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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

API Manufacturer

Part 1: General information

Name of Manufacturer	Shenyang Antibiotic Manufacturer Ltd.
Unit number	N/A
Production Block	Workshop 103
Physical address	Jianshe Third North Road, Hushitai Town, Xinchengzi District, Shenyang, China
Contact person and email address.	Ms. Wang Lianrong zlb5588@163.com
Dates of inspection	20 to 22 July 2015
Type of inspection	Re-inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Rifampicin API (Polymorph II) (APIMF083)
Summary of the activities performed by the manufacturer	Production and control of Rifampicin API from Rifampicin S-Na

Part 2: Summary

General information about the company and site

Shenyang Antibiotic Manufacturer belongs to the Tonglian group, which has many manufacturing operations at different locations in China such as Shanghai and Inner Mongolia for manufacturing of API's and FPP Dosage forms.

Shenyang Antibiotic Manufacturer Facility, located in the Northeast China, near the city of Shenyang, was constructed for manufacturing of Active Pharmaceutical Ingredients (APIs), and the main API manufactured on this site is Rifampicin. The facility started operations in 1992.

Manufacture of Rifampicin S Sodium, the intermediate used to manufacture Rifampicin API, was fully transferred to Hulun Buir North Pharmaceutical Limited Company with effect January 2015. This company also belongs to the Tonglian group of companies.

Two polymorphs of Rifampicin API are manufactured at the site. The facility and equipment were shared by the two polymorphs up to the stage of the crude Rifampicin. The final stages were performed in separate facilities and different solvent used for final crystallization. Polymorph I (0.5) is manufactured for domestic supply and Polymorph II (0.7) for international (including WHO) supply. It was stated that manufacture of Butyl Flufenamate API for an ointment, and the ointment had been discontinued at this site so that Rifampicin is now the only API manufactured here. Manufacture of Butyl Flufenamate API and its ointment had taken place in separate facilities, some distance from the Rifampicin API manufacturing facilities.

History of WHO and/or regulatory agency inspections

The Rifampicin API facilities have previously been inspected by the WHO Prequalification of Medicines Programme in October 2010 and June 2013. At these previous inspections acceptable compliance could not be determined.

Focus of the inspection

The inspection focused on the production and control of Rifampicin API. The inspection covered all the 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)

Internal audits were conducted according to a SOP. QA was responsible for the overall internal audit program, including selecting audit team members who were required to be independent from the department being audited, and approving any corrective actions.

Each Department was required to be audited every 6 months and the plan for 2015 was reviewed and found acceptable.

Product quality review

Requirements for Annual Product Review (APR) were described in a SOP. Reviews covered the period January to December and were required to be completed by end March the following year. Statistical analysis of data was required provided that a minimum of specified batches had been manufactured during the period.

The 2014 APR for Rifampicin polymorph 2 had been documented. The analysis of data concluded that there were no trends requiring corrective action. The APR included an OOS for a critical solvent and a change control for the change in supplier of Rifampicin S Na to Hulun Buir. There had been no complaints, returns or recalls during 2014.

3.2 PERSONNEL

Personnel qualifications

There appeared to an adequate number of personnel to perform and supervise the manufacture of Rifampicin API. Key personnel had adequate qualifications and experience. Responsibilities of personnel were described in job descriptions which were generally found satisfactory.

Training was conducted according to a SOP and the SOP adequately covered various types of training including induction, on the job and cGMP training. The 2015 training plan and training records selected for review were satisfactory. 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. Requirements for clothing change on entry to the final processing cleanroom areas were well described in SOP and through pictures on change-room walls.

Quality risk management

A SOP described the company's policy and general approach to risk management. Several examples of when risk assessment was required were included, e.g. when a new product was introduced or in the event of a GMP failure. The latter included a requirement to consider the possible effect on other batches of API.

An FMEA model was described in detail and included classification of severity, probability and detectability into 10 levels which were properly defined. The RPN for each hazard was calculated and specified criteria then used to determine if any action was required.

A risk assessment covering all aspects of the manufacture of Rifampicin API had been performed and was documented.

3.3 BUILDINGS AND FACILITIES

Design and construction

Warehouses for solid starting materials, packaging materials, liquid starting materials and Rifampicin API polymorph 2 were inspected and generally found satisfactory with SOPs describing the handling of materials. As required, warehouses were provided with a sampling area. Temperature and RH were specified for the warehouses and the monitoring records examined were acceptable.

Rifampicin API was manufactured in Workshop 103 and the design and construction of this workshop was considered acceptable in general. A suitable area for in-process testing had been provided. The main QC laboratory was in a separate building. Non-compliances observed during the inspection that were listed in the full report regarding the segregated block used to produce

Rifamycin S previously were addressed by the company to a satisfactory level and should be verified during future inspections.

Utilities

The company had its own power generating plant that was said to supply electricity to neighbouring areas.

The HVAC system that provided filtered air to the areas used for final processing and packing was inspected (including drawings) and this appeared to be satisfactory.

Other utilities (such as steam) used in the manufacture of Rifampicin API 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

Purified water was produced by an RO system and distribution was by means of a 316SS loop. The system was provided with a UV lamp and sanitization was performed monthly with ozone produced by an ozone generator. The sanitization procedure and records were examined and found acceptable.

Containment

Rifampicin was now the only API manufactured on the site and this was manufactured in dedicated facilities. Observations made during the inspection that were listed in the full report regarding the potential possibility of batch mix-up were addressed by the manufacturer to a satisfactory level.

Lighting

Lighting in all areas visited was satisfactory.

Sanitation and maintenance

All areas visited were clean and appeared to have maintained to an acceptable standard. Appropriate procedures and records were available.

3.4 PROCESS EQUIPMENT

Design and construction

Equipment used in the manufacture of Rifampicin API was generally considered to be of appropriate design and size, and suitably located within Workshop 103. Non-compliances observed during the inspection that were listed in the full report regarding equipment design were addressed by the manufacturer to a satisfactory level.

Equipment maintenance and cleaning

All equipment appeared to be well maintained and SOPs for cleaning were available. The sample of cleaning procedures and records examined were satisfactory. There was a system for identifying the usage and clean status of equipment.

Calibration
All measuring equipment examined was labelled with a calibration sticker. All were being used within their calibration dates.

Computerized systems
No computerized systems were used in the production of Rifampicin API.

3.5 DOCUMENTATION AND RECORDS

Documentation system and specifications
The company had a well-defined system for managing documentation. The samples of procedures requested for review were readily available and were mostly in both Chinese and English. SOPs had been properly authorized and had been kept up to date. Each SOP included a version number and a brief record of the reason for any change. Records required to be maintained were also available and were generally satisfactory.

Equipment cleaning and use record
SOPs for major equipment use and cleaning were available, and cleaning records were available. Equipment use logbooks had been maintained. Equipment SOPs, records and logbooks were generally satisfactory.

Records of raw materials, intermediates, API labelling and packaging materials
Records of the receipt, quarantine, sampling and release of raw materials, intermediate, labels and packaging materials had been maintained.

Master production instructions (master production and control records)
A master production instruction was available and the inspectors verified the control and use of this document.

Batch production records (batch production and control records)
The approved master formula of the Rifampicin were checked and compared to the ones used in practice. The in-process BMRs and the completed BMRs reviewed were acceptable.

Laboratory control records
The QC records of the working reference of Rifamycin S Na and the completed QC records reviewed were reviewed.

Microbiology control records included media preparation and QC, and records of purified water and Rifampicin API testing. These records were satisfactory.

3.6 MATERIALS MANAGEMENT

General controls
Written procedures for the handing of materials from receipt through to approval or rejection were available.
Materials were purchased against documented specifications from approved suppliers.

Supplier approval
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 to be re-evaluated every two years. An audit report for Hulun Buir North Pharma. Company was reviewed.

Receipt and quarantine
Materials were examined upon receipt and placed in quarantine until tested and released. Bulk solvents delivered in tankers were sampled and tested before transfer to the bulk tank.

Sampling and testing of incoming production materials
Production materials were sampled in a designated sampling area according to a sampling plan and tested by QC before release. The containers sampled were identified.
After transfer, bulk solvent storage tanks were sampled and tested against specification and a new control number allocated to the mixed contents.

Storage
Various warehouses for the storage of specified materials were available. Temperature and humidity requirements were specified and monitored. The records reviewed indicated compliance with the specifications. Pest control stations were evident at various points within and outside the warehouses.
All the warehouses visited were clean and tidy with materials well generally organized and appropriately labelled.
Non-compliances observed during the inspection that were listed in the full report regarding status labelling of some re-usable solvent drums were addressed by the manufacturer to a satisfactory level.

Re-evaluation
Material labels included a re-test date. Released materials examined were within their re-test dates.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations
Raw materials were weighed using suitable equipment. These weighings were required to be witnessed by a second person.

Expected yields at key stages were specified in the BMR and actual yields were required to be within the limits specified.

The processing status of major equipment was indicated by means of attached tags.

In-process sampling and controls
In-process samples were required to be taken for testing at key processing stages as indicated in the BMR. In-process testing was performed in designated in-process laboratory areas within the production workshop.
An example of TLC testing was reviewed. This testing was performed by production staff using reagents and plates prepared by the main QC laboratory. The procedure was described in an SOP and results recorded in the BMR. This testing appeared to be satisfactory.

Blending batches of intermediates or APIs
If required, a specified number of batches of Rifampicin API could be blended to produce a single batch. Blending was performed in a V-blender according to a batch record for this process. QC testing was required to be performed on the blended batch.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Packaging materials
Rifampicin API was packaged in double layer PE bags in fibre drums. Packaging materials were not re-used and were subjected to proper inspection and QC checks before being released for use.

Label issuance and control
Blank product labels were stored in a secured area with restricted access. After printing, labels were checked before being issued for application to containers.

Packaging and labelling operations
Packaging and labelling took place in a designated controlled environment area. All packaging and labelling activities were recorded in the BMR.

3.9 STORAGE AND DISTRIBUTION

Warehousing procedures
As previously indicated, designated storage areas for different types of starting materials and finished API were available. Segregated areas for the storage of quarantined, rejected, returned and recalled materials were available.

Distribution procedures
Rifampicin API was released for distribution after being released by the Quality Assurance department. Storage conditions, including during transport, were specified on the API label. The product release management procedure was reviewed and no observation was made.

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 specification and Standard Testing Procedure (STP) of Rifampicin for WHO grade were reviewed. Non-compliances observed during the inspection that were listed in the full report regarding data security and reference substances were addressed by the manufacturer to a satisfactory level.

Stability was performed under the conditions of 30^0C, FH 65% according to a documented procedure. Non-compliances observed during the inspection that were listed in the full report regarding the chamber condition monitoring were addressed by the manufacturer to a satisfactory level.

A log book of the samples in-warded and withdrawn was available and acceptable.

Reserve/retention samples

Retention samples were kept in an air-conditioned room maintained at $\leq 20^o$C and RH 40-65%. Records of twice daily checks of these conditions were satisfactory.

Samples of Rifampicin API polymorph 1 and 2 were stored in separate designated areas within the room. Samples were stored in small bags of the same material as for commercial batches and these were stored in closed fibre drums with a good indexation system. Samples were required to be stored for 1 year beyond batch expiry and the retention period was included on the fibre drum label.

Microbiology laboratory

A separate suitably designed microbiology laboratory was available and equipped to perform microbiology testing of purified water, Rifampicin API and the environment of controlled manufacturing areas.

Media was prepared in-house and the procedure for preparing and QC testing R_2A media for testing purified water was reviewed. A growth promotion test for every batch/delivery of dry media was conducted. Records of media preparation were satisfactory.

The purified water system was sampled weekly according to a sampling plan. The plan required key sampling points to be sampled weekly with other sampled on a rotational basis at least once per month. Since the last inspection the purified water test method had been changed to a membrane filtration method using R_2A media and incubation at 30 – 35^oC. Test records for 2015 were reviewed and found satisfactory.

The test method and a sample of results for microbiology testing of Rifampicin API were reviewed and found satisfactory.

Environmental testing of controlled environments was performed according to a SOP using settle plates. The results for 2015 reviewed were satisfactory.

Microbiology OOS test results were handled according to a SOP. This SOP also covered action to be taken if microbiology alert or action limits were reached. The microbiology OOS log books for 2014 and 2015 were reviewed. Records for microbiological testing of purified water indicated that alert or action limits for purified water had not been exceeded during 2014/15 period.

3.11 VALIDATION

Validation policy
The company's overall policy and approach to validation was described in a Validation Master Plan (VMP). This document was updated annually and the 2015 VMP was reviewed. Responsibilities for validation were clearly defined with the QA Department taking overall responsibility for the program.

Validation documentation
The VMP required a protocol for each validation to be prepared. This required a risk assessment to be done. Qualification covered DQ, IQ, OQ and PQ followed by process validation.
A report following the format of the protocol was then prepared and included a conclusion regarding validation status. The report was required to be approved by all key relevant personnel.

Qualification
Lists of critical and non-critical equipment were attached to the VMP as Annex 1 and Annex 2 respectively. The VMP required new equipment to be qualified before use and critical equipment to be re-qualified on regular basis unless a change required it to be performed sooner than this.
The qualification protocol and report for a vacuum dryer was selected for review and was found to be satisfactory.

Approaches to process validation
Initial validation was prospective and re-validation concurrent.

Process validation programme
A comprehensive list of validated process relevant to Rifampicin Polymorph 2 was available for review. This document included dates of last validation and the schedule for revalidation.
A protocol and associated report for validation the universal crusher was reviewed and found satisfactory.

Cleaning validation
Cleaning validation was not covered during this inspection. The facility and equipment were dedicated to the API inspected.

3.12 CHANGE CONTROL (CC)

A Change Control Procedure SOP described requirements for handling any change. The SOP required the QA Head or delegate to complete a risk assessment for changes and the Risk Management SOP was cross-referenced. Changes were classified as major, moderate or minor with examples of each provided. The QA Head was also responsible for considering regulatory impact and whether or customers required notification. The change control procedure included a detailed checklist for introduction of a new product.
Records for the change from in-house produced Rifampicin S Na intermediate to it being produced by a related company in Hulun Buir were reviewed. This change had occurred in November 2013 and appeared to have been satisfactorily documented. Copies of letters to customers were included. This change concluded that process re-validation and stability testing was required, and this had been implemented.

Non-compliances observed during the inspection that were listed in the full report regarding the cessation of Rifamycin S Na production were addressed by the manufacturer to a satisfactory level.

3.13 REJECTION AND RE-USE OF MATERIALS

Rejection
Rejected materials were required to be suitably labelled and placed in a locked area until disposed of.

Reprocessing
Reprocessing required Head of QA approval and was handled according to a SOP. Examples of reprocessing were given for guidance. The log book for reprocessing indicated that here had not been any reprocessing.

Reworking
Reworking was not permitted.

Recovery of materials and solvents
Recovery of solvents took place in a designated area using separate equipment for each solvent. Recovered solvents were tested and released by QC. Recovered solvents could only be used for the same process as the original solvent was used and only for the same polymorphic form of API.

Returns
Returned API was required to be placed in a designated area within the warehouse. It was stated that there had never been any returned Rifampicin API.

3.14 COMPLAINTS AND RECALLS

According to the Product Quality Review inspected, there had been no complaints or recalls of Rifampicin polymorph 2 API. The documented procedures for these activities were not reviewed during this inspection.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The intermediate Rifamycin S Na was manufactured by the sister company Hulun Buir North Pharma. Co. Ltd. QC testing of Rifampicin API for polymorphic form was contracted out to a university lab.

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, the Rifampicin API (Polymorph II) (APIMF083), manufactured at Shenyang Antibiotic Manufacturer Ltd. located at Jianshe Third North Road, Hushitai Town, Xinchengzi District, Shenyang, 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.