Prequalification Team
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

<table>
<thead>
<tr>
<th>Part 1</th>
<th>General information</th>
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<tr>
<td><strong>Manufacturers details</strong></td>
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<tr>
<td><strong>Company information</strong></td>
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<tr>
<td><strong>Name of manufacturer</strong></td>
<td>Hulunbuir North Pharmaceutical Limited Company</td>
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<tr>
<td><strong>Corporate address of manufacturer</strong></td>
<td>Shenyang Tongliang Group Co. Ltd. No.18 Yucai Lane, East Shuncheng Road, Dadong District, Shenyang, P.R. China 110042</td>
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<tr>
<td><strong>Inspected site</strong></td>
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<td><strong>Address of inspected manufacturing site if different from that given above</strong></td>
<td>1. Industrial street, Yakeshi City Hulun Buir which is the third gate of original Complex. the Nei Monggol Autonomous Region, China, GPS: 49.301772N, 120.716881E 2. New warehouse GPS: 49.313458N, 120.704542E</td>
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<tr>
<td><strong>Unit / block / workshop number</strong></td>
<td>Rifamycin S-Na block (301 and 302 workshop),</td>
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<tr>
<td><strong>Manufacturing license number</strong></td>
<td>NEI 20180061</td>
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<tr>
<td><strong>Inspection details</strong></td>
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<tr>
<td><strong>Dates of inspection</strong></td>
<td>23-26 July 2018</td>
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<tr>
<td><strong>Type of inspection</strong></td>
<td>Routine re-inspection</td>
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<tr>
<td><strong>Introduction</strong></td>
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<tr>
<td><strong>Brief summary of the manufacturing activities</strong></td>
<td>Production and quality control of intermediates and APIs</td>
</tr>
<tr>
<td>General information about the company and site</td>
<td>Hulunbuir North Pharmaceutical Co., Ltd. is a subsidiary of the Shenyang Tonglian Group Co., Ltd. and is located in the northwest city of Yakeshi, Inner Mongolia Autonomous Region, China. Manufacture of Rifamycin S-Na was started in June 2013. Approximately 1420 people are employed on site, of which 161 are operators involved in the Rifamycin production workshops. Other products manufactured at the site are Vitamin C, Penicillin G Potassium, Carrimycin and Erythromycin however manufacturing of these APIs, except Vitamin C, was temporarily put on hold.</td>
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<tr>
<td>History</td>
<td>This was the third WHO inspection. The last inspection was conducted 14-17 July 2015. The site has been regularly inspected by the local FDA. No foreign drug regulatory agency had inspected this manufacturing site for Rifamycin S-Na.</td>
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| Brief report of inspection activities undertaken | Document review included:  
- Quality management  
- Personnel  
- Buildings and facilities  
- Process equipment  
- Documentation and records  
- Materials management  
- Production and in-process controls  
- Packaging and identification labelling of APIs and intermediates  
- Storage and distribution  
- Laboratory controls  
- Validation  
- Change control  
- Rejection and reuse of materials  
- Complaints and recalls  
- Contract manufacturers (including laboratories)  

Area visited:  
- Fermentation workshop 301  
- Extraction workshop 302  
- QC laboratories including general and microbiology laboratory  
- New warehouse |
<p>| Scope and limitations | N/A |
| Areas inspected | Restriction |
| Out of scope | Any product other than Rifamycin S Sodium |
| WHO product numbers covered by the inspection | Rifamycin S Sodium - intermediate for further processing into Rifampicin (APIMF083) |</p>
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
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<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
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<tr>
<td>APQR</td>
<td>annual product quality review</td>
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<tr>
<td>BDL</td>
<td>below detection limit</td>
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<td>BMR</td>
<td>batch manufacturing record</td>
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<tr>
<td>BPR</td>
<td>batch packaging record</td>
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<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<td>CC</td>
<td>change control</td>
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<td>CFU</td>
<td>colony-forming unit</td>
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<tr>
<td>CoA</td>
<td>certificate of analysis</td>
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<tr>
<td>CpK</td>
<td>process capability index</td>
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<td>DQ</td>
<td>design qualification</td>
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<td>EM</td>
<td>environmental monitoring</td>
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<td>FAT</td>
<td>factory acceptance test</td>
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<td>FBD</td>
<td>fluid bed dryer</td>
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<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<td>FPP</td>
<td>finished pharmaceutical product</td>
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<td>FTA</td>
<td>fault tree analysis</td>
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<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<td>GC</td>
<td>gas chromatograph</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<tr>
<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<td>IR</td>
<td>infrared spectrophotometer</td>
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<td>IQ</td>
<td>installation qualification</td>
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<td>KF</td>
<td>Karl Fisher</td>
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<td>LAF</td>
<td>laminar air flow</td>
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<td>LIMS</td>
<td>laboratory information management system</td>
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<td>LoD</td>
<td>limit of detection</td>
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<td>LOD</td>
<td>loss on drying</td>
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<td>MB</td>
<td>microbiology</td>
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<td>MBL</td>
<td>microbiology laboratory</td>
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<td>MF</td>
<td>master formulae</td>
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<td>MR</td>
<td>management review</td>
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<td>NRA</td>
<td>national regulatory agency</td>
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<td>OQ</td>
<td>operational qualification</td>
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<td>PHA</td>
<td>process hazard analysis</td>
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<td>PM</td>
<td>preventive maintenance</td>
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<td>PpK</td>
<td>process performance index</td>
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<td>PQ</td>
<td>performance qualification</td>
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<tr>
<td>PQR</td>
<td>product quality review</td>
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Part 2  Brief summary of the findings and comments

1. Quality management

Principles
A formal documented system for quality assurance was established, with procedures covering key quality elements being in place. Operations were specified in written form and critical GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard.

In general managerial responsibilities were appropriately specified in written job descriptions. Product and processes were monitored and these results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products and several quality metrics were being conducted according to documented schedules and procedures. The Quality Department was divided into QA and QC, which was separate from the production department.

Product quality review (PQR)
PQR was performed according to written procedure with the stated objectives of demonstrating the reliability of processes and products. This procedure required PQR to be performed annually using data collected from all manufacturing batches of Rifamycin S-Na and to be completed annually before end of March, even when no batches were produced. The SOP specified the review of IPC test results and final product test results, summary of validation work done, OOS batches, deviations, changes, stability monitoring, returns, complaints and recalls, and adequacy of CAPAs.

PQRs for Rifamycin S-Na were reviewed. The 2017 PQR was approved in compliance with timeline specified in the SOP for PQR. In this PQR, OOS, return, change control and deviation etc. were reviewed and documented. Non-compliances observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.
Quality Risk Management
Quality risk was managed according to an SOP. The risk assessment employed the FMEA tool and risk was categorized into high, medium and low. As an example, the report number for the assessment of contamination risks of penicillin in the Rifamycin S-Na facility was reviewed. The report looked well laid out. A reference was made to the test for penicillin residue in the environment and product in case of concurrent production of Rifamycin and Penicillin. The latest test report for residues was documented. No comments were made. An SOP on introduction of a new product was reviewed and discussed.

Internal audits (self-inspection)
An SOP on Self-inspection was in place. The frequency of self-inspection was at least once in a year.

Handling of out of specification (OOS) results
OOS was managed according to an SOP. The procedure, OOS flow chart and several OOSs were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding OOS handling were addressed by the manufacturer to a satisfactory level.

2. Personnel

Personnel qualifications
Key personnel had adequate qualifications and experience. Job descriptions of quality vice general manager, quality director, production vice general manager and production manager were reviewed.

Personnel hygiene
Personnel were required to wear protective clothing appropriate to the stage of production and quality control.

Training
The people met during the inspection were adequately trained for their jobs and demonstrated good knowledge and understanding of the production process of Rifamycin S-Na throughout.

A procedure for personnel training was briefly reviewed and discussed. After induction training new staff received on-the-job training as well as GMP training. The selection of trainers was done considering their experience in the subject field.

The training schedule for 2018 was reviewed. Records were requested for two analysts who were qualified to do the Rifamycin test. In the files were their current job responsibilities, qualification document for the test and training progress cards showing when they participated in GMP training. The training evaluation documents were included in the package.

3. Buildings and facilities

Design and construction
The buildings and facilities inspected were generally designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Manufacturing areas provided sufficient space for the placement and cleaning of equipment. The main QC laboratory was separate from production areas and in-process QC areas within the production block were appropriate.
Utilities
The company had its own power generating plant.

Water system
Mainly drinking water from the municipality supply was used in the production of Rifamycin S-Na intermediate.

Containment
Rifamycin S-Na was produced in a production block dedicated to the production of this intermediate. Fermentation areas were separated from the extraction and purification areas.

Penicillin G API was produced in a dedicated production block approximately 1km from the Rifamycin S-Na production block. The Penicillin residue close to the Rifamycin S-Na production block has been regularly monitored. A separate QC laboratory for penicillin was in place.

Lighting
Lighting in all areas visited appeared to be appropriate except some area in the warehouse.

Sanitation and maintenance
The Rifamycin S-Na production block was clean and tidy and appeared to be suitably maintained.

4. Process equipment

Design and construction
Equipment used for the production of Rifamycin S-Na appeared to be of appropriate design and size for its intended use. The equipment used for manufacturing Rifamycin S-Na was dedicated to this intermediate. Major equipment and processing lines were appropriately identified.

Equipment maintenance and cleaning
Equipment maintenance procedure was in place. Documented cleaning procedures were available for equipment.

Calibration
The system for calibration was not assessed during this inspection. All equipment seen during the inspection was in a calibrated state. No comments were made.

Computerized systems
A computerized system was used for the fermentation of Rifamycin S-Na.

5. Documentation and records

Documentation system and specifications
Documents were managed according to a written procedure. This was a high-level document in which a number of specific SMPs were mentioned, including those for drafting, approval, control of SMPs and SOPs, for Validation Master Plan, for specifications and analytical methods etc. The review period for all documents was specified in procedures. Archiving of documents was described and acceptable generally.
Documents looked well laid out. The main text was well structured, and a history of changes was maintained in each version.

**Master production instructions and Batch production records**
Approved master production instructions were available and reviewed. After copying master batch records, BMRs were signed, dated and independently checked by a person in the quality assurance unit before use.

**Batch production record review**
The productions records for a batch of Rifamycin S-Na the associated records for the intermediates were reviewed and discussed.

**Batch numbering system**
Batch numbering, production date and shelf life were managed according to an SOP. The batch record issuing log book for the fermentation process was reviewed and acceptable.

**Laboratory control records**
Laboratory testing records were kept and available in general.

### 6. Materials management

Raw materials were received at the warehouse and checked against a qualified supplier list. The use of this list was not addressed in an SOP for receipt of materials. An SOP on suppliers’ approval was reviewed. Audit reports for two suppliers were reviewed and acceptable.

A new warehouse was visited which was situated 2kms from the main site entrance. The building was access controlled and consisted of two major areas, one for raw materials and one for finished products. Generally, there seemed to be sufficient space for the orderly placement and separation of goods. Separate rooms existed for rejected materials. The warehouse looked clean and no infestations were seen. Quarantine or release status of materials was indicated. Temperature and humidity were monitored. The monitoring records were available and reviewed. Air curtain and devices for the control of pest; mouse trap, glue rat board and pest-o-flash were in operation and pallets were provided for the storage of materials.

### 7. Production and in-process controls

Production of Rifamycin S-Na took place in dedicated and self-contained facilities. The various production stages were in operation at the time of inspection.

**Production operations**
Production operations in Workshops 301 and 302 were reviewed and found acceptable. As applicable, reactors and material tanks were labelled with the batch in progress in general and the associated batch documentation was up to date.

**In-process sampling and controls**
In-process sampling and testing was conducted as specified in the relevant BMR. In process tests were conducted in an IPC lab close to the workshops.
8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling operations were performed in the area dedicated for this purpose. The packaging and labelling was not in operation at the time of inspection. The labels of Rifamycin S-Na appeared acceptable as an intermediate.

9. Storage and distribution

Distribution procedures
APIs and intermediates were released for distribution following the review and release by the Quality Unit. They were physically stored in the finished products part of the new warehouse.

10. Laboratory controls

General controls
The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments. QC laboratories including microbiological laboratory were separated from production areas. The microbiological laboratory was segregated from the chemical laboratory.

Testing of intermediates and APIs
QC testing was conducted as specified in the relevant specification and according to documented test methods. The sample receiving and distribution log book was checked. Samples for testing were kept in a designated area.

The computer access control, authorization of the functions and data management were checked during the inspection. A QC electronic data management procedure and an SOP on Manual integration were reviewed.

Non-compliances observed during the inspection that was listed in the full report regarding data management were addressed by the manufacturer to a satisfactory level.

Stability monitoring of Rifamycin S-Na
A range of stability chambers were available. Stability monitoring program and sample were checked. Non-compliances observed during the inspection that was listed in the full report regarding temperature excursion of stability study were addressed by the manufacturer to a satisfactory level.

Microbiological testing laboratory
A tour was made of the microbiological laboratory. The Rifamycin S-Na was tested in the microbiological laboratory. The testing procedure was in place and reviewed. In-house standard substance was traceable to a reference standard from the National Institute for Food and Drug Control. It was checked that the batch number was current.
11. Validation

Validation master plan
The 2017 and 2018 Rifamycin S-Na Validation Master Plans were briefly reviewed and discussed. The term Master Plan was used for the yearly program of items that should be re-validated or re-qualified. A yearly document lists items/equipment that would be validated, with their planned dates of validation was provided. Execution dates confirmed that the planning was generally maintained.

Process validation
The process validation for Rifamycin S-Na performed in 2017 was reviewed including PV protocol, report and three validation batches. Non-compliances observed during the inspection that was listed in the full report regarding process validation were addressed by the manufacturer to a satisfactory level.

Equipment qualification
A qualification report on a liquid measuring tank as example of equipment qualification was reviewed and acceptable generally.

Cleaning validation
Cleaning validation was performed for seed tanks and a fermentation tank in 2018. No comments were made.
A cleaning validation report of a centrifuge was also reviewed. No problems were found.

Analytical method validation
Analytical method validation was performed according to an SOP which was briefly reviewed and found acceptable.

12. Change control

There was a procedure for change control. Change controls were classified as major, moderate and minor.
Change control registers for 2016 and 2017 were available and reviewed. Several change controls were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding change control management were addressed by the manufacturer to a satisfactory level.

SOPs for handling Deviations were reviewed. Deviation included planned and unplanned deviation and was classified into critical, major and minor according to their criticalities. A deviation register and records were maintained.

13. Rejection and re-use of materials

Rejection
There were secured dedicated areas in the warehouses for rejected materials.

Reprocessing
Reprocessing procedure was not checked in detail during this inspection.
Recovery of materials and solvents
An SOP on recovery of solvents was reviewed. Recovered solvents were collected in separate storage tanks and a sample was tested by the QC lab before approval.

Returns
Returned goods were regulated as per written procedure and the return register and records were available for inspection.

14. Complaints and recalls

Complaints
Product complaints were handled according to an SOP. Complaint log books of 2016 and 2017 were checked. Non-compliances observed during the inspection that was listed in the full report regarding complaint and CAPA implementation were addressed by the manufacturer to a satisfactory level.

Recalls
Recalls were required to be handled according to an SOP. Three levels of recall were described timeframes for the initiation. There had been no recalls of Rifamycin S-Na since last inspection. A level one mock recall had been carried out in 2018.

15. Contract manufacturers (including laboratories)

There was no contract manufacturing of Rifamycin S-Na or key starting materials.

PART 3
Conclusion
Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned: Rifamycin S Sodium - intermediate for further processing into Rifampicin manufactured at Hulunbuir North Pharmaceutical Co. Ltd., Industrial street, Yakeshi City Hulun Buir, third gate of original Complex, the Nei Monggol Autonomous Region, China, 022150 was considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

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 report


   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf