WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

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(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Macleods Pharmaceuticals Limited
Unit number	Plot No 25-26-27
Production Block	Phase II & Phase III
Physical address	Survey N° 366 Premier industrial estate, Kachigam Daman – 396 210 (UT), INDIA
Contact address	Mr Sushil Jaiswal Vice President, CQA, RA and Analytical Development Phone: +91 22 61132900, Ext 123 Fax: +91 22 28304641 Email: sushil@macleodspharma.com
Date of inspection	20, 21, 22 and 23 May 2014
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Non-sterile oral solid dosage forms (tablets, capsules and granules)
WHO product categories covered by the inspection	Tablets, Capsules and Granules
Summary of the activities performed by the manufacturer	Production and control of finished pharmaceutical products

Part 2: Summary

General information about the company and site

Macleods Pharmaceutical Limited (hereafter Macleods) was incorporated in 1986 and employed more than 10,000 employees. The corporate office is located at 3rd Floor, Atlanta Arcade, Marol Church Road, Andheri (E), Mumbai. Macleods has 5 finished pharmaceutical products (FPPs) manufacturing units (three in Daman, one in Himachal Pradesh and one in Palghar) and one active pharmaceutical ingredient (API) manufacturing unit in Sarigram, Gujarat.

Macleods Pharmaceutical Limited Kachigam, Daman was started in 2001. About 311 officer/staff were enlisted at the site inspected (Plot No 24-28, Premiere Industrial Estate, Kachigam, Daman, U.T.). In addition, the site employed operators and contract workers which total to more than 700 employees. The Daman site manufactures tablets (coated and uncoated), hard gelatine capsules, granules and dry powder injectable products.

As part of the last WHO GMP inspection held in June 2012, the company has upgraded their existing manufacturing facility by incorporating additional warehouse, non-Rifa manufacturing area, packaging line, purified water system and microbiology laboratory (referred as Phase III).

History of WHO and/or regulatory agency inspections

WHO Geneva has inspected the site in 2004, 2005, 2007, 2010, 2011 and 2012. In addition, the manufacturing site had been inspected by several regulatory authorities.

From the presentation, it was noted that following regulatory authorities have inspected Daman facility:

- USFDA – US (2008, 2011, 2013),
- WHO – Geneva (2004, 2005, 2007, 2010, 2011, 2012),
- MHRA – UK (2007, 2010, 2012),
- TGA-Australia,
- INVIMA– Colombia,
- MOH – Ukraine,
- PMPB – Malawi,
- MCAZ – Zimbabwe,
- TFDA – Tanzania,
- NDA – Uganda,
- MOH – UAE,
- PPB- Kenya,
- MCC - South Africa,
- ANVISA – Brazil

Focus of the inspection

The inspection focused on the production and control of WHO prequalified and currently under prequalification products manufactured at the new manufacturing facility (Phase III, non-Rifa). The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 20th May 2014

- Introductions
- Opening meeting
- Organization chart
- Job descriptions
- Procedure on batch release
- Training
- Preventive maintenance
- Product quality review
- Change control pertaining to new manufacturing facility including risk analysis
- Review of previous inspection CAPA confirmed construction of new manufacturing facility (Phase III), removal of one packaging line from small scale facility (SSF) and only one line will be used at one time, for non-Rifa, one complete primary/secondary line removed and converted to carton coding area
- Feedback on observation of day 1

Day 2, 21st May 2014

- Personnel
- Preventive maintenance
- Supplier qualification of selected materials
- Review of site layout
- Inspection of warehouse (Phase III)
- Feedback on observation of day 2

Day 3, 22nd May 2014

- Performance qualification document for AHU supplied to new warehouse (raw material store, first floor, Phase III)
- Temperature & humidity monitoring
- Review of manufacturing floor plan for Phase III
- Inspection of manufacturing area of Phase III covering day store, granulation I and II, wash area, clean bin storage area, granulation spares area, granules storage area, in-process quality control lab, compression area (I, II, III), coating area (I, II, III), spares, tablet storage area, cleaned IPC storage area, bottle cleaning & storage area, bottle packing

- Inspection of quality control laboratory covering sample receiving and logging management, inspection of GC and HPLC system and verification of audit trail setting, access rights, integration parameters,
- SOP on Good Chromatography Practice
- Inspection of microbiology laboratory covering sampling plan of purified water, testing procedure for performing microbial limit test (MLT), handling of cultures (strains), growth promotion test (GPT) for media, autoclave (bowie-dick test), handling of working standards and control samples for raw materials

Day 4, 23rd May 2014

- Review of incident report
- Review of purified water (PW) system (Phase III),
- Inspection of PW system (for Phase III) covered generation, distribution, sanitization and routine monitoring
- An inspection of air handling unit (Phase III)
- Compressed air system
- Secondary packaging area of Phase III
- Exit meeting with the site management

2.1 QUALITY ASSURANCE

A quality assurance system was in general terms in place. Quality Assurance (QA) and Quality Control (QC) departments were independent from production. The QA Head reported to the Corporate QA based in Mumbai. Production and control operations were specified in writing. The necessary controls on starting materials, in-process checks and finished products were in place.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The necessary documentation, equipment and facilities were available to perform the manufacturing activities for anti-TB, anti-retroviral and anti-malaria products.

Necessary resources were generally provided, including adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls. During the inspection it was noted that the areas were generally clean and tidy.
The new manufacturing facility (Phase III) was in general designed in accordance with the current GMP requirement.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.3 SANITATION AND HYGIENE

Specific SOPs were established to cover the hygiene program. Personnel entering the manufacturing area were required to put on the appropriate garments (such as suits, gloves, cap and face-mask) according to the gowning procedure. The facilities and equipment were found to be in a good state of cleanliness with cleaning records maintained.

2.4 QUALIFICATION AND VALIDATION

Validation master plan/VMP (Phase III) was available which provided company philosophy on validation activities covering equipment, facilities, utilities, processes, environment, cleaning, analytical, personnel, PLC / control system validation and SOPs. The company is using analytical instruments & equipment (HPLC, GC, FTIR, NIR, UV, Dissolution etc) which are operated using different software, and excel sheets for various calculations; this aspect was not included in VMP.

Process validation protocol and report for Isoniazid tab 300mg were reviewed. Cleaning validation protocol for Phase III was briefly reviewed and noted that protocol described objective, approach, scope, responsibility, execution and revalidation criteria, training etc. A product matrix for cleaning validation of Phase III was available which confirms three products (Isoniazid 300mg tablet, Pyridoxine 500mg tablet and Irbesartan 150/300mg tablets) were selected for cleaning validation based on solubility and maximum daily dose (MDD).

The performance qualification protocol and report for AHU No 1 supplying to granulation room number 1 was reviewed.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.5 COMPLAINTS

Handling of customer complaint was reviewed and noted that QA Head was responsible for handling complaints. A flow chart was available for complaint handling which requires logging of complaint by the site QA, investigated by site QA team and response to complainant.

2.6 PRODUCT RECALLS

Recalls were handled using the SOP for product recalls. It described different classes and types of recalls. Recalls were categorized into Class I, II and III and the types of recall into Type A, B and C. Class I recalls CQA was responsible for executing and coordinating recalls. Reconciliation reports are to be sent in 15 days to CQA. Recalls were to be completed within 30 business days. A mock recall to evaluate the effectiveness of the procedure had been performed in May 2012. The distribution records contained sufficient information of the distributors, product and quantities. A mock recall is to be conducted every 2 years ± 3 months.

2.7 CONTRACT PRODUCTION AND ANALYSIS

It was noted that WHO prequalified products were not contracted out for manufacturing. Some of the analytical tests were performed by the outside laboratories as described in the Site Master File (SMF).

2.8 SELF INSPECTION AND QUALITY AUDIT

Procedure for self-inspection was availed and verified. The site has identified list of self-inspection team members who were heads of departments and senior officers selected based on qualification, experience and technically competency.

Nevertheless, self- inspection plan was appropriately adhered, inspection checklists were properly filled and inspection reports were appropriately communicated to inspected departments before CAPA was implemented. Records for recently conducted self-inspection to QC, production (Rifa and Rifa facility) and raw materials warehouse were verified and it revealed that, no critical or major observations were identified.

Vendor qualification was handled in accordance with the SOP for vendor qualification. Vendor qualification audits were planned by CQA. The scope of the SOP covered active pharmaceutical ingredients, packaging materials and excipients.

2.9 PERSONNEL

There were about 311 officers (staff), 133 permanent operators and 398 contract workers were employed by the site. Among the permanent operators, 32 were under Engineering, 8 HR, 77 Production, 5 QA & QC and 11 Stores. All 398 contract workers worked in the secondary packaging. It was observed that, contract workers were trained at the time of joining and routinely on GMP basics, personnel Hygiene and Safety. Training involved verbal and pictorial presentation on cGMP module XXVI and SOPs Entry Exit Procedure, SOP Personnel Hygiene Procedure and SOP Cleaning House Keeping and Factory Sanitation Procedure.

2.10 TRAINING

Training was imparted to newly appointed staff during employment and to all staff yearly. SOP for training of personnel in factory, training programme and training records were verified. Annual training programme was prepared based on training need assessment of staff for individuals and groups of staff whose job responsibilities were similar. Details of training activity were kept in the training format which indicated list of participants attended the training, their designations, comments and signatures.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.11 PERSONAL HYGIENE

There were facilities and procedures for changing and entering into production areas which required staff members to wash their hands and change into clean factory garments. The facilities and procedures were generally adequate except that

2.12 PREMISES

The premises of Phase III were located, designed, constructed and maintained to suit storage, manufacturing, quality control and related operations. The layout and design of premises generally facilitated the logical flow of materials and personnel to minimize the risk of errors and permitted effective cleaning and maintenance. The areas where dust was generated were fitted with dust containment and extraction systems; however dust extraction system for granulation I & II was found to be inadequate as only one line was provided for the whole granulation suit.

There were separate warehouses for raw materials, packaging materials and finished goods. They were generally well designed, controlled and monitored to provide appropriate temperature and relative humidity conditions. There was a covered receiving bay and an area where incoming consignments were verified and cleaned.

The laboratory was located in the Phase I building but separated from production areas and consisted of microbiology laboratory, physico-chemical laboratory (chemical lab, instrument labs), stability and retention sample room. The size of the laboratory was found to be insufficient in comparison to the number of equipment and personnel.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing products manufactured at the site. The equipment reviewed were suitably designed, qualified and calibrated.. There were procedures and records for equipment use, cleaning and maintenance.

Preventive maintenance (PM) of all production equipment, some of the quality control equipment, utilities, AHUs, Dust Collection System, Ventilation & Exhaust Units as well as Air Preparation Units were done in accordance to SOP for PM and Filter Cleaning Program Policy.

Calibration SOP and relevant records for equipment calibration were verified. The factory had identified the master equipment whose calibrations were performed yearly by the external agency. All balances were also calibrated by the external agency once per year. In house calibration was done by Engineering Department yearly or half yearly for critical and non-critical equipment respectively. Calibration certificates were also verified against the records kept in the 2014 Calibration Plan.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.14 MATERIALS

Materials were managed through ERP . It was noted that temperature (22±3°C) and RH (40-60%) was maintained for the warehouse. Materials in the warehouse were kept in a logical order and appropriately tagged**.** Entry and exit procedure was provided at personnel with pictorial presentation of gowning and de gowning. The finished goods warehouse located at Phase III building was meant for short-term storage of finished goods manufactured at Phase III building before they sent to the central warehouse.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.15 DOCUMENTATION

A documentation system was in place to guide production and control of products. These included: Site Master File (SMF); Validation Master Plan (VMP); standard operating procedures (SOPs); Batch Manufacturing and Packaging Instructions and records (MIs, BMRs, BPRs); specifications of starting materials, packaging materials, packaging components and finished products; standard testing procedures, analytical records and certificates of analysis; qualification and validation protocols, schedules and reports; training schedules and records. There were corresponding records in form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.
QA department was responsible for the coordination and control of preparation, review, approval, distribution and review of documents. The system was generally comprehensive and well managed.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

2.16 GOOD PRACTICES IN PRODUCTION

Production operations were guided by approved written procedures in form of manufacturing instructions (MIs) and batch manufacturing records (BMRs). Records reviewed and practices witnessed indicated that records were made promptly in the BMRs and any deviations were also recorded and handled in accordance with an approved procedure.

Line clearance was conducted before and after production and packaging operations. The check list used appeared to be exhaustive except that there was no pictorial presentation provided for line clearance.

In-process controls were performed and documented at appropriate stages and intervals. There were provisions for checks on yields and reconciliation of quantities.

Materials and equipment were adequately labelled with identity, stage of processing and status as appropriate.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

Secondary packaging area of Phase III has three packing lines (bulk/bottle pack, blister and strip packing). These lines were clearly separated from one another through fixed separator.

The primary and secondary packaging operation was controlled with a number of automatic sensors, weight and bar codes. It has been found that there was no check weigher provided for the bottle (bulk) packing line.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The laboratory was located in Phase I but separate from production areas (Phase III) and their functions were independent of other units including production. They were manned by qualified analysts and had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution. Although, it has been noted that laboratory has been revamped from the last inspection, still this appears to be small taking into account the number of equipment and personnel working there.

Stability program was handled using SOP for stability program. The scope covered stability studies on finished products.

The observations raised from this section have been satisfactorily addressed, and will be verified during future inspections.

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, as well as the corrective actions taken and planned, *Macleods Pharmaceutical Limited, Daman, India* was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.