TMDA/DMC/MCIE/F/001

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

MACLEODS PHARMACEUTICALS LIMITED, INDIA
PUBLIC GMP INSPECTION REPORT

09th December, 2020

Part 1: General information about the company

Manufacturers details	
Name of manufacturer	Macleods Pharmaceuticals Limited
Corporate address of manufacturer	Atlanta Arcade, Church Road, Near Leela Hotel, Andheri-Kurla Road, Andheri (East),Mumbai-400059, India Tel: 91-22-66762800 Email: Yashk@macleodspharma.com Website: www.macleodspharma.com
Inspected site	
Name & address of inspected manufacturing site	Macleods Pharmaceuticals Limited, Phase I, II & III Plot No. 25-27, Survey 366, Premier Industrial Estate, Kachigam, Daman-396 210 (U.T), India
Plot number	Phase I, II & III Plot No. 25-27, Survey 366, Premier Industrial Estate, Kachigam, Daman
Inspection details	
Date of inspection	18th – 19th February, 2020
Type of inspection	Renewal inspection
Introduction	
General information about the company and site	Macleods Pharmaceuticals Limited (Phase I, II, III) is located about 200Km North of Mumbai on Mumbai – Ahmedabad highway. The facility had three phases namely I, II and III each in a different building. Phase I manufactures Non-beta lactam Dry Powder injectable, phase II manufactures Rifampicin and non-Rifampicin medicines and phase III manufactures Large (bulk) size non-beta lactam tablets and capsules.
History	The facility was inspected and licensed by the Local National Regulatory Authority. The site was inspected and approved by other NMRA such as USFDA in 2019, MHRA

	(UK) 2019, MCAZ - Zimbabwe 2014, TGA-Australia and Germany 2017, and WHO Geneva 2019. It was lastly inspected by TMDA on 12th – 13th June, 2016 and complied with the requirements of EAC GMP Compendium, 2014.
Brief report of the activities undertaken	
Areas inspected	Areas inspected include external surroundings, utilities, warehouses manufacturing areas and quality control laboratory. In particular, the following areas were inspected: • Qualification and validation processes • Complaints handling • Vendors evaluation • Contracts • Premises layout and hygiene • Personnel • Equipment • Production • Quality control • Documentation • Utilities
Restrictions	The GMP inspection was restricted to Phase I, II & III for the lines which manufactured registered products.
Out of scope	Lines whose products are neither applied for registration nor registered in the country
Production lines inspected by TMDA	Phase I - General pharmaceutical products in form of Dry Powder injectable; Phase II - Rifampicin and non-Rifampicin medicines and Phase III - Large bulk size - General pharmaceutical products in form of tablets and capsules
Abbreviations	**Meaning**

AHU	Air Handling Unit
BSR	Bounded Store Room
DI	De ionization
cGMP	Current Good Manufacturing Practices
EAC	East African Community
FG	Finished Goods
HEPA	High Efficiency Particulate Air
HVAC	Heating, ventilation and air conditioning
LAF	Laminar Air Flow
NMT	Not more than
OOS	Out of Specifications
PM	Packaging Materials
PW	Purified Water
QC	Quality Control
RO	Reverse Osmosis
SMF	Site Master File
SOP's	Standard Operating Procedures
SSF	Small Scale Facility
TMDA	Tanzania Medicines and Medical Devices Authority
UK MHRA	United Kingdom Medicines and Health Care Regulatory Agency
USFDA	United States Food and Drug Administration
UV	Ultraviolet
WFI	Water for Injection

Part 2: Brief summary of the findings and comments

The surroundings of the facility including the utilities were inspected followed by tracing the logical flow of production from incoming raw materials to the finished goods warehouses. During the inspection various relevant working documents were evaluated and technical staffs interviewed on various aspects of GMP relevant to their areas of work.

1. Personnel

The manufacturer had sufficient number of technical staff with necessary qualifications and experience to carry out the tasks assigned. Job descriptions were provided to staff including key personnel to define individual responsibilities in-line with the recruitment profile

Personnel met were aware of the principles of GMP which proved that they received basic principles of GMP training and on job training relevant to their needs. The SOP and schedule for GMP training and selected records for some technical staff were reviewed and found to meet the requirements.

Production and Quality Control (QC) posts were filled by full time personnel and each was independent from each other as evidenced in the organization chart.

The procedure for medical checkup was in place. Pre-employment health check was done for new employee and all other personnel were checked biannually.

Adequate measures were taken for personnel hygiene. Personnel were observed properly dressed with neat and clean gowns, gloves and masks.

2. Premises

i. Layout and Design

The facility was provided with all necessary areas/sections as per Good Manufacturing Practices (GMP) guidelines. The layout allowed for a unidirectional flow of materials and personnel and the areas had adequate working space for orderly and logical placement of equipment and materials to avoid mix-ups and cross contamination.

The facility had eight (8) buildings of which building 1 & building 2 contained the Phase – I and Phase - II manufacturing areas. Warehouse for Packaging Materials (PM), Finished Goods (FG) and QC testing laboratory were in Phase II building. Building 3 consists of the offices' document storage, canteen area, utility area, service area and tertiary PM stores. Building 4, 5 and 6 contained Phase III manufacturing area, receipt, quarantine, sampling and approved area for raw material as well as finished goods store, stability testing area. Building 7 consisted of packaging area, BSR area, control sample area and document storage area. Building 8 consisted of QA area, training hall and QC area.

The facility was accommodated in ferro-concrete buildings with reinforced concrete floors. Walls and ceilings in all processing areas were painted with epoxy paint while that in change rooms and packing material stores are painted with enamel paint. The floor areas were covered with concrete except packing material stores was tiled with natural Indian stone (Kota). Sharp comers were avoided by giving epoxy covings at the junction of ceiling-wall, wall-wall, and wall-floor for easy cleaning and to avoid accumulation of dust and dirt.

Generally, the premises were suitably located, designed, constructed and maintained to suit the operations which were carried out.

ii. Sanitation and Hygiene

High levels of sanitation and hygiene were generally observed in all areas, including the surroundings.

The changing rooms for males and females were provided and well equipped with cabinets for storage of street and factory gowns, stainless-steel shoe racks, step over benches and sanitizing solutions. The procedures for entry and exit in different production areas were also in place and supported with pictorial presentation as well as mirrors to ensure proper gowning.

The receiving bays had adequate infrastructures including air shower, clean lint free duster & vacuum cleaner for de-dusting of received items and cleaning procedures.

The production rooms and equipment were observed to be clean and SOPs for cleaning and relevant records were checked and found to be properly maintained. Disinfectants used were alternated and cleaning methods were routinely monitored by microbiological analysis. Sanitization of water treatment plant was also being conducted as per schedule.

3. Production

The raw materials warehouse located on the ground floor was well arranged and had segregated areas for quarantined and rejected materials. Temperature and relative humidity were monitored and records kept. There were three sampling booths; one (1) dedicated for rifampicin containing products and the remaining two (2) were for general products. The upper floor comprised of two cold chambers for special storage conditions.

i. Production Line I - General pharmaceuticals dry powder for injection

Manufacturing of dry powder injectable was being performed on the first floor of the Phase I building. Raw materials were received from Phase III building, then directed to Phase I raw materials store that had an area segregated for storage of sterile material only. Received packaging materials were channeled directly to the de-cartooning, vial loading area, vial washing, sterilization and de-pyrogenation. Filling and vial sealing were carried out under extended LAF i.e. grade A, then followed by online visual inspection prior to labeling and storage.

ii. Production Line II - Rifampicin containing products

Production of rifampicin containing products was done in a separate building (Phase II building). In the production area, dispensed raw materials were being received from 1st floor through a hoist. The building was supplied with interlocking doors to control man and materials movements to production areas. There were enough rooms for different production stages filled with various equipments depending on the need. In process quality check was being carried out as per the SOP. However, there was a room for tablets/capsules storage prior to packaging. Secondary packaging was done manually; however, blistering and labeling processes were automated.

iii. Production Line III antiretroviral and antibiotics (Small Scale Facility - SSF)

Production of antiretroviral and antibiotics was done in the second floor of the Phase II building. Dispensed raw materials were coming from the 1st floor. Packing process was semi automated.

iv. Production Line IV - Non Rifampicin Anti-tuberculosis products

Anti-tuberculosis (Non-rifampicin) production was carried out in the 1st floor of the Phase II building. Dispensed raw materials were coming from the same 1st floor where production was carried out. Generally, production area was well equipped.

In the packing section, there was a blister packing line and strip packing line. Packaging material and finished goods warehouses for Phase I and Phase II products were located on the ground floor of Phase II building and were effectively secured.

v. Production line V - Tablets and capsules large scale production

The production was done on the first and second floor of the Phase III manufacturing facility. Storage of approved raw materials and dispensing activities were carried out in the same floor. The materials were processed through a rapid mixer granulator, fluidized bed drier then blender. Compression was conducted on the first floor; three rooms were available for this process each containing a bi-layer compression machine with an inbuilt metal detector. Coating was carried out in two rooms within the same floor. The ground floor had two areas for blister packing, one for bulk packing and one for strip packing.

4. Quality Control

The laboratory had sufficient number of analysts, distributed into various functional sections of the laboratory, such as finished products testing, raw materials testing (with subsections for sampling, chemical and wet laboratory), stability testing, packaging materials, microbiology, analytical method validation, good laboratory and documentation sections. Entry in the QC laboratory was controlled and had a cross-over bench, secondary gowning with hand sanitization. The laboratory was equipped with modern analytical instruments for quantitative and qualitative testing of all raw materials, excipients, packaging materials and finished goods. The reference standards and working standards were well stored and easily retrieved. Tests were performed according to written procedures and recorded appropriately. Traceability of the records and instruments/equipment used for analysis was verified and proved that, the records and instruments/equipment used for analysis can be retrieved.

Stability studies were part of the QC laboratory activities, and the facility had nine (9) stability chambers for studying manufactured products and formulation development batches. Control sample room was inspected and observed to be under access control

and monitored as per SOP for finished product control sample collection, storage and disposal

5. Equipment

The facility had sufficient and required number of production equipment and machines, which were designed, located, installed, qualified and maintained to suit the operations carried out. The design also facilitated effective cleaning and avoidance of recesses to prevent chances of contamination and cross contamination. Labels were affixed on the machines for both calibration and maintenance as well as for machine status.

6. Water Treatment System

The facility had independent water treatment plants for each manufacturing phase. The source of water was a bore well. Water was pumped and passed through a chlorine dosing followed by a quartz filter to produce soft water that was collected in underground storage tanks with the total capacity of 40,000 liters. The soft water covered the uses of the facility, but for manufacturing process, the soft water was processed through qualified and acceptable methods (Reverse Osmosis (RO) and De ionization (DI)) to Purified Water (PW), which was collected in SS316L overhead storage tanks.

Purified water was subjected to UV sanitization before passing to loop system where circulating water was maintained at ambient temperature. Purified water was passed through Multi Columns Distillation Plant (MCDP) to produce Water for Injection (WFI), which was collected in 5000L storage tank and maintained at 80^0 to 85^0C. The monitoring, sanitization and distribution process were as per validated SOPs.

7. Heating, Ventilation and Air Conditioning

Each building of the three phases was equipped with separate and dedicated Air Handling Unit (AHUs). In aseptic and other processing areas, air was supplied through terminal HEPA filters. Critical areas were designed to achieve temperature of NMT 25 ˚C and relative humidity of NMT 45% or as per product requirement. LAF units were installed in critical operating areas like vials washing, cooling zone, vials filling and sealing areas.

The system was monitored by utility department that enables detection of any out of specification (OOS) conditions mainly temperature, relative humidity and pressure differentials across AHU fillers. Preventive maintenance SOPs were in place, cleaning procedures were validated and the qualification documents for the HVAC system were available in support of the functionality and suitability of the system.

8. Document Review

The review of documents proved that the company had a good documentation infrastructure as the documents were well designed and prepared as per GMP requirements. The documents were approved, signed and dated by the appropriate responsible persons and distributed with care. Records were kept up to date and documents reviews were done in timely manner.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, **Macleods Pharmaceuticals Limited, Phase I, II & III, Plot No. 25-27, Survey 366, Premier Industrial Estate, Kachigam, Daman-396 210 (U.T), India** was considered to be operating at an acceptable level of compliance with EAC GMP Guidelines for the manufacturing of General pharmaceuticals dry powder for injection (Phase I), Rifampicin and non-Rifampicin medicines (Phase II) and Large bulk size General pharmaceuticals products in form of tablets and capsules (Phase III).

This TPIR will remain valid for three (3) years from the date of approval unless the site is no longer considered to be in compliance with current GMP requirements.

Part 4: References

1. EAC, (2014), *Compendium of Good Manufacturing Practice Guidelines Technical Documents for Harmonization of Medicines Regulations,* EAC Secretariat, Arusha, Tanzania

2. TMDA *Good Manufacturing Practices Regulations, Manual and SOPs*, Tanzania Medicines and Medical Devices Authority, Dar es Salaam, Tanzania.

3. Tanzania Medicines and Medical Devices Act, Cap 219.