

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

**PART 1: GENERAL INFORMATION**

Name of Manufacturer	MSN Pharmachem Private Limited
Unit	NA
Production blocks	D, E and F
Physical address	MSN Pharmachem Private Limited , Plot No 212/ A, B, C, D, Phase II, IDA Pashamylaram, Pashamylaram (Village) Patancheru (Mandal), Medak District, Pin Code - 502 307, Telangana, India.
Postal address	Same as above
Latitude	17°32.504`
Longitude	78°10.829`
Microbiological laboratory	MSN Laboratories Private Limited. Sy.No.317 & 323, Rudraram (village), Patancheru (Mandal), Medak District, Pin Code – 502 329, Telanagana, India.
Date of inspection	14 – 16 October 2015
Type of inspection	Routine GMP inspection
Active PharmacEUTical Ingredient(s) included in the inspection	Moxifloxacin Hydrochloride (Monohydrate) API
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished non-sterile APIs. No toxic or hazardous substances were handled or manufactured

## **PART 2:**

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

The MSN Pharmachem Private Limited (MSN) manufacturing site is located at Pashamylaram village near to Patancheru about 35 km from Hyderabad city. The MNS is specialized in the manufacturing of active pharmaceutical ingredients and their intermediates. It is part of the MSN Group of six pharmaceutical companies and was established in 2004. Production started in January 2005. MSN has manufacturing facilities located at Pashamylaram, Patancheru, Medak District, Telangana State, India.

The number of persons working at MSN Pharmachem was about 385, of which 179 were involved in production, 84 in Quality Control (QC), and 23 in Quality Assurance (QA). Forty two (42) contract workers were involved in materials transfer operations.

MSN holds valid CEP-2007-355 for moxifloxacin Hydrochloride (Monohydrate) API.

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

The site was previously inspected by the WHO team on 16 – 19 April, 2012.

The site has been inspected by the following authorities within the last 7 years

- National Institute of Pharmacy (NIP), Budapest, Hungary – April 2008
- Drugs Control Administration, A.P, India – April 2009
- Korea food and drug administration – November 2010
- Federal Commission for Protection against Health Risks; Mexico – February 2011
- United States Food and Drugs Administration – August 2011
- Drugs Control Administration, A.P, India – September 2011
- Ministry of health & Consumer protection, Germany - October 2012
- Federal Commission for Protection against Health Risks; Mexico – July 2013
- Drugs Control Administration, A.P, India – November 2013
- Federal Commission for Protection against Health Risks; Mexico – April 2014
- United States Food and Drugs Administration – June 2014

### ***Focus of the inspection***

The inspection focused on the production and quality control operations related to the moxifloxacin Hydrochloride (Monohydrate) API.

### ***Inspected Areas***

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- 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 (QM)**

#### Principles

In general, a system for managing quality was established, documented and implemented. The quality unit was independent of the production department. The person responsible for release of intermediates and APIs was specified. Systems for handling any deviations from established procedures were in place and documented. Materials were released by the quality unit after satisfactory evaluation.

#### Management review (MR)

The SOP “Management review” was checked. The management review group consisted of the department’s heads. The following items were discussed, but not limited to:

- Follow up actions from previous MR
- Review of quality policy and objectives
- Results of internal/external audits
- Customer feedback
- Process and product conformance
- Status of corrective actions and preventive actions (CAPA)
- Changes that could affect QM system
- Review of incidents / deviations / out of specification (OOS) results
- Review of customer complaints
- Market related factors
- Performance of suppliers and vendors
- Recommendations and improvement
- Others

The MR was carried out every three months; meetings summary was prepared as “Minutes”. The last MR meeting was carried out on 30 July 2015. MR meeting minutes were spot checked.

#### Internal audits (self-inspection)

The SOP “Internal audit” was checked. The internal audit team leader was the QA manager. The team consisted of persons from QM, production, quality assurance (QA), quality control (QC), regulatory affairs, engineering services and warehouse. Qualification and attributes of auditors (education, training and experience) were specified in the SOP. According to the SOP production, QC, warehouse, engineering services and QA departments shall be audited every three months and other departments every six months. Internal audit schedule for 2015 was presented to the inspectors.

Internal audits were performed according to the department check lists. After the audit, report was written and the deficiencies, observed during the inspections, were listed. Deficiencies were classified as:

- Major
- Minor

CAPAs were proposed by the audited department and evaluated by QA. Audit findings and corrective actions were documented and reported to the management.

The training records of one internal audit team member were spot checked. Training effectiveness was evaluated by multiple choice open questions.

#### Product quality review (APQR)

The SOP “Annual product quality review” was checked. According to the SOP APQRs should be prepared by the end of March of the subsequent year. The graphic representations of quality attributes and manufacturing parameters in the PQRs were based on limits calculated by  $\pm 3$  sigma method.

The regular quality reviews of APIs were conducted and included:

- Product general information
- Review of starting materials
- Review of critical parameters and in-process controls
- Review of intermediates
- Review of finished product
- Review of changes
- Review of deviations
- Review of out of specifications (OOS)
- Review of stability studies
- Review of complaints, returned goods and recalls
- Review of validation
- Review of reworked /reprocessed batches
- Review of regulatory documents
- Review of audits
- Review of primary packaging materials
- Review of adequacy of corrective actions and preventive actions (CAPAs)
- Review of retained samples
- Review of microbial limit tests
- Review of training programmes
- Qualification status of relevant equipment and utilities

Separate annual review reports were available for:

- General systems
- Water system

### Quality Risk Management (QRM)

The SOP “Quality Risk Management” was checked.

The SOP was applicable for:

- QM
- Facility
- Equipment / instruments
- Utilities
- Systems
- Process
- Packaging
- Labelling

The SOP described how to use failure mode and effects analysis (FMEA).

## **3.2 PERSONNEL**

### Personnel qualifications

There was an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing. A separate reporting structure was established for production and quality departments.

The current organogram was approved on 30.09.2015. The reason for revision was supported by the change in designations of two key functions due to promotions. The previous version of the organogram was also available for inspection. The organogram outlining the structure of the QA department was reviewed and it was noted that the departments were segregated based on the seniority of QA Managers/Associates and not by activity types.

The following SOPs were reviewed:

- “Quality Assurance Responsibilities”
- “Quality Control Responsibilities”
- “Responsibilities of the Production Department”

Job description of the Assistant General Manager, QA was reviewed and found to be acceptable.

As per “QC Responsibilities” sampling and handling of the material for in-process testing was the responsibility of QC personnel. In practice, this statement applied only for the in process sampling of blended and validation batches, at all other times production chemists performed the in-process sampling as outlined in SOP “Sampling Procedures”.

### Personnel hygiene

Good sanitation habits were observed on site. Direct contact with intermediates or APIs was avoided. Personnel was wearing clean clothing suitable for the manufacturing activity that they were performing.

### Training

The SOP “Training”, was checked. The following training modules were provided:

- Induction & orientation training
- On job training
- cGMP training
- Safety training
- Specific training
- External training

The training effectiveness was evaluated by pre-given selective multiple choice questions. The training records for a new operator employed in Block E were checked. Operator personal file contained personal responsibilities and training records.

The SOP “Analyst qualification” was checked. According to the SOP after the completion of a 4 weeks training program, the analyst shall undergo qualification process for all tests/techniques relevant to his/her working area. The analyst’s re-qualification criteria was specified. A new analyst had to perform duplicate tests on a previously approved batch; the acceptance criterion was based on allowed variations from the original test results within specifications.

An analyst qualification for high performance liquid chromatograph (HPLC) were checked. After the qualification analyst was certified to perform HPLC tests (assay and related substances).

### Consultants

The site did not use services offered by consultants.

## **3.3 BUILDINGS AND FACILITIES**

### Design and construction

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Buildings and facilities had adequate space for the orderly placement of equipment and materials. The flow of materials and personnel through the buildings and facilities were designed to prevent mix-ups or contamination. Laboratory areas and operations were separated from production areas.

### Utilities

Utilities were qualified and monitored. Adequate ventilation, air filtration and exhaust systems (HVAC) were provided. HVAC systems were designed to minimize the risks of contamination and cross-contamination. The permanently installed pipework and the direction of flow were identified.

Air Handling Units (AHU) consisted of the following filter cascade:

- 20  $\mu$  - G3
- 10  $\mu$  - G4
- 5  $\mu$  - F5

- 2  $\mu$  - F8
- H13 - HEPA

The HEPA filters were installed in the plenum. Pressure differentials were monitored between filters; 10 % fresh air was provided for re-circulation.

“Clean air ventilation system periodic validation report for E block” was checked. The re-qualification was carried out on October 2015 according to the ISO 14644 standard.

#### Water

Purified water (PW) action and alert limits were in place. The SOP “Purified water” was checked. Water sample from the return loop was collected daily and chemical tests were performed. From other user points, samples were collected weekly (for chemical and microbiological tests) on rotational basis, so that all user points were covered in one month. Samples from distribution loop and return loop were collected weekly for chemical and microbiological tests.

PW annual product quality review was spot checked. All results were well within alert limits.

#### Containment

Highly sensitizing or highly potent materials were not manufactured on site.

#### Lighting

Adequate lighting was provided to facilitate cleaning, maintenance and proper operations.

#### Sewage and refuse

Not inspected.

#### Sanitation and maintenance

Buildings used in the manufacture of intermediates and APIs were properly maintained and repaired and kept in a clean condition.

### **3.4 PROCESS EQUIPMENT**

#### Design and construction

Equipment used in the manufacture of intermediates and APIs was of an appropriate design and adequately sized, and suitably located for its intended use. Major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified. Mainly closed systems were used in production. Stainless steel or glass-line reactors were used for production of moxifloxacin Hydrochloride (Monohydrate) API as appropriate to the process stage.

#### Equipment maintenance and cleaning

Schedules and procedures were established for the preventive maintenance of equipment. The SOP “Preventive maintenance procedure (PM)” was spot checked – this was general SOP. PM SOPs were available for all equipment. As example the SOP “Preventive maintenance for reactor” was checked. PM was done according to the check lists. PM schedules and check

lists were cross checked for the certain reactors. Cross checks showed that PM schedules were followed. Clean rooms equipment PM was carried out once in three months, other equipment PM was carried out twice per year.

Equipment and utensils cleaning after campaign production was recorded in the relevant batch cleaning records (BCR). Batch to batch cleaning was recorded in the batch production records (BPR).

#### Qualification

The SOP “Equipment qualification” was checked. The SOP was applicable to the major production equipment and analytical instruments. According to the SOP production equipment re-qualification should be carried out every 5 years.

The qualification report and “Tray Dryer Operating Procedure” SOP for intermediate tray dryer was spot checked. The temperature mapping of the tray dryer was conducted on 01.10.2011, using 48 probes placed on alternate trays throughout the oven. Evidence for the certification of the probes was available for review.

#### Calibration

Control, weighing, measuring, monitoring and test equipment that was critical were calibrated according to written procedures and an established schedule. Records of calibrations were maintained. The current calibration status of critical equipment was known and verifiable.

The SOP “Schedule of instruments calibration / performance check” and calibration schedule was spot checked. This SOP was applicable for QC instruments. QC department master calibration schedule for 2015 was cross checked with calibration records. Cross checks showed that calibration schedule was followed.

#### Computerized systems

The laboratory computerized systems had sufficient controls to prevent unauthorized access or changes to data. The records were available of any data change made, the previous entry, the person who made the change and when the change was made. Back-up system was provided.

Computerized systems were not used in the warehouse and production.

### **3.5 DOCUMENTATION AND RECORDS**

#### Documentation system and specifications

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw material, intermediates, packaging materials and finished API. Acceptance criteria were established and documented for in-process controls.

#### Master production instructions

Master production instructions had been established and appropriately approved.



#### Batch production records and packaging records ( BPR)

BMR/BPR were prepared for each intermediate and API. Issuance of the BPR was controlled by QA. BPR were numbered with a unique batch number, dated and signed.

#### Laboratory control records

Standard tests methods and analytical reports were available. Moxifloxacin Hydrochloride (Monohydrate) API batch No. XXXX analytical print out data (HPLC – assay and impurities) was cross-checked with electronic data. Cross check showed identical data.

#### Out of specification (OOS)

SOP “Investigation of out of specification results” described phase I and phase II investigations of the out of specification results along with a flow chart. The registers for 2014 and 2015 were reviewed.

#### Out of trends (OOT)

The SOP “Laboratory investigation of out of trend results” was checked. The SOP was applicable to OOT results for related substances, residual solvents and chiral impurities from APIs release and stability testing.

### **3.6 MATERIALS MANAGEMENT**

#### General controls

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available. In the warehouse, materials were managed according to first in first out (FIFO) principle and using a manual bin card system.

The SOP “Supplier Qualification” was reviewed. According to the SOP manufacturers of the key starting materials (KSM) and primary packaging materials should be audited every three years. Evaluation of approved manufactures was performed yearly and contained information of number of batches received, approved and rejected. Supplier’s audits were carried out by the QA and QC managers / deputies.

The KSM XXXX supplier audit was carried out on 16 September 2015 by the deputy manager QA. Audit report was checked and found to be very detailed.

The KSM XXXX audit was carried out on 2 June 2015 by the deputy manager QA.

There was no computerized record keeping in the warehouse; the usage of all materials was recorded manually on bin cards. The general material storage was orderly on racks identified alphabetically: A-F. The storage of a critical starting material XXXX was verified. Material retest date was monitored by a double control system such as bin cards and logbooks.

Raw materials that required cold room storage (2-8 °C) were kept in cold walk in chamber. The temperature monitoring logbook of the cold room indicated that verification was performed once per shift (during a 3 shift operation). When cold storage materials had to be

dispensed, they were transported to the warehouse using bin cards for record keeping. These bin cards were retained in the warehouse.

#### Solvents

Three organic solvents were used for the production of moxifloxacin Hydrochloride (Monohydrate) API:

- Methanol (Met OH)
- Isopropyl alcohol (IPA)
- Acetonitrile

Met OH was stored in underground tank; IPA was stored in the above ground tank and acetonitrile in dedicated drums. Solvents were delivered in the dedicated tankers, tankers cleaning certificates were provided. Check list was used to receive solvent deliveries. Samples of delivered solvents were taken from the tankers. After QC release, solvents were mixed with existing stock, analysed and a new batch number was assigned.

Acetonitrile in drums was stored in dedicated liquids warehouse. Sampling and dispensing was carried out in a liquids sampling/dispensing room equipped with an exhaust system.

#### Receipt and quarantine

Materials were held under quarantine until they were sampled, tested and released for use.

#### Sampling and testing of incoming production materials

Containers from which samples were withdrawn were marked to indicate that a sample has been taken. Sampling and dispensing of KSMs was carried out in the warehouse in separate rooms, protected from environment. Primary packaging materials sampling SOP “Sampling handling” was reviewed. Sampling of primary packing materials was carried out in the sampling room, protected from environment.

Samples from the solvents in drums and KSMs were taken from all containers, then composite sample was made and full analysis was carried out. Before the vendors of the KSMs were approved, three batches were 100 % sampled and identity tests were performed on each container, full analysis was performed on composite sample. Every year the first batch of the KSM was 100 % sampled and identity tests were performed on each container.

#### Storage

Finished products storage temperature was specified 20 – 25 °C and temperature mapping studies were carried out accordingly in December 2012..

### **3.7 PRODUCTION AND IN-PROCESS CONTROLS**

#### Production operations

Production of moxifloxacin Hydrochloride (Monohydrate) API used for manufacture of solid dosage forms was carried out in two steps.

#### Block X

The manufacturing process for moxifloxacin HCl was conducted in Block X. In this block there were XX reactors.

The in-process (IP) samples taken were transported to the QC laboratory for thin layer chromatography (TLC) testing to confirm the progress of the reaction at this stage of processing.

The centrifuge bags were changed after 10 batches (during campaign production) or between product change-over. For washing of centrifuge bags a compatible solvent was used and visual verification was performed before use and after washing. Batch Cleaning Record (BCR) was available when product change-over was applicable.

#### Block XX

The intermediate was placed in plastic drums in Block XX using one layer of polyethylene bag. The drums were transferred via pass box into the transportation trolley and taken to Block D for drying.

Logbook record for the drying of moxifloxacin HCl intermediate on XXXX was verified. Duration of initial cleaning, drying and post cleaning were recorded.

#### Block XXX

The following production operations were carried out in the block XXX:

- Storage of intermediates
- Sampling and dispensing of intermediates.

Intermediates were stored at ambient temperature; temperature was monitored daily. The intermediates were delivered to the sampling & dispensing rooms via pass box. Sampling & dispensing was carried out in a room protected from environment.

Intermediates what required storage at 2-8 °C were stored in block D.

#### Block XXXX

After drying finished products were transferred to block XXXX. In block F finished products were sampled and stored under quarantine until final release. After final release, finished products were repacked. Sampling of finished products was carried out in “clean room (ISO 8)”. Samples were taken by QC personnel in the presence of QA personnel. Dispensing was done in “clean room (ISO 8)”. Labelling operations were also carried out in the dispensing room. Labelling operations were performed by the QA personnel.

Micronization operations were also carried out in block XXXX in a separate “clean room (ISO 8)”. In the block XXXX three individual AHUs were provided for the “clean rooms” (sampling, dispensing and micronization).

#### In-process sampling and controls

In-process sampling was done by production chemist; controls were carried-out in the Quality control laboratory.

#### Blending batches of intermediates or APIs

The SOP “Blending process validation” was checked. The expiry or retest date of the blended batch was based on the manufacturing date of the oldest tailings or batch in the blend. According to the SOP blending validation should be carried out and one batch should be placed for on-going stability. Blending should be carried out according to the BPR.

#### Contamination control

The environmental monitoring (EM) in clean rooms was carried out every 3 months.

#### Deviations

According to the SOP “Handling of Incidents” departures from written procedures were classified as major or minor events. Only major incidents were qualified as Deviations.

Laboratory and production incidents were kept in a common record controlled by QA. Major incidents (deviations) were investigated by an investigation team; upon completion each member of the team approved the Deviation Report Form.

#### Corrective Actions and Preventive Actions (CAPA)

The SOP “Handling of Corrective and Preventive action for Non-conformities” and CAPA registers were reviewed.

CAPAs originating from major incidents (deviations) were reviewed in the General Annual Review and minor incidents were trended quarterly.

General Annual Review Report XXXX was prepared by QA and signed off by all relevant departments.

CAPA procedure included methodology for corrective actions in the event microbiological test for water and environmental analysis failed.

### **3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

#### General

There were written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.

#### Packaging materials

Primary packaging materials were stored in the warehouse in specific storage location.

#### Label issuance and control

Finished product labels were partly pre-printed labels. Information to the labels was printed by the QA staff. Printer was located in the QA department. Computer connected to the label printer was password protected.

The SOP “Receipt, issue, control and reconciliation of labels & seals” was checked. Labels receipt, issue, control and reconciliation was the responsibility of the QA department.

The SOP “Preparation of product labels and QA release of labels” was checked. Photocopies of all labels (product labels and QA release) were attached to the BPRs.

Packaging and labeling operations

Not performed during the inspection.

### **3.9 STORAGE AND DISTRIBUTION**

Warehousing procedures

Facilities were provided for the storage of all materials. Released, rejected and returned materials were stored separately. Quarantine areas were identified.

Distribution procedures

APIs were released for sale after QA approval. The SOP “QA release” was checked.

### **3.10 LABORATORY CONTROLS**

General controls

APIs were released for distribution to third parties after they have been released by the head of the QA. The SOP “Handling of batch production records (BPR) and analytical raw data” was checked. According to the SOP the production shift in charge should review BPR / BCR and area cleaning records (ACR) and fill the relevant sections of the batch production check list. According to the SOP analytical raw data should be cross verified by the QC shift supervisor; the QA shall verify BPR/BCR/ACR and analytical raw data according to the check list.

HPLCs and gas chromatographs were connected to the Empower 3 software. Back-ups were made on-line daily and weekly. HPLC columns usage was recorded.

At the request of the inspectors the audit trail for project XXXX was unlocked and viewed.

The SOP “Software administration activities and audit trail activation” software access privileges was reviewed.

Infrared spectrophotometers and ultra violet spectrophotometers were stand-alone instruments, audit trails were activated and back-ups were made every 4 hours on-line and every 15 days on CDs.

In Chemical laboratory only class A volumetric glassware was used.

Reagents prepared in the laboratory were properly labelled. In case solvents / dry chemicals did not have expiry date the following expiry dates were set up by the QCL:

- Solvents - 1 year from the date of receipt
- Dry reagents – 3 years from the date of receipt

#### Testing of intermediates and APIs

Intermediate and APIs, were tested to determine conformance to specifications in the QC laboratory.

#### Validation of analytical procedures

Equivalence report for related substances HPLC method between in-house test method and Ph Eur 6.2 HPLC for related substance “Adaptation for Routine Monitoring Report”: XXXX was available and complemented by the Certificate of suitability.

Moxifloxacin HCl Assay by HPLC as per United States Pharmacopeia (USP) validation report XXXX has been demonstrated to be equivalent to In-house method based on the report XXXX. Two matching impurities have been verified for equivalency during the inspection. Structural elucidations and structural equivalence were also demonstrated for the two impurities. The equivalency was using the results obtained from 6 batches. Both methods indicated that the level of impurities were within specification.

#### Certificates of analysis (CoA)

The SOP “Reporting and issuing of analytical test report & CoA” was checked. CoAs were signed by the person who compiled the CoA, the person who checked the CoA and the head of QC or designee.

The SOP “Batch numbering system” was checked.

#### Stability monitoring of APIs

The SOP “Stability study on commercial products” was checked. Samples were stored under the following conditions:

- 40 °C ± 2°C, 75% ± 5%
- 25 °C ± 2°C, 60% ± 5%
- 30 °C ± 2°C, 65% ± 5%
- 30 °C ± 2°C, 75% ± 5%

Window periods between withdrawal of samples and analysis were specified. One batch per year was placed on long term stability monitoring programme.

Long term stability data was checked for moxifloxacin Hydrochloride (Monohydrate) API batch No:

- XXXX
- YYYY
- ZZZZ

10 stability chambers were provided for stability studies, 2 chambers were “stand-by”. temperature (T) and relative humidity (RH) in the chambers were recorded on-line using ICDAS software and print outs were taken and checked daily. Chambers were provided with sound alarm.

### Reserve/retention samples

The SOP “Storage of reserved samples” was checked. Reserve samples should be packed in market simulated conditions for two complete analyses. According to the SOP APIs reserve samples should be retained for 7 years. The longest expiry date for APIs was established 5 years.

Retention samples were collected by QC chemists in the presence of QA. The quantity sampled was determined based on test requirements. The storage of a reserve sample XXXX was verified during the inspection.

### Reference standards

If available pharmacopoeia reference standards were used for impurities tests, if not, in-house working standards were used. Working standards (WS) were used for assay tests and were qualified against Pharmacopoeia reference standards, if available. Reference standards were stored in desiccator and refrigerators.

### Microbiological laboratory (MBL)

Microbiological tests were carried out at MSN Laboratories Private Limited. Sy.No.317 & 323, Rudram (village), Patancheru (Mandal), Medak District, Telangana, Pin Code – 502 329, India.

Entrance to the MBL was via change room and air lock. Separate rooms (ISO 7) were provided for the following operations:

- Plate preparation
- Microbial limit test
- Endotoxin test
- Culture preparations.

Operations in the above listed rooms were carried out in laminar air flow cabinets (LAF). The laboratory performed PW and environmental monitoring (EM) tests as well as microbial limit test and endotoxin test. Endotoxin test was performed only upon specific customer requests. Two autoclaves were in use – one for the media sterilisation and one for waste decontamination of waste material.

PW samples and samples for EM monitoring (passive, active and surface ) were collected by the microbiologist. PW microbial test was carried out using pour plate method. Settle plates were incubated at 20 – 25°C for 3 days followed by at 30 – 35 °C for 2 days[Total incubation period 5 Days]. Settle plates for EM were exposed for 4 hours, exposure time was validated. For active air sampling 1000 L of air was taken.

R2A media was used for PW analysis and soy casein digest media for EM tests. Growth promotion test was carried out for all batches of dehydrated media and sterilised media. Media was sterilised for 15 minutes at 121 °C. Sterilisation autoclave validation was carried out every 12 months.

### 3.11 VALIDATION

#### Validation policy

Current Validation Master Plan was verified. The master plan was revised once in 3 years. The VMP outlined the validation strategy and documentation according to latest requirements. The continued process verification criteria was also defined.

The cleaning validation strategy included: maximum allowed carryover (MAC)-1 calculations based on TDD (therapeutic daily dose) and MAC-2 calculations based on non toxicological data (MACO calculations).

Cleanroom validation was also defined. The HEPA filter efficiency test was required to be performed once per year, air velocity test frequency once in 6 months. The permitted number of airborne particles, acceptance criteria was set as per ISO 14644.

Water system validation included the requirement to execute performance qualification (PQ) in three phases. The long term control phase required one year data collection to demonstrate consistency over all seasonal variations. Alert and action levels as well as sanitization requirements were established, frequency of testing and specifications were outlined. Validation of the utilities (such as compressed air) and computer validation strategy was also included in the VMP. Requalification of major manufacturing equipment was planned once in 5 years (tolerance 6 months). Software changes in the QC instruments also required revalidation.

The schedule for validation was prepared quarterly.

Master validation plan schedule for the time period Oct-Dec 2015 was reviewed. It included process and cleaning validations due to new product, scale-up, method validation and periodical validation activities.

#### Qualification

Qualification of critical equipment and utilities was carried out.

#### Approaches to process validation

The SOP “Validation of Micronization, Milling, Sifting and Compacting additional operations” was checked.

#### Cleaning validation

The SOP “Equipment Cleaning” contained a list of solvents used for equipment cleaning. Cleaning validation was based on MACO calculations taken in consideration factors such as equipment, solubility etc.

The limit for carry over in case of non-availability of therapeutic dosage and toxicological data was 10ppm.



### **3.12 CHANGE CONTROL (CC)**

A formal CC system was established. The SOP “Change Control” described an evaluation matrix to provide guidance regarding the initiation, classification and closure of change controls according to area of occurrence and nature of the change (minor/major).

Temporary change control had a separate SOP: “Procedure for Handling of Temporary Changes” and a separate log. Temporary change control XXXX was evaluated.

### **3.13 REJECTION AND RE-USE OF MATERIALS**

#### Reprocessing and reworking

The SOP “Reprocess and rework” was checked. According to the SOP the separate reprocessed / reworked BPR should be prepared by the production department, reviewed by the research and development (R &D) department and approved by the QA. Reprocessed batches of the APIs shall be kept for stability studies (accelerated and long term). According to the SOP reworked batch shall not be dispatched to the regulated market & customers to whom Drug Master File is submitted.

#### Recovery of materials and solvents

The SOP “Recovery of solvents and materials” was checked. Recovery of the solvents was done according to the recovery BPR. Recovered solvents could be used as such or mixed with the fresh solvents. According to the SOP recovered solvents should be stored in dedicated drums /tanks and should be used in the same stage of the same product. Furthermore, recovered solvents recovered from one stage shall not be used in another stage of the same product or in a different product.

#### Returns

Returned APIs were identified, quarantined and stored in a dedicated place in the warehouse.

### **3.14 COMPLAINTS AND RECALLS**

Market complaints were recorded and investigated according to the SOP “Handling of market complaints”. The SOP was checked. The responsible person for dealing with complaints was the head of QA; if the head of QA was not present QA assistant manager was responsible for the investigation. According to the SOP, the QA department should investigate the complaint to identify the route cause(s). Complaint investigation was carried out by an investigation team. If the root cause was identified, appropriate CAPAs were initiated. If required, the investigation team shall verify the analytical and process details of the batches produced before and after the occurrence that caused the complaint. Based on the conclusion of the investigation report, QA shall initiate the appropriated follow up action, including recall, if necessary. Effectiveness of CAPAs should be evaluated by the QA department.

Complaints registers for 2014 and 2015 were reviewed.

The SOP “Product recall procedure” was checked. Responsible person for dealing with recalls was the head of QA, if the person was not presented, the QA assistant manager was responsible for recalls. Recalls were classified as:

- Class I - recall within 24 hours

- Class II – recall within 2 working days
- Class III – recall within 2 working days

According to the SOP recalls could be:

- Voluntary recall
- Mandatory recall

Up to the date of inspection there had been no recalls. Recall effectiveness was evaluated by mock recalls. Mock recall was carried out every 5 years or whenever changes were made in the SOP or in regulatory updates. The last mock recall was performed on 5 October 2015 and covered moxifloxacin Hydrochloride (Monohydrate) API supplied to Macleods Pharmaceuticals.

### **3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

Manufacturing operations were not contracted out.

Microbiological tests were carried out at MSN Laboratories Private Limited. Sy.No.317 & 323, Rudraram (village), Patancheru (Mandal), Medak District, Telangana, Pin Code – 502 329, India. The Technical agreement (TA) with the above mentioned site was reviewed. The TA covered water analysis, environmental monitoring analysis and API sample analysis. According to the TA the contract laboratory should be audited every three years. The last audit was carried out in 2014.

## **PART 4: CONCLUSION**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, API Moxifloxacin Hydrochloride (Monohydrate) manufactured at MSN Pharmachem Private Limited, located at MSN Pharmachem Private Limited, Plot No 212/A, B, C, D, Phase II, IDA Pashamylaram, Pashamylaram (Village), Patancheru (Mandal), Medak District, Pin Code - 502 307, Telangana, India, 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.