

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
of the FPP manufacturer**

Part 1: General information

Name of Manufacturer	MSN Laboratories Private Limited
Unit number	Formulations Division
Physical/postal address	Plot No. 42, Anrich Industrial Estate, Bollaram, Medak District – 502 325 Andhra Pradesh, India Phone: +91 40 3043 8600
Focus of inspection	Film coated tablets for treatment of TB
Scope and type of inspection	Routine
Date of inspection	7-10 April 2014

Part 2: Summary

General information about the company and site

MSN Group of companies was established in the year 2003. The group was widely established in API Manufacturing and further ventured into Formulations in 2007. MSN Group had seven API Manufacturing plants in and around Hyderabad. One Formulation Facility is located in Bollaram.

The MSN Laboratories Pvt. Ltd. (hereafter referred to as “MSN”) factory was located in Bollaram, about 25 km from the city of Hyderabad. The factory comprises of four buildings including the main Production building, Utility block, Security block and the HRD building.

The site manufactured both oral solid dosage forms and injectable dosage forms.

There were approximately 182 permanent and 40-50 contract employees.

Production consisted of 2 separate manufacturing areas located in the same block: one for sterile injectable products and another one for oral solid dosage forms.

History of WHO and/or regulatory agency inspections

The site was previously inspected by WHO inspection team on 13 – 15 May, 2013.

The site was audited/inspected by the following authorities:

- ISO 9001:2008
- Kenya – PPB
- Uganda – NDA
- Tanzania – TFDA
- Namibia – NMRD
- Zimbabwe – MCAZ
- Malawi - PMPB
- Nigeria – NAFDAC

- Colombia – INVIMA
- Yemen - SBDMARM
- Belarus - MOH
- Ivory - DPM
- Kazakhstan - CCMPA
- Ethiopia - FMHACA
- Ukraine - SAUMP

Focus of the inspection

The inspection focused on the production and control of film coated tablets for treatment of TB. The inspection covered main sections of the WHO GMP text.

Inspected Areas

- Pharmaceutical Quality Assurance system
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

2.1. PHARMACEUTICAL QUALITY ASSURANCE SYSTEM

Annual product quality review (APQR)

The SOP “Product Quality Review” was checked. Only 4 batches were manufactured in 2013. The data were presented in graphical form. Separate reports were said to be available for excipients and packaging materials. Three batches were used for process validation.

Deviations

The SOP “Reporting and Monitoring of Deviations” was checked. This SOP covered the deviations which were planned as temporary changes. The SOP defined that deviation is an activity performed differently and /or modified manner from the specified approved documents/standard procedures and opted deliberately for a temporary period of time to handle the unavoidable situations.. Deviation reference No was specified in BMR/BPR.

An annual summary report of deviations was spot checked for 2013.

Incidents

The SOP “Reporting, Investigating and Closing of Incidents” was checked along with an annual summary report of incidents for 2013. The SOP was applicable to the reporting investigations and closing of activities occurred in unplanned/unknowing manner e.g. incidentally either directly or indirectly associated with manufacturing/packaging or analytical operations (which do not fall under the Out of Specifications) due to either system failure or machine breakdown or manual errors in different departments.

Change control (CC)

The SOP “Change Control” was reviewed along with its registers and annual summary for 2013. Change controls were divided into levels A, B and C, depending on their impact on the quality attributes of the product and on their potential regulatory impact.

Annual summary report on change control for the year 2013 was presented to the inspectors and was checked.

CC registers were product based. A separate register was available for general CCs.

According to the SOP a review of CC’s should be done on monthly basis. Monthly review of CCs was started in January 2014.

Risk Assessment (RA)

The SOP “Quality Risk Management (QRM)” was reviewed. QRM process was based on the ICH Q9 guideline. Failure Modes and Effects Analysis (FMEA) was used as a tool for risk assessment. A 10 score system was used for FMEA. All risk assessments done was re-assessed using 10 scoring system.

A list of process quality risk assessments (Master list – department wise) was presented to the inspectors.

A specific risk Assessment was checked.

Management review

The SOP “Management review meeting” was checked. Management meeting were carried out monthly, quarterly and yearly.

Corrective and preventive actions (CAPAs)

The SOP “Corrective and preventive actions” was reviewed along with the annual summary report for 2013. CAPAs were applicable for:

- Handling of deviations
- Out of Specifications (OOS) investigations
- Out of Trend (OOT) investigations
- Self-inspections
- External audits
- Annual reviews
- Market complaints

- Or any other system failure that needs preventive and corrective action plan.

Separate CAPA log books were available for:

- General system
- Deviations
- Incidents
- Market complaints
- Self-inspection
- External audits

2.2. GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

In general good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

2.3. SANITATION AND HYGIENE

Premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

2.4. QUALIFICATION AND VALIDATION

Validation master plan

A specific validation master plan was checked. The VMP was strategic document. Requalification was specified with a frequency of once every 5 years for all pieces of major equipment. Re-validation/verification criteria's were specified for process revalidation, cleaning revalidation and analytical method revalidation.

Process validation

Process validation had been done for 3 batches with batch size of 1,05,000 tablets and 3 batches with batch size of 25,000 tablets .

Tablets hold time validations

Protocol for hold time study and report for specific product were checked. The following was covered by the validation:

- Blend
- Compressed tablets
- Coated tablets

Cleaning validation and verification

Worst case approach was used for cleaning validation studies. Worst case product was identified based on solubility, batch sizes and dose and presented in a matrix.

Purified water system validation

Change control to the Purified Water (PW) system was checked. Users Requirement Specification (URS) was prepared. PW was upgraded by introducing ultrafiltration, RO and UV. Total Organic Carbon (TOC) tests were done off line. PW system schematic drawings were available for storage and distribution. Isometric drawings were also available.

During the qualification, some joint welds were verified; the slope was verified as 1:100; the PW system was equipped with alarms and alarms were verified.

The loop was sanitized weekly, with hot water above 80 °C. There was a record for the sanitization, and the temperature values.

RO membranes were also included in a procedure for sanitation.

Air Handling Unit (AHU) qualification

A specific AHU was inspected. AHU Qualification documentation showed that the IQ was done in August 2007. Requalification had been performed since.

AHU's Qualification reports for the different tests were checked, for example:

- Particle counts
- Air flow direction
- Air changes
- **Filter integrity**

Equipment IQ, Operational Qualification (OQ), Performance Qualification (PQ)

The IQ, OQ and PQ reports were reviewed for specific compressed air equipment.

2.5. COMPLAINTS

Complaint log for 2013 was checked. A specific complaint was reviewed. Fish bone diagram was used to identify the root cause.

2.6. PRODUCT RECALLS

The SOP "Product recall" was reviewed as well as the mock recall protocol and report, conducted in out March 2014. Mock recall protocol was checked. Mock recall was carried out for overseas.

2.7. CONTRACT PRODUCTION AND ANALYSIS

A specific agreement with external agency (laboratory) was checked.

2.8. SELF INSPECTION AND QUALITY AUDIT

Not covered during this inspection.

Supplier's audits and approval

The SOP "Supplier Qualification and approval" was checked. Attention was paid to the Supplier development for primary packing materials.

Approved suppliers list for the primary packaging materials and secondary packaging materials was presented to the inspector.

A specific audit report for supplier of printed and plain aluminium foils was checked.

2.9. PERSONNEL

In general the manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs' specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training.

2.10. TRAINING

Training was provided for all permanent and contract workers.

The SOP "Training of employees" and training plan were reviewed. Training was based on the following categories:

- Orientation and Induction training program
- On Job training
- cGMP training
- Safety training
- External training

The cGMP training Annual Planner for the 2014 was checked. A specific training documentation for GMP training was checked.

Contract workers (labour workers) were used in secondary packaging. Contract workers list was presented. Contract workers training was also explained in the SOP "Training of employees". Training effectiveness was evaluated by multiple choice questions.

Training materials and evaluation questionnaires were available in local language.

The SOP "Analysts qualification" and training plan were checked. New analysts were qualified by giving for analysis already analysed sample. Only necessary information to perform an analysis was disclosed. After analysis, obtained results were compared with already known test results. Acceptance criteria between analyses were specified in the SOP.

Analyst Qualification Certificates were issued for qualified tests.

2.11. PERSONAL HYGIENE

Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewellery were not being worn in clean areas.

2.12. PREMISES

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Premises were designed to ensure the logical flow of materials and personnel. In-process laboratory was located in the production block. Quality control laboratories were separated from production areas. Sufficient space was given to avoid mix-ups and cross-contamination. Premises were protected from entry by insects, birds and animals. Premises were clean and well maintained.

Storage areas

Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products.

Warehouse for the storage of different materials was found to be adequate. Temperature mapping was carried out.

Production areas

In general, the production area was laid out to allow the production steps to take place in a logical order. In general the surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components.

Temperature, relative humidity and pressure differentials were regularly monitored.

Quality control areas

Quality control areas were separated from production areas. Sufficient space was provided for samples, reference standards, solvents and reagents.

2.13. EQUIPMENT

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment.

Calibrated standard weights used for in-house verification of balances were available. The calibration certificate for the set of standard weights was presented to the inspectors.

Preventive Maintenance (PM)

The SOP “Preventive maintenance” was checked. PM schedules for 2013 and 2014 were checked for a specific FBD and Octagonal blender. Spot checks showed that PM schedules were followed. PM was carried out monthly, half yearly and yearly. PM was carried out using separate monthly, half yearly and yearly check lists.

Equipment calibration

The SOP “Calibration of equipment was checked. Calibration was carried out by external agency every 6 months or one year based on the criticality..

Calibration schedule was checked. Spot checks showed that calibration schedule was followed. Calibration certificates were shown to the inspectors and were traceable to the instruments used for calibration.

Compressed air

The SOP "Procedure for operation and Preventive maintenance of air compressor" was checked.

The following protocols/reports were checked:

- Installation Qualification
- Operational Qualification
- Performance Qualification

Air quality tests were carried out every 6 months.

Tests were carried out by external agency (laboratory). Test certificates for various sampling points were presented and spot checked. Checked test results were well within the specifications.

2.14. MATERIALS

There was no electronic system for material management. Materials were controlled by means of bin cards

2.15. DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. In general, documents were approved, signed and dated by the appropriate responsible persons. Documents were laid out in an orderly fashion and were easy to check. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date.

2.16. GOOD PRACTICES IN PRODUCTION

In general the surfaces were smooth and free from cracks. Equipment and materials were orderly positioned to minimize the risk of confusion between different pharmaceutical products or their components.

Temperature, relative humidity and pressure differentials were regularly monitored.

The oral solid dosage form production areas were inspected, with a focus on the equipment used for the manufacturing of specific tablets.

2.17. GOOD PRACTICES IN QUALITY CONTROL

The Quality Control (QC) function was independent from other departments. Samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by approved methods. Sufficient samples of starting materials and products were retained to permit future examination of the product. A brief inspection of the quality control laboratory was done. Some documents including SOPs, log books/registers, reports and analytical reports were reviewed.

Out of specifications (OOS)

The SOP “Handling of out of specifications results” was reviewed along with the register for 2013 and 2014. SOP was written following MHRA guidelines.

Out of Trends (OOT)

The SOP “Handling out of trend results was checked.

Laboratory incidents

The SOP “Chromatographic analysis and documentation in quality control” along with Annual summary report on Incidents 2013 was checked.

Stability testing

Six (6) walk in stability chambers were available. Temperature (T) and Relative Humidity (RH) in chambers were continuously monitored using data loggers and print outs were taken. Stability chambers were equipped with an alarm system. T and RH mapping was carried out every year.

Reference standards

Working standards (WS) were kept in a desiccator equipped with a humidity indicator, at room temperature. WS were prepared in a balance room, dispensed into 24 bottles for use within 2 years. One bottle was used in one month. Chemical Reference Standards (CRF) for specific product were verified to be available and stored in the refrigerator at 2 – 8 °C. T in the refrigerator was continuously monitored using 4 T sensors and print outs were taken. The refrigerator was equipped with an alarm system.

Microbiology laboratory

Not covered during this inspection

Retention samples

Finished product retention samples were stored 1 year after expiry date.

API retention samples were stored for 7 years. The temperature was controlled and monitored twice per day.

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, *MSN Laboratories Private Limited Plot No. 42, Anrich Industrial Estate, Bollaram, Medak District – 502 325, Andhra Pradesh, India*, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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.