API supplier NCPC Huasheng together with the quality agreement was considered acceptable.

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. An organization chart was available.

A sample of job descriptions for key staff was reviewed and they were generally considered to be satisfactory. However, arrangements for delegation in the event of

absence were not included in job descriptions and although partially covered in a SOP for staff leave, this did not cover all possible situations.

2.10 TRAINING

Personnel training was conducted according to SOP. New staff were required to undergo 2 levels of induction training, orientation and basic GMP. Each Department manager was then responsible for arranging job-related training that was specific to the work the person would be doing. Detailed specific training required for aseptic operators was considered to be appropriate.

Requirements for ongoing training were included in the SOP and there was Training Plan for 2014. Training effectiveness was required to be evaluated according to a separate SOP. Assessment was by questionnaire and/or written test. The pass-mark was specified.

2.11 PERSONAL HYGIENE

All personnel employed received training in disciplines relevant to the correct manufacture of sterile products. New staff was required to undergo a medical examination and then were repeated annually.

No notable concerns were identified during the inspection. The approach to sanitation and hygiene was acceptable in general; however minor issue in the hand washing was raised. The CAPA taken was considered to be acceptable.

All changing rooms were provided with SOPs with clear photographs which pictorially described the gowning procedures. Adequate hand sanitation was practiced in all areas using automated hand disinfectant dispensing systems.

2.12 PREMISES

Generally premises were located, designed, constructed and maintained to suit the operations to be carried out. The layout and design of premises minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination. Premises were designed and constructed to facilitate good sanitation.

Production premises were laid out to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

The construction of core clean area and the operations were of the good 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 flushed with filtered air. Changing rooms were designed as airlocks and used to provide physical

separation of the different stages of changing. Changing rooms were equipped with mirrors. Airlock doors did not opened simultaneously.

The observed areas used for aseptic powder filling were of a good standard and suitable for this type of production activity.

Storage areas

The starting materials warehouse was protected by rapid-roller door and adjustable receiving dock for unloading trucks. An approved supplier list for Streptomycin injection was available in the area and used to check that incoming materials were supplied by approved suppliers.

After receival checking, raw material containers were labelled with a bar-coded control label that included a computer generated internal control number for traceability and status control.

Non-sterile raw materials were sampled in an environmentally controlled sampling room with appropriate controls. A separate locked reject area and designated area for returned goods were provided.

Printed packaging material was stored in a separate area with restricted access. Some issues regarding the application of bar-coded control labels to these materials were noted. The CAPA was made and considered acceptable.

The finished goods warehouse was an advanced high-rise warehouse with automated loading and picking systems.

There were temperature and humidity specifications for each warehouse and these were monitored.

Quality control areas

QC laboratories including microbiological laboratory was 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.

2.13 EQUIPMENT

The equipment installed was of a high standard. The facility was well designed and the equipment appeared to be running well.

The manufacturing equipment and vessels systems were designed to be CIP and SIP. The detailed procedure together with the picture was well documented.

All fixed pipework was labelled to indicate the contents and the direction of flow.

Laboratory equipment and instruments suited to the testing procedures undertaken.

All critical equipment such as sterilizers, air-handling and filtration systems, air vent and water treatment, generation, storage and distribution systems were subject to planned maintenance.

2.14 MATERIALS

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedure. Finished products were held in quarantine until their final release according to the procedure.

A computerized Warehouse Management System was used in warehouse for material status control. Materials were labelled with a bar-coded control label and the status managed by the system. Materials were not otherwise status labelled. Other than an issue with level of control over the application of these labels, the system appeared to operating effectively. The CAPA taken was considered to be acceptable.

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.

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.

2.16 GOOD PRACTICES IN PRODUCTION

There was no commercial batch produced of WHO PQ product yet. There were only three validation batches manufactured with batch size of 50000 vials. There are two products Capreomycin and Streptomycin Sulfate so far produced on this production line. The filling step was in operation for product of Streptomycin powder for injection 1.0g at the time of inspection.

The general design of the facilities was appropriate. Processes were appeared stable and under control.

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. 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.

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 filling in a Grade A plus grade C room. Filled containers were inspected individually. Inspection was carried out visually in an adequately maintained light inspection station, to ensure proper illumination and background panels.

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.

The Microbiology Laboratory and Microbiology QC test was segregated from the Chemistry Laboratory.

Sample receiving and distribution

Procedure for sample receiving and distribution were inspected. Records of sample receipt and allocation of analysis was kept. ID test for incoming API was checked.

Reference Standards

Reference standards and register used for testing of Streptomycin FPP were reviewed. The company claimed that only EP RS is used for testing of Streptomycin FPP other than working standards.

OOS

SOP on OOS procedure including investigation of sterility test positives was reviewed. Observation was made regarding the provision for retesting. CAPA have been made and reviewed.

Sterility testing

The sterility test method validation was reviewed. Acceptance criteria were established.

Stability Testing

A written programme for stability study was 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, NCPC New Preparation Branch Factory located at No.115 Hainan Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China was considered to be operating at an acceptable level of compliance with WHO GMP.

All the non-compliances observed during the inspection that were listed in the full report 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.