

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1: General information about the inspection

Name of manufacturer	MSN Laboratories Private Limited
Contact address	Plot No. 42, Anrich Industrial Estate, Bollaram, Medak District – 502 325 Andhra Pradesh, India Phone: +91 40 3043 8600
Unit	Formulations Division, Solid oral production unit
Date of inspection:	13 – 15 May 2013
Type of inspection	Initial
Dosage form included in the inspection	Coated tablets
Summary of the activities performed by the manufacturer	The scope of activities of MSN Laboratories is manufacturing, packaging, quality control and stability testing
WHO product category covered by the inspection	Film coated tablets for treatment of Tuberculosis

Part 2: Summary

General information about the company and site

The MSN Laboratories Pvt. Ltd. (here with referred to as “MSN”) factory was located in Bollaram, about 25 km from the city of Hyderabad. It was acquired in 2007 and gradually refurbished. MSN Laboratories held other manufacturing sites, including a new R&D facility at different addresses in Hyderabad.

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

There were approximately 146 permanent and 30-50 contract employees.

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

The site was specialized in contract manufacturing for several large companies such as Ranbaxy. The MSN branded products were also sold and distributed on the local market.

Moxifloxacin came into 2 different tablet appearances. The application for WHO prequalification was for a brown-colour, caplet-shaped tablet. The product for export to other countries is yellow coloured round shaped tablet.

History of WHO and/or regulatory agency inspections

This was the first WHO inspection of this site. It had not been inspected by Stringent Regulatory Authorities (SRAs). It was informed during the course of the inspection that United States Food and Drug Administration (USFDA) inspected the Active Pharmaceutical Ingredient (API) site.

Focus of the inspection

The inspection focused on the production and control of specific medicine used for treatment of Tuberculosis. The inspection covered all the sections of WHO Good Manufacturing Practice (GMP) text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

2.1 QUALITY ASSURANCE

Product quality reviews (PQR or Annual product quality reviews (APQR) as per the company’s terminology)

The APQR Standard operating procedure (SOP) was reviewed. It contained all of the necessary elements, except for an absence of details on how PQRs would be subdivided.

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

The APQR for specific tablets for the 2012 calendar year for local and export markets was reviewed. It was conducted in line with the company SOP. The PQR was found to contain all of the necessary sections in accordance with the SOP.

Deviations

The SOP for reporting and monitoring of deviations was reviewed. This SOP covered the deviations which were planned as temporary changes. The SOP stated that change controls would be initiated through corrective actions and preventive actions (CAPAs) for reoccurring deviations. Deviations were defined as “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”. The SOP stated that any activities that occur unknowingly or incidentally due to machine breakdown or manual error shall be handled as per SOP “Reporting, Investigation and Disposition of Incidents”.

The registers were seen for 2012. It was noted that individual logbooks were filed for each product code – this was not clearly described in the SOP.

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

An annual summary report of deviations was reviewed for 2012. A graphical representation of product specific deviations was attached to the report. There was no adequate/systematic analysis of reoccurring deviations.

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

Incidents

The above mentioned SOP and its associated register (general for 2012 and 2013, and product specific) were reviewed. Several Incident reports were reviewed.

The handling and recording of incidents was considered to be acceptable overall.

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

Change controls (CC)

The SOP for change controls was reviewed along with its registers and annual summary for 2012. 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.

The handling and recording of CC was considered to be acceptable overall.

Quality Risk Management (QRM)

SOP “Quality risk management was reviewed. The procedure was applicable for:

- Warehouse
- Processing
- Packing
- Quality control (QC)
- Engineering

- Various other GMP aspects if applicable
- QRM process was based on the International Conference on harmonisation (ICH) Q9 guideline. Failure mode and effects analysis (FMEA) was used as a tool for risk assessment. FMEA was applicable for:
- Equipment
 - Utilities
 - Process
 - Documentation
 - Training
 - Quality defects
 - Audits
 - Periodic reviews
 - Change controls
 - Material management
 - Analysis
- 5 score system was used for FMEA.

List of carried out risk assessments (RA) was presented. Till the date of inspection following RA had been executed:

- 22 for production equipment's
- 5 for engineering equipment's
- 2 for QC equipment's
- 5 for production processes
- 5 for utilities (engineering)
- 1 handling of raw materials

Several RA reports were reviewed. These RA were carried out on site.

Non-compliances observed during the inspection that was listed in the full report regarding RA carried out on site were addressed by the manufacturer to a satisfactory level.

Several RA were carried out by external company using 10 ranking system. Reviewed RA carried out by the external company generally were found to be carried out adequately. Validation reports associated with those RAs were not reviewed during the inspection.

Management review

Management review SOP was not available specifying topics what should be discussed and how frequently meetings should be held. It was explained that management meetings were held twice per year and there was quite a possibility that important topics as complaints, recalls, rejects etc. and associated CAPAs could be missed required actions were not taken in appropriate time limit.

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

Corrective and preventive actions (CAPAs)

The SOP on CAPAs was reviewed along with the annual summary report for 2012. There was no register of CAPAs related to deviations.

A specific CAPA was reviewed. CAPA document was very simple and not detailed enough.

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

**2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR
PHARMACEUTICAL PRODUCTS**

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**

The validation master plan was reviewed. Requalification was specified with a frequency of once every 5 years for all pieces of major equipment.

The equipment requalification schedule for specific equipment was shown. Requalification was performed once every 5 years. The most recent requalification was performed in 2012.

Analytical method validation

The SOP for validation of analytical test procedures for related substances by HPLC was reviewed. It was deemed acceptable overall.

Cleaning validation and verification

The procedure for cleaning validation was reviewed.

It was noted that for specific product cleaning verification was conducted instead of cleaning validation. It was the company policy that when a new product was introduced which was not a worst case product; cleaning verification was conducted with one run of the cleaning procedure. Only swabbing (no rinse samples) was done for the solid oral dosage form trains, with the exception of fluid bed dryer bags.

In general cleaning validation was considered to be adequate.

Clean equipment hold time study

Clean equipment hold time studies were seen and some observations were made.

Non-compliances observed during the inspection that was listed in the full report regarding clean equipment hold time studies were addressed by the manufacturer to a satisfactory level.

Validation of analytical method for quantitation of residues

Recovery from stainless steel only was considered, which may not cover gaskets used in sieves. There was no documentation of the swabs used in the report. Sampling location was described as “feed hopper”, “discharge chute”, “shaft with knives”, or “bowl inside surface” for the rapid mixer granulator. There was no detail of the actual sampling points within these larger areas diagrams.

Non-compliances observed during the inspection that was listed in the full report regarding validation of analytical method for quantitation of residues were addressed by the manufacturer to a satisfactory level.

Purified water system validation

Purified Water (PW) system was upgraded by introducing ultrafiltration, Reverse Osmosis (RO) and Ultraviolet light (UV) in 10 August 2012. PW system Phase I validation was started on 11 August 2012 and finished on 24 August 2012 (2 weeks). Performance Qualification (PQ) report for Phase I was reviewed. Sampling was carried out daily from all sampling points. All tests were within specified limits. PW was used after the Phase I completion in 29 August 2013.

PW system Phase II validation was started on 25 August 2013 and finished 12 September 2013 (2 weeks). Performance Qualification (PQ) report for Phase II was reviewed. Sampling was carried out daily from all sampling points. Microbiological alert and action limits were set up after the Phase II. All tests were within specified limits.

PW system Phase III validation was started in 19 September 2012. Till the date of inspection Phase III validation was not completed. According with validation protocol PW was sampled after UV and return loop on daily basis, other sampling points will be sampled on rotation once per week or twice per week. All tests up to day of the inspection were within specified limits.

Loop and storage tank was sanitized weekly by the hot water about 85 °C. Reverse Osmosis system chemical sanitization was carried out every 3 month.

Welding performance qualifications record was reviewed. Orbital welding was used for the connecting of the 316 L tube joints. Altogether there were 425 joints. Radiography inspection report and photos for 43 joints (10% of all joints) was presented. Some photos were reviewed during inspection.

Reviewed PW system validation (Phase I and Phase II) was found to be carried out adequately.

Air Handling Units qualification

Heating, ventilation, and air conditioning HVAC system was installed in 2007. Separate AHU were provided for each production cubicles.

Summary report and raw data for re-validation of HVAC system AHU No 1 was spot-checked.

Air was recirculating; intake of fresh air was more than 10 %. Some tests were carried out by a third party, some by the MNS Engineering staff.

The following filter cascade was installed in the AHU: EU 3 →EU 4. Terminal HEPA filters H13 were installed in the production suites.

The following tests were carried out according with ISO 14644 requirements:

- HEPA filter integrity poly-alpha-olefin (PAO) tests was done one per year by external agency
- Air velocity / air changes per hour was done every 6 months by external agency
- Different pressure gradient – daily monitoring
- Airborne particle count test was done every 6 months in-house
- Environmental monitoring temperature & humidity – daily monitoring
- Air flow visualization was done one per year by external agency and CD showing airflow directions was presented. Some videos were watched
- Recovery / decontamination rate test was done one per year by external agency. Viable particulate matter test was done every 15 days in-house

Measuring equipment calibration certificates were presented and were traceable. In general HVAC system re-qualification was found to be adequately carried out.

Equipment IQ, OQ, PQ

The Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) reports were reviewed for the 60 kg fluid bed dryer as an example. These were found to be outdated as they were from 2007 and no requalification was done.

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

Microbiological laboratory autoclave validation

Autoclave re-validation was carried out once in a year. Validation protocol and report were spot checked.

Validation was carried out for:

- Heat distribution for empty chamber
 - Heat distribution and heat penetration studies for garments and accessories and media
- 12 thermocouples (TC) were used for the validation study. TCs were calibrated before and after the study. Maximum load T records were checked.

Non-compliances observed during the inspection that was listed in the full report regarding microbiological laboratory autoclave validation were addressed by the manufacturer to a satisfactory level.

Process validation

A specific tablets process validation protocol/report and some analytical raw data were spot checked and not reviewed in details due to the time limit. Validation studies were carried out in September 2010.

The following critical production steps were validated:

- Dry mixing and granulation.
- Granulation
- Drying
- Blending
- Compression
- Coating

On spot checks reviewed data were found to be adequate.

2.5 COMPLAINTS

The SOP entitled “Handling of market complaints” was reviewed. There was only 1 register covering all complaints. The register for 2012-2013 was reviewed along with the annual summary for 2012.

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

2.6 PRODUCT RECALLS

The SOP on “Product recall” was reviewed as well as the mock recall protocol and report, conducted in June 2012. It defined a full recall timeline of 24 hours in the case of a critical defect. There was no timeline specified for minor or major recalls.

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

2.7 CONTRACT PRODUCTION AND ANALYSIS

Quality agreement between for contract manufacturing was reviewed. Contract was related to the manufacture of 6 products. Reviewed contract was found to be comprehensive.

2.8 SELF INSPECTION AND QUALITY AUDIT

SOP “Self-inspection / internal audit” was reviewed. Audit team consisted of experienced and qualified persons from all departments; the lead auditor was Head Quality Assurance (QA) or designed deputy. Self-inspection was conducted twice per year for:

- Production
- Quality Control (QC)
- Microbiology

- QA
- Warehouse
- Engineering
- Supply chain management
- Human resources
- Regulatory affairs
- Marketing
- Management
- Management representative

According with the SOP Self-inspection also might be conducted in the following cases:

- Following Out of Specification (OOS) results
- Following a product complaint
- Following a batch failure

Self-inspection was conducted using the check lists dedicated to the departments. Check lists were approved by the Head QA. Observations were recorded in the Self-inspection report. Deficiencies were categorized as:

- Critical
- Major
- Minor

Proposed Corrective Action report containing Root cause analysis had to be prepared within 7 working days and submitted for QA. QA was responsible for evaluation of the CAPAs and root cause analysis. Afterwards follow up inspection report was prepared. Head QA prepared Self-inspection conclusion report and this report was submitted to the Executive Director. Reviewed documents were found to be adequate.

Supplier's audits and approval

SOP “Supplier Qualification and approval” was reviewed. Supplier should be subsequently evaluated based on the following qualification criteria:

- Satisfactory on-site inspection shell be audited, however, the manufacturing site, which was officially certified by accredited bodies like WHO, Brazilian Health Surveillance Agency (ANVISA), Health Canada, International Organization for Standardization (ISO), Medicines and Healthcare Products regulatory Agency (MHRA) or Member countries of European Commission (EC), New Zealand, Therapeutic Goods Administration, Australia (TGA), USFDA etc. can be accepted as approved supplier based on Supplier Qualification Questionnaire, unless there was a specific requirement for compliance to standards with respective to manufacturing process and other applicable aspects, However the site inspection is recommended for all the API sites.

It was noted that 80% of APIs were received form MSN API manufacturing units.

API supplier’s re-audits on site should be carried out every 3 years $\pm$ 3 months. Raw materials other than API and packaging material’s supplier’s audits should be carried out

every 5 years $\pm$ 3 months. Audits were carried out according with different Supplier audit check list for related departments. Observations were graded as:

- Adequate
- Inadequate
- Missing

After finishing the audit, observation report was sent to the audited company. CAPAs should be submitted by the audited company and evaluated by the MSN Head QA.

Supplier's approval procedure and reviewed audits were found to be adequate.

2.9 PERSONNEL

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.

The following job descriptions (JD) were reviewed and in general found to be adequate, authorized deputies were specified for reviewed job possessions:

- Senior manager QA
- Manager QC
- Senior General Manager (production) was not responsible for Approval and monitoring of suppliers of materials
- Assistant General Manager

2.10 TRAINING

Training was provided for all permanent and labour workers.

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

Almost all questionnaires related to the training evaluation were open questionnaires.

Contract workers (labour workers) were used in secondary packaging. Contract workers list for 13 May, 2013 (day of inspection) was presented. Contract workers training was also explained in the SOP "Training of employees" section "Training of temporary employees". Training records for three temporary employees were reviewed.

Training effectiveness was evaluated by multiple choice questions. Temporary workers were trained 5 times per year for the following topics:

- Plant and personal hygiene
- Good documentation practices

- cGMP
- Gowning and entry procedure for controlled and critical rooms
- Manufacturing area practices

Training materials and evaluation questionnaires were available on local language.

SOP “Analysts qualification” and training plan were reviewed. New analysts were qualified by giving for analysis already analysed sample. Only necessary information to perform an analysis was disclosed. After analysis the obtained results were compared with already known test results. Acceptance criteria between analyses were specified in the SOP. Analyst’s re-certification was carried out every 3 years. Supervisors re-certification was carried out once in a year.

Executive QC qualification certification file was reviewed. Reviewed training files were found to be adequate.

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.

SOP “Plant and personnel hygiene” and training plan were reviewed and found to be adequate.

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. Appropriate storage conditions were provided. Temperature (T) mapping of the Raw materials and primary packing materials warehouse was carried out by external agency in three seasons.

Raw materials sampling and dispensing was carried out in two sampling/dispensing RLAF booths. One booth was used for APIs sampling/dispensing and one booth for inactive substances/primary packaging materials sampling/dispensing.

Production areas

Production area was laid out to allow the production 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 checking of balances were available. Standard weights calibration certificated were presented to the inspectors.

Preventive Maintenance (PM)

SOP “Procedure for preparation and execution of preventive and break down maintenance” was reviewed. The entire SOP did not cover Quality control laboratory (QCL) instruments and equipment. PM was carried out according with check lists for all equipment’s. Plan was prepared once per year. PM schedules were system based e.g. Water system, HVAC system and services, utilities, production equipment etc. On spot checks the schedules were followed. The following documents were spot checked:

- SOP “PM of Fluid Bed Dryer FBD” and check list FBD 300 kg
- SOP “AHU” and check list AHU-01
- SOP “Operation and Preventive maintenance of Air handling units”

Equipment calibration

SOP “Procedure for instruments calibration” was reviewed. This SOP was also applicable to the QC instruments as temperature controllers, digital thermo hydrometers etc. Instruments were calibrated by external agency. Instruments were categorized as:

- Critical
- Monitoring
- Indicator

Calibration plan was prepared once per year. Calibration schedules were system based e.g. Water system, HVAC system and services, utilities, production equipment etc. and carried out according with instruments and equipment’s manual’s.

QC instruments as HPLC, UV etc. were calibrated internally and externally. Calibration schedule was presented and on spot checks followed.

Compressed air

Air compressor had in built heater.

The compressed air flow chart was following:

- Air compressor → air receiver → 5 micron filter → 1 micron filter → 0.2 micron filters before every user point.

Filters were cleaned monthly and were changed once per year. PM schedule and PM log books for 2011 and 2012 were presented and reviewed. Air quality tests were carried out every 6 months. Tests were carried out by external agency. Test certificates for various sampling points were presented and spot checked. Checked test results were well within the specifications. Compressed air maintenance and quality were found to be adequate.

HVAC balancing

Room pressure differential test protocol/report was reviewed. The purpose of the test was to verify the pressure differentials in the solid dosage facility when all AHU were not running concurrently. The test was carried out by external agency. Conclusion was that even with certain AHUs of processing area being stopped the pressure differential between the corridor and all the processing area was being maintained more than – 1.0 mm of water (10 Pa).

2.14 MATERIALS

Material management and tracking of inventory was paper based and was found to be acceptable overall.

However non-compliances observed during the inspection that was listed in the full report regarding the warehouse temperature and humidity monitoring were addressed by the manufacturer to a satisfactory level.

SOP “Sampling, testing and release of raw material” was reviewed. APIs were sampled and tested 100% for identification.

SOP “Sampling, testing and release of raw material” did not specify how many samples from individual containers could be combined together for composite sample.

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

100% sampling plan was not applied for excipients sampling.

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

SOP “Sampling, testing and release of packaging material” was reviewed. Sampling SOP specified that the sampling plan should follow acceptable quality limit (AQL). AQL was not followed in the number of Boxes/packs to be opened.

Non-compliances observed during the inspection that was listed in the full report regarding sampling of packaging materials (AQL) were addressed by the manufacturer to a satisfactory level.

Rejects

The SOP on Handling of Rejected Materials was reviewed. It stated that rejection should be done by preparation of slurry and should be witnessed by designated person from Warehouse and Quality Assurance.

2.15 DOCUMENTATION

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.

SOPs had a 3 year review period. The master list of SOPs was reviewed and all of the SOPs listed were found to be in existence and to match the numbers.

Paper based logbooks were issued and controlled by QA.

The level of control of documentation was considered to be acceptable overall.

Batch Manufacturing Record /Batch Packaging Record (BMR/BPR)

A specific product BMR/BPR were reviewed and found to be adequate.

The batch manufacturing records contained the necessary level of detail (e.g. area checks, environmental conditions), as seen.

2.16 GOOD PRACTICES IN PRODUCTION

The production area was laid out to allow the production 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.

The solid oral production unit was inspected, with a focus on the equipment used for the manufacturing of specific product.

The SOP on “In Process Quality Assurance for Drug Product was reviewed. It included a procedure to be followed in case of deviations (Appendix II) to the normal manufacturing process.

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

Batch release

SOP “Batch release” was reviewed. SOP was applicable for finished product release. Process QA reviewer or authorized deputy were responsible for reviewing BMRs and BPRs. Analytical reviewer or authorized deputy was responsible for reviewing analytical raw data and CoA. Mentioned documents were reviewed following the check lists. Batch release was done by the Head QA or authorized deputy.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The 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.

Stability testing

The packaging format for WHO product under assessment was 3 x blisters. Stability studies were performed in bulk and in all of the packaging formats under the 40°C/75%RH, 30°C/75% RH, 25°C/65%RH and 30°C/65% RH long-term.

Samples were verified to be present in adequate amounts to perform full long-term stability testing in the 30°C/75%RH stability chamber. Reconciliation was shown through the stability chamber equipment logbook and stability samples bin-card. Opening balance, drawn quantity and closing balance were recorded and initialled.

The IQ, OQ and PQ of the 30°C/75% RH stability chamber were reviewed. Temperature mapping was initially performed during qualification using both the built in sensors (8 in total) and 8 additional data loggers. Alarm challenge studies were done during performance qualification. Temperature and humidity monitoring printouts were also taken daily. Furthermore, the company stated that there would be visits of the area every day, regardless of holidays.

Infrared spectroscopy (FTIR)

FTIR test results for specific API batch were reviewed. Individual spectra were verified to have been performed for each container (6 in total) and each time, different potassium bromide pellets containing the 6 samples as well as a composite potassium bromide pellet, were prepared, as evidenced by the appearance and characteristics of the spectra that was seen. The correlation factor of spectra to the standard was performed by the software; all of the IRs were verified to be unique. The fields used for date, time, batch number were locked by the software in use.

High-performance liquid chromatography (HPLC) analyses

Analytical stability reports pending in QA for completion of review were reviewed.

A specific tablets were selected as an example and related substances testing was verified in the chromatographic system which was used to perform the analyses. For all systems, data was automatically backed up to a server every 12 hours.

In the system there was a data audit trail, method audit trail and a system audit trail. These were reviewed.

Analyst worksheets for in-process samples were reviewed and were found to contain an adequate level of detail.

Reference standards

Working standards were kept in a desiccator equipped with a humidity indicator, at room temperature. Bottles were kept up to 1 month and then discarded. Handling of reference standards was found to be adequate.

Out of specifications (OOS)

The SOP for OOS was reviewed along with the register for 2012. The manner in which these OOS's were documented was found to be acceptable.

Microbiology

Each dry media batch was tested for growth promotion upon receipt. All of the required samples for purified water sampling points were found for 13 May 2013 in the 37.5°C incubator. Issues were noted with regards to the labelling of equipment in the laboratory.

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

SOP "Procedure for viable monitoring in oral manufacturing facility environment" and Environmental monitoring summary report for microbial count of oral manufacturing area by passive air sampling period January 2013 to March 2013 were reviewed. Action and alert limits were set up. Samples were taken from predefined locations every 15 days on rotation basis. Settle plates were exposed for 4 hours. Settle plate's exposure time was validated in 2010. All environmental monitoring (EM) test results were within limits and under the alert limit.

Glycerol was added to the settle plates to avoid drying out of the media during exposure. Glycerol validation for settle plate exposure protocol and report was spot checked. Two Medias and six cultures were used for the study. Positive and negative control contained 1% Glycerol.

SOP "Microbiological analysis of water" was reviewed. Samples were collected from the used points using the same delivery devices as employed by production.

Retention samples

The temperature was controlled and retention samples were seen to have been kept for the 5's presentation for all batches manufactured up to date with a retention policy of 1 year over the expiry date.

Electronic data

Excel spread sheets were locked and validated. The protection of different types of electronic data (HPLC, FTIR), was deemed to be satisfactory.

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 located at 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 2 years, provided that the outcome of any inspection conducted during this period is positive.