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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	North China Pharmaceutical Co., Ltd. New Preparation Branch Factory
Corporate address of manufacturer	No. 217-1 East Heping Road, Shijiazhuang, Hebei, China.
Inspected site	
Address of inspected manufacturing site if different from that given above	No.115 Hainan Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China
Unit / block / workshop number	Workshop 201
Inspection details	
Dates of inspection	01 to 05 February 2016
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Production and quality control of the aseptically prepared FPP
General information about the company and site	NCPC New Preparation Branch Factory is located at No.115 Hainan Road, Economic & Technological Development Zone, Shijiazhuang, Hebei, China and was established in 2011. It is an affiliate of North China Pharmaceutical Co., Ltd. (NCPC). 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 1099 people employed on the site at the time of inspection. The company claimed that there is no toxin or hazardous substances manufactured at the factory.

History	This was the second WHO inspection with the previous inspection by WHO PQT performed 20-24 October 2014. The plant was inspected and licenced by the provincial FDA.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	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, labeling and inspection, and finished product storage • Quality control laboratory (chemical, HPLC testing) • Water system Documents reviewed included but were not limited to: • Facility layouts • Quality assurance and documentation • Quality risk management • Change control • OOS procedure • Specifications and testing procedure • Supplier's Audit • Performance qualification and validation of steam sterilizer • Protocol and report of media fill Protocol and report of process validation of Capreomycin • BMRs for streptomycin and Capreomycin filling • Environment monitoring • Technical agreement with export and registration company • HPLC and data integrity • Retention sample storage and control • Sterility testing • PW, WFI and steam testing • HVAC requalification
Restrictions	The inspection was restricted to the production line A in workshop 201.
Out of scope	All other products and workshops were outside of the inspection scope and were not visited.

WHO product numbers covered by the inspection	Streptomycin for injection 1.0g (TB296) Capreomycin for injection 1.0g (TB316)

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis

PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2
Brief summary of the findings and comments:

1. Pharmaceutical quality system

Product quality review
Product quality review was performed according to an annual product quality review management procedure which covered the product annual review process. At the time of the inspection a product quality review for Streptomycin injection had not yet been done because only process validation batches were available manufactured in July 2014.

The PQR for Capreomycin powder for injection PQR 2014 and 2015 were reviewed. The Capreomycin powder for injection FPP code for WHO PQ was designated grade J005. There were critical and major changes made to Capreomycin manufacture and control in 2014. Some changes were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control were addressed by the manufacturer to a satisfactory level.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices generally were well 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 routinely performed. Manufacturing steps were recorded in batch manufacturing record (BMR) and packaging records. Manufacturing processes were defined and reviewed. Product was being released by the authorized persons of the Quality unit in accordance with written procedures.

3. Sanitation and hygiene

In general, premises and equipment were well maintained and observed to be of a satisfied level of cleanliness. The company had standard operating procedures controlling its approach to personal hygiene and sanitation in its production facility.

4. Qualification and validation

The company had identified what qualification and validation work was required to be performed and the key elements of the qualification and validation programmer were generally well defined in the validation master plan (VMP) and specific study protocols and reports. Appropriate documentary evidence was available that relevant equipment and processes for the products under review had been designed, installed, and performed in accordance with their design specifications.

The process validation of Capreomycin for injection 1.0g was performed on production Line A of Workshop 201.
During the inspection procedures and validations were reviewed for

- Process validation of the Capreomycin sulfate 1.0g.injections including
  - Process validation protocol
  - Process validation report
  - Three validation batches
- Media simulation: Protocol and Report
- Risk assessment report of Capreomycin sulfate injections

The reports and procedures reviewed were generally comprehensive and well prepared.

5. Complaints

A procedure for handling product complaints was available for review. QA was responsible for coordinating complaint handling. The procedure has not been changed since last inspection. There had been no complaint for the two products in the inspection scope because they have not been prequalified and no PQ product distributed at the time of this inspection. Complaints for other product codes manufactured on this line were reviewed with nothing of significant note.

6. Product recalls

Recalls were handled according to written SOP. There had been no recall for the inspected products.

7. Contract production, analysis and other activities

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

8. Self-inspection, quality audits and suppliers' audits and approval

Self- inspection
Self-inspections were not covered in detail by this inspection. It was stated that a programme was in place and it had not changed significantly from the SOPs reviewed previously.

Quality audit and supplier's approval
A supplier evaluation and approval management procedure was available for inspection. Site audits of critical materials suppliers were performed once a year. The API manufacturer of Capreomycin sulfate and Streptomycin sulfate is North China Pharmaceuticals Company Huasheng, a sister company of NCPC. WHO has recently inspected this API site in February 2015.

9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Personnel interviewed were aware of the principles of GMP. An organization chart was available. The functions of the quality unit were adequately separated from responsibility for production.

10. Training

Personnel training were conducted according to a SOP and an annual programme. Records of trainings are kept. Training required for aseptic operators was inspected and this was supported by evidence from discussions with staff interviewed during the inspection and indicated that training appeared to be appropriate.

11. Personal hygiene

All personnel employed received training in disciplines relevant to the correct manufacture of sterile products. No notable concerns were identified during the inspection.

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

12. Premises

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

Production premises had been laid out to allow the production processes to take place in areas in a logical flow corresponding to the sequence of the operations and under the requisite cleanliness levels required by the GMP for sterile products.

The construction of core clean area and the operations were of a good standard. Exposed surfaces were smooth, impervious and unbroken so as to minimize the shedding or accumulation of particles or microorganisms and were of materials suited to the repeated application of permitted cleaning agents and disinfectants, where used. The areas used for aseptic powder filling that were inspected were seen to be of a good standard and suitable for this type of production activity.

Storage areas

The starting materials warehouse was protected by rapid-roller doors and there was an adjustable receiving dock for unloading trucks under conditions that provided suitable protection.

After receival checking, raw material containers were identified with a bar-coded control label that included a computer generated internal control (batch) 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.

The finished goods warehouse was a high-rise warehouse with automated loading and picking systems. There were temperature and humidity specifications for each warehouse and these were monitored.

Sufficient space was provided to allow orderly storage so as to avoid mix ups and cross-contamination.

Quality control areas

QC laboratories including microbiological laboratory was separated from production areas. The laboratories were of sufficient space and design to allow for proper segregation of activities and avoid mix up during testing activities. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

13. Equipment

The equipment that had been installed was generally of a high standard. The facility was well designed and the equipment appeared to be running well at the time of the inspection. Generally the equipment had been selected and designed to allow for a well contained process and was generally well protected from possible manual direct intervention and adventitious contamination, although a small number of comments were raised regarding local HEPA protection of some operations that could be further protected by reconsideration of process flows.

The manufacturing equipment and vessels systems were designed to be CIP and SIP capable and these processes were in routine use. The detailed procedures for operation (illustrated with picture were appropriate) were well documented.

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

14. Materials

Incoming materials were purchased from approved suppliers, sampled and tested according to written specifications and testing procedures. Finished products were held in quarantine until their final release according to the relevant written 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. The inventory system verified current status when materials were issued to the BMR electronically. Other than an issue with traceability of the status control over the application of these labels, the system appeared to operating effectively and securely with no other matters of concern.

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were marked as such and stored separately. There was a general SOP covering finished product reworking and reprocessing. Rework was not allowed but the SOP stated that product could be reprocessed according to the general terms of this procedure. It was stated that this SOP was not applicable to the sterile products.

15. Documentation

In general written documentation was well designed, comprehensive, and prepared, reviewed and distributed with appropriate care and control. SOPs were in place for document approval, issue and control. Documents reviewed during the inspection had generally been approved, signed and dated by the appropriate responsible persons.

16. Good practices in production

There had been no commercial batch production of WHO PQ product yet. There had been three products so far produced on this production line, these being Capreomycin sulfate, Streptomycin sulfate and Streptomycin hydrochloride for injection. The filling steps were in operation for Capreomycin powder for injection 1.0 g at the time of inspection.

The general design of the facilities was appropriate. Processes were appeared stable and under control. The following procedure and record documents were reviewed:

- Powder production line for environment monitoring
- Powder for injection production Line A washing and sterilization process
- 201 workshop HEPA change

Manufacture of Sterile preparations
Clean areas for the manufacture of sterile products were classified in accordance with the required characteristics of the environment demanded by the sterile products GMP. 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 steps. To control the microbiological cleanliness of Grades A–D in operation the clean areas were monitored. Appropriate alert and action limits had been set for the results of particulate and microbiological monitoring. The monitoring area and equipment for environment particulate monitoring and recording was visited.

Finishing of sterile products
The inspection and packaging area were inspected but was not operation at the time of inspection. The areas appeared to be of suitable size and design so as to avoid mix up and allow appropriate segregation of unit operations. Filled containers were inspected individually. Inspection was carried out visually in light inspection station.

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 testing was appropriately segregated from the Chemistry Laboratory.

OOS
The SOP on OOS procedure including investigation of sterility test positives was reviewed and considered generally acceptable.

Sterility testing
The sterility testing procedure and facilities were reviewed and considered generally acceptable.

Stability Testing
There was a written programme for stability studies and from the records reviewed this appeared to be appropriately implemented. Stability samples of Streptomycin injection and Capreomycin Sulfate injection for the relevant submitted dossier batches were seen to be stored in the stability incubator with condition of $30^0C \pm 2^0C$, RH75%±5%. Temperature in the incubators was continuously monitored. Incubators were equipped with alarm system and power back up.

Retention samples
Retention samples of each batch of the product manufactured were noted as being kept in a secure temperature controlled room of 10^0C to 30^0C. Appropriate records of receipt and any issue for testing or inspection were being kept.

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, **North China Pharmaceutical Company** (FPP 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 good manufacturing Practices for pharmaceutical products.

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.

PART 4

List of GMP guidelines referenced in the inspection

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf