# WHO PUBLIC INSPECTION REPORT

# (WHOPIR)

# API Manufacturer

## Part 1: General information

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|---|---|
| Name of Manufacturer | Hulun Buir North Pharmaceutical Limited Company |
| Unit number | N/A |
| Production Block | Rifamycin S-Na block (301 and 302 workshop), |
| Physical address | No.0188, Industry Centre street , Hulun Buir Yakeshi, the Nei Monggol Autonomous Region, China |
| Contact person and email address. | Ms. keli Zhu<br>byzlb2186@163.com |
| Dates of inspection | 14 to 17 July 2015 |
| Type of inspection | Full re-inspection |
| Active Pharmaceutical Ingredient(s) included in the inspection | Rifamycin S Sodium - intermediate for further processing into Rifampicin (APIMF083) |
| Summary of the activities performed by the manufacturer | Production and quality control of intermediates and APIs |

**Part 2: Summary**

***General information about the company and site***

Hulun Buir North Pharmaceutical Co., Ltd. is a subsidiary of Shenyang Tonglian Group Co., Ltd. and is located in the northwest city of Yakeshi, Inner Mongolia Autonomous Region. The site covers a total area of 1.12 million square meters and approximately 3000 people are employed at the site.

Manufacture of Rifampicin S-sodium commenced in June 2013. Besides Rifamycin S-Na, Penicillin G Potassium and Vitamin C are manufactured at the site.

***History of WHO and/or regulatory agency inspections***

This was the second WHO inspection. The last inspection of this site was conducted 19-21 June 2013. No foreign agency has inspected the site for Rifamycin S-Na manufacture.

***Focus of the inspection***

The inspection focused on the production and control of Rifamycin S Sodium, an intermediate for further processing into Rifampicin API. The inspection covered all the relevant sections of WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

***Inspected Areas***

The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text:

- 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)

## PART 3: INSPECTION OUTCOME

### 3.1 QUALITY MANAGEMENT

Principles

A quality management system that included all of the required elements had been established, documented and implemented. It was noted that many of the procedures were in Chinese and English.

As shown in the organograms reviewed, QA/QC departments were separate from the production departments.

The documentation requested was generally able to be shown to the inspectors without delay.

Responsibilities

Responsibilities for the quality units and for production activities were described in job descriptions and in SOPs. The sample of these documents reviewed during the inspection indicated that key quality and production responsibilities had been adequately described.

Internal audits (self-inspection)

Self-inspection was performed according to a SOP with responsibility for this activity stated as being the Quality Department Manager. The frequency of self-inspection was at least once each year.

Handling of out of specification (OOS) results

The OOS handling procedure and Microbial testing OOS investigation procedures were reviewed and discussed. There have been no OOS of Rifamycin S Na during the last and current years. Non-compliances observed during the inspection that were listed in the full report regarding the OOS investigation procedure were addressed by the manufacturer to a satisfactory level.

Product quality review

Requirements for PQR were documented in a SOP. This procedure required an annual PQR to be completed by the end of March the following year.

A report was reviewed as the 2014 PQR for Rifampicin S Na intermediate. The review included in-process and intermediate QC test results, OOS batches, deviations, changes, stability, returns, complaints and recalls, and concluded that no corrective actions were required. Non-compliances observed during the inspection that were listed in the full report regarding the product quality review were addressed by the manufacturer to a satisfactory level.

Quality Risk Management (QRM)

QRM was conducted according to a SOP. Responsibilities were defined for this activity. The approach described in the above mentioned SOP included analysis to identify potential risks and an FMEA model was used to analyze and quantify the risks. QRM reports for Rifamycin S Na facility layout were selected for review and were generally acceptable. Non-compliances observed during the inspection that were listed in the full report regarding the quality risk management were addressed by the manufacturer to a satisfactory level.

## 3.2 PERSONNEL

Personnel qualifications

There appeared to an adequate number of personnel to perform and supervise the manufacture of Rifampicin S Na intermediate. Key personnel had adequate qualifications and experience. Responsibilities of personnel were described in job descriptions which were generally found satisfactory. Delegation in the event of absence was included and job descriptions had been signed by the incumbent, the delegate and by HR. Training was conducted according to a documented procedure and covered initial and on-going training. Non-compliances observed during the inspection that were listed in the full report regarding the training were addressed by the manufacturer to a satisfactory level.

Personnel hygiene

Personnel were required to wear protective clothing appropriate to the stage of production.

## 3.3 BUILDINGS AND FACILITIES

Design and construction

The general design and standard of construction of the Rifampicin S Na intermediate production block was considered acceptable. Since the last inspection a new material warehouse had been constructed and this was considered to be of good standard with defined areas for each material status.

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 that was said to supply electricity to neighboring areas. Other utilities (such as steam) used in the manufacture of Rifampicin S Na intermediate were not specifically reviewed, but no particular issues were noted during the inspection of production areas. Pipework seen during the inspection was appropriately labelled.

Water

Mains drinking water from the municipality supply was used in the production of Rifampicin S Na intermediate. Water was tested by the local government laboratory to ensure that it met WHO guidelines for drinking water.

Containment

Rifampicin 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.

Since the last inspection a self-contained microbiology area had been constructed within the fermentation area for culture preparation. This included a Class A environment with Class B background. Continuous particle monitoring was provided and the controlled areas could be visually monitored by video camera. This area was generally considered to be of good standard.

Penicillin G API is produced in a dedicated production block approximately 1km from the Rifamycin S Na production block. In response to the serious concern about the possibility of penicillin cross-contamination raised during the last inspection, a number of measures had been implemented. The Penicillin residue close to the Rifamycin S Na production block has been regularly monitored. There was no longer a smell of penicillin on the site and it was evident that further work was underway at the penicillin block to

strengthen containment here. In addition, a separate QC laboratory for this product had been constructed since the last inspection and personnel from the penicillin production block were now provided with a separate canteen.

Lighting

Lighting in all areas visited appeared to be appropriate.

Sanitation and maintenance

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

## 3.4 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. Major equipment and processing lines were appropriately identified. The equipment used for manufacturing Rifamycin S Na was dedicated to this intermediate.

Equipment maintenance and cleaning

Equipment maintenance was performed according to a written SOP. Documented cleaning procedures were available for equipment. As an example, the SOP for cleaning centrifuges and their bags was reviewed. The SOP included frequency and detailed instructions for dismantling centrifuges. Clean holding time for both centrifuges and bags was specified.

Calibration

Equipment Calibration was performed as per a SOP. A list of calibrated equipment was available. The temperature probe calibration record of a fermentation tank was checked. Non-compliances observed during the inspection that were listed in the full report regarding the calibration by the manufacturer to a satisfactory level.

Computerized systems

A computerized system was used for the fermentation of Rifampicin S Na.

## 3.5 DOCUMENTATION AND RECORDS

Documents were prepared and approved according to a SOP. The SOPs described the requirements for drafting, review and approval. The sample of documents reviewed during the inspection indicated that the documentation system was acceptable in general.

Records of equipment cleaning and use, records relating to the raw materials, intermediates and packaging materials were available for inspection.

Master production instructions and Batch production records for Rifamycin S Na including fermentation and extraction stages were reviewed and considered acceptable in general.

The in-process QC records and the completed QC records were reviewed.

## 3.6 MATERIALS MANAGEMENT

General controls

Written procedures for the handing of materials from receipt through to approval or rejection were available. The SOP for receiving and storage of packing materials, and a QC SOP for operating the sampling hood were reviewed as examples.

Suppliers of materials were required to be approved according to a SOP. The approval process included a questionnaire, a sample for trial and analysis, and an audit of critical suppliers. Critical suppliers were required an on-site audit before approval and required re-evaluation on a regular basis.

Receipt and quarantine

Materials were examined upon receipt and placed in quarantine until tested and released.

Sampling and testing of incoming production materials

Sampling of materials was performed in a dedicated sampling room equipped with a sampling booth. The sampling plan was considered suitable and the containers sampled were identified.

Storage

The newly constructed material warehouse was generally considered of suitable design and was clean and tidy. Temperature and humidity requirements were specified and monitored. The records reviewed indicated compliance with the specifications.

All material was status labelled and the non-compliances observed during the inspection that were listed in the full report regarding material status labelling were addressed by the manufacturer to a satisfactory level.

## 3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production of Rifamycin S Na took place in dedicated and self-contained facilities.

**Production operations**

Production operations in Workshops 301 and 302 were reviewed and generally found acceptable. As applicable, reactors and material tanks were labelled with the batch in progress 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. IP tests were conducted in an IPC lab close to the workshops.

Contamination control

The production block and equipment were dedicated to the inspected intermediate Rifamycin S Na. The contamination control between batches in the drying and packaging area was discussed.

There was a Penicillin G API production block on the site. The risk assessment and management procedure and report were reviewed. See the QRM section.

Time limits

Time limits were specified in the BMR where necessary.

## 3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

**General**

Packaging and labelling operations were performed in an area dedicated for this purpose. The packaging and labelling area was not in operation at the time of inspection. The labels of Rifamycin S Na appeared acceptable as an intermediate (used only by its sister company Shenyang Antibiotic Manufacturer). The procedure for labelling of the staging materials at the workshops was checked and discussed.

## 3.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Starting materials, packaging materials and intermediates were stored in a newly built warehouse with temperature control and monitoring. The material release labels were checked. This warehouse was 1-2 Km from the production site and the non-compliances observed during the inspection that was listed in the full report regarding the identity code of the warehouse were addressed by the manufacturer to a satisfactory level.

## 3.10 LABORATORY CONTROLS

General controls

The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments.

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.

HPLC was used for related substance (RS) testing of Rifamycin S Na and working reference standards were used to determine the RRT. The computer access control, authorization of the functions and testing method validation were checked during the inspection. Non-compliances observed during the inspection that were listed in the full report regarding the QC labs were addressed by the manufacturer to a satisfactory level.

Stability monitoring of APIs

A range of stability chambers were available. The records for stability samples in the chambers were available for review. The Rifamycin S Na stability sample was kept in the chamber with conditions $25^0$C, RH60%.

Reserve/retention samples

There was a designated temperature controlled area (10 to $30^o$C) for storage of retention samples. Access to this area was restricted. A sample of each batch of API manufactured was kept. Retention samples were stored in container systems that were comprised of the same materials as those used for the final intermediate.

## 3.11 VALIDATION

Qualification

Requirements for the qualification of equipment and utilities were included in the Validation Master Plan. Periodic requalification was specified as required every three years. The equipment qualification OQ and PQ report of the vacuum dryers in the extraction workshop was reviewed. Non-compliances observed during the inspection that were listed in the full report regarding the equipment qualification were addressed by the manufacturer to a satisfactory level.

Process validation

The company's validation policy was described in the Process validation standard management procedure. The revalidation period was three years as mentioned.

The process validation Protocol, process validation report and the three validation batches were reviewed and found to be generally acceptable.

Cleaning validation

Cleaning validation was not covered during this inspection. The facility and equipment were dedicated.

Computer validation

A computerised system was used to control and monitor the fermentation process. Validation of the software had been performed by an external company according to a SOP. The validation report was reviewed and discussed. Non-compliances observed during the inspection that were listed in the full report regarding the validation were addressed by the manufacturer to a satisfactory level and should be verified during future inspections.

Validation of analytical methods

The analytical method validation of Rifamycin S Na was performed in 2013. The validation report was reviewed.

## 3.12 CHANGE CONTROL (CC)

There was a written procedure for change control. There have been a few changes made since last inspection.

The SOP for handling Deviations was reviewed. A deviation register and records were maintained. A deviation regarding fermentation process was reviewed.

## 3.13 REJECTION AND RE-USE OF MATERIALS

Rejection

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

Reprocessing

Reprocessing was controlled according to a SOP.

Recovery of materials and solvents

A solvent used in the production was recovered, with the process included in the BMR. It was collected in separate storage tanks and a sample tested by the QC lab before approval. The mother liquid was recycled in the same process within specified times.

Returns

Returned goods were controlled according to a SOP. There had been no Rifamycin S Na batches returned so far.

## 3.14 COMPLAINTS AND RECALLS

Complaints were handled according to a SOP. There has been no complaints since the SOP come into effective on 4 September 2013.

Recalls were required to be handled according to a SOP. Three levels of recall were described with timeframes for initiation specified. Mock recalls had been carried out in 2013 and 2014. There had been no recalls of Rifamycin S Na.

## 3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

No production related to Rifamycin S-Na intermediate was contracted out. Testing of source water was contracted out to the local government laboratory.

## Part 4: 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, the intermediate Rifamycin S Sodium, manufactured at Hulun Buir North Pharmaceutical Limited Company located at No.0188, Industry Centre street, Hulun Buir Yakeshi, the Nei Monggol Autonomous Region, China, 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.