SAROJINI NAIDU VANITA PHARMACY MAHA VIDYALAYA

Report on Industrial Visit to Mars Therapeutics Pvt. Ltd., Hyderabad for Monitoring the Audit of PuroxanTOP (Finished Product) of Eurodrug Laboratories Ltd., Hong Kong

AUDIT DATE: 12-03-2024

AUDIT OBJECTIVE: GMP Compliance Assessment Audit of Finished Dosage Form Manufacturing Facility

AUDIT SERVICE PROVIDER:

Pharm Sol Europe Limited
The Victoria Centre, Unit 2,
Lower Ground Floor, Valletta Road,
Mosta, MST 9012, Malta

AUDITORS:

Mr. K. Pavana Narasimhulu

Senior Manager – Compliance
APIC certified auditor
ECA Certified QA Manager and Auditor for APIs

Mrs. Mogga Saraswathi

Manager – Compliance
ASQ Certified Quality Auditor CQI & IRCA Certified Auditor

AUDIT CRITERIA:

- EudraLex Volume 4 - Part I - Medicinal Products for Human and Veterinary Use: Guidelines to Good Manufacturing Practice.
- US FDA 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals.
- PIC/S Guide to Good Manufacturing Practice for Medicinal Products, Part I, August 2023.
- PharmSol' s In-house Audit Agenda & Checklist.

Mars Therapeutics Pvt. Ltd., Hyderabad

Mars Therapeutics Private Limited is a Pharmaceutical Company established in Hyderabad, India in 1993. With three decades of experience in the manufacturing and marketing of pharmaceuticals, Mars is the strategic choice for qualitative and affordable medicines. Mars is primarily into oral finished dosages (Tablets, Capsules, and Liquids) and semi-finished dosages (DC Granules).

The industrial audit visit to Mars Therapeutics Private Limited, 4-4/1/2 D.Pochampally, Dundigal-Gandimaisamma Mandal, Medchal-Malkajgiri District, Hyderabad 500043, Telangana, India was organized by **Dr. B. Prabha Shankar,** Chairman, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya (SNVPMV) and CEO, Eurodrug Laboratories India on 12-03-2024. We (**Dr. S. Anuradha Bai, Professor, Department of Quality Assurance, SNVPMV and Dr. K. Sirisha, Professor, Department of Pharmaceutical Analysis, SNVPMV**) started to Mars therapeutics at 08:30 AM along with our Chairman **Dr. B. Prabha Shankar Sir** and reached the destination at 10.00 AM. The auditing team also reached Mars therapeutics on time.

The audit commenced with a briefing session by **Mr. P. Rajasekhar,** Managing Director of Mars Therapeutics Pvt.Ltd. and his team in the board room, providing an overview of the company's operations, quality management systems, and regulatory compliance.

The auditors **Mr. K. Pavana Narasimhulu** and **Mrs. Mogga Saraswathi** conducted thorough inspections of various departments, including production, quality control, quality assurance, and safety protocols.

Detailed discussions were held with department heads and personnel to understand processes, procedures, and challenges.

Initially we were taken to the gowning room and provided with gowns, caps and masks following the instructions given in posters kept in that room. Soon after we started for Plant Tour at 10.30 am and visited the following areas:

- Warehouse - Raw materials, Intermediates, packing materials and Finished goods stores,
- Manufacturing Area
- Utilities
- Water treatment plant
- Quality Control
- Stability and control samples area

We moved along with **Mrs. Mogga Saraswathi** to QC Department and observed various analytical instruments like WATERS-HPLC, TOC, Atomic absorption spectrophotometer, furnace, stability testing chambers for long term, real time and intermediate analysis and also observed various sampling procedures.

The following documents were checked during the Audit:

I) PHARMACEUTICAL QUALITY SYSTEM

Quality Policy
Quality Objectives:
Change Controls Management System
- SOP for Change control management - Change controls log for the last 2 years - Change control record related to the reference product

Deviations/Incidents

- SOP for Handling Deviations - Deviation Log for the last 2 years - One deviation record related to the Reference Product - SOP for Handling Incidents - Incidents log for the last two years - One incident record of the Reference product

CAPA

- SOP for CAPA Monitoring - CAPA Log for the last 2 years - One CAPA record related to the Reference Product - Verification of previous Audit CAPA

Quality Management Review

- SOP on Quality Management Review
- Recent Quality Management review records

Product Quality Review

- APQR SOP - Latest APQR report for the Reference Product

Quality Risk Management

- QRM SOP - QRM document for the Reference Product - Cross-contamination risk assessment study report - Risk assessment and control of DNA reactive (mutagenic) impurities - Risk assessment and control of Nitrosamine impurities - Risk assessment and control of Elemental impurities

II) PERSONNEL

Organogram

- Organogram SOP
- Site Organogram including Senior Management

Key Personnel

- Total Employees in the facility, (QA, QC, Production and Others)
- List of Key Personnel
- Job responsibility SOP
- Job responsibility documents of the QA Head, QC Head, Production Head and their deputies.

Training

- Employee Training SOP
- cGMP Training schedule for the current year
- Employee Training records

Personnel Hygiene

- SOP for Health and Hygiene of the Personnel working in the Facility.
- Gowning procedure for Production area, Sampling/Dispensing areas, Microbiology Lab, etc.
- SOP on Medical check-ups and the related records
- Contract agreement with the external medical consultant, if applicable

Consultants

- Records of Consultants employed at the site
- Agreements with the consultants

III) PREMISES AND EQUIPMENT

General

- Plant layout - Layouts for the Manufacturing area, Warehouses and QC laboratory - Man and Material Movement Layouts - SOP for Entry & Exit into critical and non-critical areas in the facility - Gowning procedures - Buildings and facilities preventive maintenance SOP - Buildings and facilities preventive maintenance schedule for the current year

Pest control

- Pest and rodent control SOP - Pest control activity layout - Pest control services and a valid agreement with the contracting agency, if any. - Records of the recent pest control activity

Utilities

- List of Utilities available in the facility

HVAC System

- HVAC Operation and Maintenance SOP - HVAC Qualification SOP - HVAC Layout – cater to Mfg. area of the reference product - Reference product-related HVAC System recent qualification documents - Annual Review Report of the HVAC System

Water system

- SOP for Operation of Purified water generation and distribution systems. - Phase-wise qualification documents of the purified water system. - Purified water specification - Annual review report/Quality trends of the Purified Water system

Production area

- Area cleaning and disinfection SOP & records - Environmental Monitoring SOP & records - Area Logbook - SOP for Preventive measures to avoid contamination and cross-contamination

Storage Areas

- SOP for Storage of raw materials (API & Excipients), packaging materials, finished products and other materials - Temperature mapping records for each storage area - SOP for Area Cleaning and Environmental monitoring of storage areas - SOP for handling and storage of returned, recalled and expired goods and related records.

Equipment

- Equipment Qualification/requalification procedure - Initial and recent Qualification documents of the critical equipment (in the core manufacturing area) used for the manufacture of the reference product - Equipment Preventive Maintenance SOP - Equipment Preventive Maintenance Schedule for the current year - Equipment preventive maintenance checklist/record - Equipment cleaning and types of cleaning SOP - Equipment cleaning records

Calibration

- Instruments Calibration SOP (Individual Instruments / Equipment) - Calibration Schedule for the current year - Calibration record for weighing balances and temperature sensors or Hygrometers available in warehouse and production area

IV) DOCUMENTATION

Site Master File

- SOP for Preparation of SMF - Site SMF

Specification & Test Methods

- For Starting Materials (Raw Materials) - For Excipients - For Packaging Materials - For Finished Products

Batch Records

- SOP for Batch Record Issuance - SOP for Batch Numbering System - Batch record of the reference product (Batch No. will be informed during the audit.

Analytical Records

- Analytical record worksheet preparation & issuance - Analytical record of the reference product - COA of the reference product

Documentation system

- Document Control SOP - Good documentation practices SOP - Data Integrity SOP - Retention period of Documents

V) PRODUCTION

Dispensing

- SOP for Dispensing Raw materials- Dispensing area cleaning SOP & records- SOP for transfer of dispensed materials from warehouse to production area & related records

Validation Master Plan

- SOP for Preparation of Validation Master Plan- VMP document for the current year

Process Validation

- SOP on Process validation- Initial and Recent Process validation protocols & reports of the Reference products. (Silodosin Capsules)- Process flow diagram

Handling of Reprocess

- SOP for Reprocessing- Reprocessing log for the last 2 years- Reprocess batch record of the reference product

Vendor Qualification

- Vendor Qualification & Requalification SOP- Approved Vendor list for API, Excipients & Packing materials-Recent Vendor Qualification documents for API, excipients and primary packing material vendors of the reference product

Packaging Operations

- SOP for Line Clearance of Primary and Secondary packing operations- Challenge tests for Automated System sensors SOP & records- Printed packing material handling SOP & reconciliation records.Handling of online rejects SOP & records- Handling of the metallic and rubber stereos SOP & recordsContainer Closure System- Packing configuration of the Reference product- Packaging material specifications (Primary and secondary PM of the Reference product).

Container Closure System

- Packing configuration of the Reference product - Packaging material specifications (Primary and secondary PM of the Reference product)

Label Issuance and Control

- SOP for Label issuance and control- SOP for Labelling Finished Product- Label issuance and reconciliation record

Artwork

- SOP for Artwork Approval- Approved Artwork, Specimen and Shade card related to the reference product.

Batch Release Procedure

- SOP for Batch release- Batch Release checklist- Authorized personnel list for Batch release

Handling of Returned and Rejected Goods

- SOP for Handling Rejected Finished Goods- Rejections log for the last 2 years.- SOP for Handling Returned Finished Goods- Returns log for the last 2 years- Return records related to the reference product.

Cleaning Validation

- SOP for Cleaning Validation- Cleaning validation protocol and report for the reference product-Analytical method validation report for the test method used for analyzing the cleaning samples-Clean equipment hold time and Dirty equipment hold time study reports.

Computerized systems

- List of computerized systems/software used in the facility - SOP for Computer System Validation-Performance Qualification documents for Computerized systems used in the QC

laboratory-SOP for Electronic data backup, restoration, and verification of restored data- Backup data restoration and verification records- SOP for Electronic Signatures

VI) QUALITY CONTROL

Quality control

- List of Instruments in QC Laboratory - Calibration Schedule for QC Instruments - Calibration record for Analytical balance, HPLC and GC systems.

Sampling Procedures

- SOP for Sampling of Raw Materials, Excipients and Packaging Materials - SOP for Sampling of the finished product

Volumetric Preparations

- SOP for Volumetric Solution Preparation and standardization - SOP for Reagents Preparation - Volumetric Glassware Cleaning & Calibration SOP

Reference standards & Working Standard

- SOP for Reference standards and working standards management - COAs of Working standards and Reference standards of the Reference product

Analytical method validations

- FP Specification and standard test procedure of audit scope product. - SOP for Analytical Method Validation/Verification/Transfer - Analytical method validation/verification/transfer documents (protocol & report) for the test methods of the reference products (Silodosin Capsules) - Analytical methods used for assessment of DNA reactive (mutagenic) impurities and Nitrosamine impurities.

Stability

- SOP for Stability Study - Stability indicating test methods and specification of the audit scope product. - Stability Protocol of the Reference product - Stability data (Accelerated & Long-term conditions) supporting the shelf-life of the reference products (Silodosin Capsules) - Recent process validation batches stability study data - Annual add-on batch stability study data-Hold-time study data for intermediates of the Reference product - Calibration/Preventive maintenance of stability chambers - SOP for Assigning manufacturing date, expiry

OOS and OOT

- OOS SOP and OOS log for the last two years - OOT SOP and OOT log for the last two years - One OOS record and one OOT record related to the reference product.

Control samples/Retention samples

- SOP for Retention samples management - Retention sample register - Temperature monitoring record of Retention sample room - Visual Inspection SOP & records - Handling of inspection rejects SOP Training record and Qualification program for Visual Inspectors

Audit Trails

- Audit Trail SOP - Audit Trail Checklist

Microbiology Laboratory

- Entry/exit procedure - Area cleaning and sanitization procedure - Media preparation & discarding procedure. - Media consumption records - Microbial test procedures and records related to the reference product.

VII) OUTSOURCED ACTIVITIES

Handling of Outsourced Activities

- SOP for Qualification of Contract Manufacturers and Contract Laboratories- Qualification Documents of Contract manufacturers/Laboratories- Contract Agreement with the contract manufacturer/ laboratory

VIII) COMPLAINTS, QUALITY DEFECTS AND PRODUCT RECALLS

Customer Complaints

- SOP for Handling Customer Complaints- Complaint Log for the last 2 years- Complaint record related to the reference product.

Recalls

-SOP for Handling Recalls- Recall Log for the last 2 years- Recent mock recall protocol and report

IX) SELF-INSPECTIONS (INTERNAL AUDITS)

Internal Audits (Self Inspection)

- Internal Audits SOP - Internal Audit Calendar for the current year - Last performed internal audit-related documents

Auditors checked all the documents and finally gave their report. At the Wrap-up session they appreciated the management team of Mars Therapeutics Pvt. Ltd. for maintaining high standards of production quality, safety, and environmental responsibility. They gave some suggestions for maintenance viz., API Vendors sources data correction, unavailability of Punch & dyes establishment data, avoidance of torn and unauthorized papers kept in facility and BMR, lack of yields and critical processing parameters in PV report, mentioning of tolerance in building maintanance, partitioning of packing lines, absence of pictoral entry display in QC, Variation in preventive and calibration SOP’s, qualification for working standards and reference standards kept in the same refridgerator, correction of time in hydrometers, establishment of OOT limits as per SOP’s and address them in APQR, analysis of nitrosamine and elemental genotoxic impurities, maintananace of SOPs for computer system validation, lack of Empower software validation etc.

Overall, the audit visit to Mars Therapeutics Pvt. Ltd. provided valuable insights into the company's operational processes, quality standards, and regulatory compliance. We were glad to see the facility and observed few latest equipment's which are useful for R&D. We thank our Management, Director, Principal and Vice-Principal for their unwavering support and

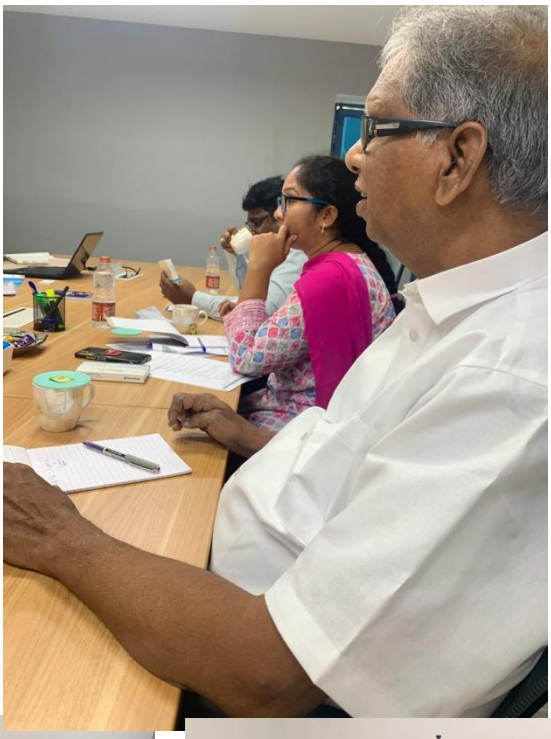
encouragement in facilitating our participation in the industrial audit visit to Mars Therapeutics Pvt. Ltd.

We extend our heartfelt gratitude to our esteemed Chairman, Dr. B. Prabha Shankar, for affording us the invaluable opportunity for the industrial audit visit to Mars Therapeutics Pvt. Ltd. Furthermore, we wish to express our appreciation for Dr. B. Prabha Shankar's hospitality, care, encouragement, guidance and mentorship throughout our visit. We are truly grateful for his guidance and support, which have enriched our experience and contributed to the success of this audit visit.

Dr. S. Anuradha Bai, Professor, Department of Pharmaceutical Quality Assurance

Dr. K. Sirisha, Professor, Department of Pharmaceutical Analysis


Facility




HSMG
RDI-021
Gansons


IMPRESSION MACHINE
PDE-021


RODENT BAIT STATION
Pestochem
9811318505


PDE-114
COMPRESSION MACHINE
CM64
METAL DETE
PDE-11
cadmach


FLUID BED DRYER
RDI-002


AXIS


Пуроксан®-Топ
Доксофиллин 650 мг Таблетки MR
20 таблеток
PUROXAN®-TOP
Doxofylline
650 mg MR Tablets
eurodrug


Long Term
25° ± 2° C/ 60% ± 5% RH