

WHO PUBLIC INSPECTION REPORT API Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**
Part 1: General information

Name of Manufacturer	Macleods Pharmaceuticals Limited
Unit number	Unit-V
Production Block	Block C, Block B & Block A
Physical address	Plot No. 2209, GIDC Industrial Area, Sarigam, District: Valsad, Gujarat 396 155, INDIA
Contact person and email address.	Mr Sushil Jaiswal sushil@macleodspharma.com
Date of inspection	26, 27, 28 and 29 May 2014
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	APIMF103 Ethionamide APIMF150 Tenofovir Disoproxil Fumarate APIMF 165 Emtricitabine APIMF 182 Cycloserine
Summary of the activities performed by the manufacturer	Production and control of active pharmaceutical ingredients

Part 2: Summary

General information about the company and site

Macleods Pharmaceuticals Ltd is located at GIDC industrial area in Sarigam, near Vapi city, in Gujarat state with its corporate headquarters located in Andheri, Mumbai. The construction of the site was started in December 2005 and completed in January 2007. The manufacturing facility has multipurpose production block (block A to E currently in use, while block G & H currently under construction). The production facility manufactures several active pharmaceutical ingredients (APIs) in Sarigam. The company has only one API facility, while they have five finished product sites in India (Unit II, III & VII in Daman, Unit VI in Nalagarh and Unit I in Palghar).

History of WHO and/or regulatory agency inspections

- The site was last inspected by WHO in 2008 and 2012.
- The site was also inspected by the USFDA in 2011 and outcome was reported as satisfactory. It was noted that the USFDA had performed an unannounced inspection of the API site from 12 to 15 May 2014 and the outcome was reported as satisfactory.
- The site was also inspected by the Korean FDA in year 2013 and outcome was reported as satisfactory.

Focus of the inspection

The inspection focused on the production and control of APIs listed under Part 1.0. The inspection covered most of the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 26th May 2014

- Introductions
- Opening meeting
- Product quality review (PQR) procedure and review of PQR
- Organization chart
- Job descriptions
- Training
- Review of stability study procedure and protocols (Cycloserine)
- Out of specification (OOS) and out of trending (OOT)
- Vendor qualification
- Quality risk management (QRM)

Day 2, 27th May 2014

- Feedback on day 1 observations
- List of products with codes
- Procedure for batch numbering system
- Procedure on reprocessing and reworking
- Procedure for maintaining records for additional operations of blending, milling and micronization
- Inspection of manufacturing area focusing on Ethionamide and Cycloserine
- Inspection of block C where Ethionamide Stage I and II
- Inspection of block B where preparation of Ethionamide Stage III (only hydrogenation stage) and inspection of Cycloserine Stage I
- Inspection of block A for preparation of Ethionamide Stage III (final stage) and Ethionamide Stage IV (Pharma)

Day 3, 28th May 2014

- Feedback on day 2 observations
- Inspection of warehouse covering material receipt, de-dusting area, verification of weights of incoming containers
- Inspection of quarantine, approved, rejected areas
- Inspection of quality control laboratory covering logging of raw materials, intermediates and finished products, instrumentation section (particle size analyser, HPLC, GC, FTIR), handling and storage of reference and working standards
- Review of batch records, complaints and CAPA

Day 4, 29th May 2014

- Feedback on day 3 observations
- Review of P&ID of Purified Water System (generation and distribution)
- Review of P&ID of HVAC system (air handling unit comprised of EU4 (10), EU7 (3) and EU 13 (terminal HEPA))
- Review of P&ID of Compressed air system
- Inspection of PW system covering raw water treatment, double pass, EDI, Ultra filtration and storage tank
- Inspection of air handling unit, compressed air system and microbiology laboratory
- Review of change controls and deviations
- Validation Master Plan (VMP)
- Review of analytical method validation for Ethionamide, preventive maintenance program and calibration of equipment
- Review of process validation and batch manufacturing records of Ethionamide
- Meeting among inspectors
- Exit meeting with the site management

2.1 QUALITY MANAGEMENT

The quality management system was generally well established, documented and implemented. The site organizational structure was presented and was acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production.

Product quality reviews were conducted on an annual basis according to SOP. PQR of Ethionamide and Cycloserine for the batches produced in 2013 were reviewed and found to be adequate. As Emtricitabine and Tenofovir have not been produced by site since the validation batches manufactured, these were not reviewed.

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

2.2 PERSONNEL

All personnel met appeared to be well trained, suitable, and the organization chart was generally acceptable. Training of company employees covered Induction Training, cGMP Training, On Job Training, Safety Training and External Training. Induction training was provided to each newly joined employee depending on the designation. Training evaluation was conducted for each training session by using written questionnaires for Officers and Operators employed as permanent employees and orally for Contract operators.

Direct contact with intermediates or APIs was avoided. Overshoes, gowning and hand washing were required in areas where product was exposed.

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

2.3 BUILDINGS AND FACILITIES

Buildings and facilities used in the manufacturing 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. Pressure differentials between different production rooms were monitored in the powder processing areas.

The site has single pass air handling unit (AHU) in the chemistry area. For powder process area, the AHU was comprised of EU4, EU7 and EU13. AHU AG-04 was reviewed and noted that this supplies air to milling/sifting, blending, jet milling and packaging areas.

P&ID of pretreatment water plant was briefly reviewed. The generation system is housed in the first floor of block A and distribution was done through ground floor.

The source water was the municipal water. The water generation system consists of a double pass RO with EDI.

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

2.4 PROCESS EQUIPMENT

Equipment used in the manufacture of intermediates and APIs was of appropriate design and adequate size, 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.

The system was in place for conducting preventive maintenance (PM) for equipment and utilities in the factory. The same was conducted as per preventive maintenance and filter cleaning program policy. Engineering department was responsible for conducting PM. PM for some QC equipment was conducted by the external suppliers.

There was calibration policy that defines policy for calibration of all master instruments and critical measuring devices. Calibration Policy was in place, and Master equipment & critical measuring devices as well as annual calibration schedule were prepared. During the inspection, calibration records for randomly selected instruments were verified and found to be acceptable.

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

2.5 DOCUMENTATION AND RECORDS

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

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

2.6 MATERIALS MANAGEMENT

There was one central warehouse used for storage of APIs, raw materials and primary packaging materials. In addition, block C had two storage areas for holding dispensed materials. Starting materials were transferred from the main warehouse to respective blocks in vehicle (tempo) and then through hoist to the first floor.

Vendor qualification was handled in accordance with the SOP for vendor qualification and approval. The scope of the SOP covered key starting raw material, non-key starting raw materials and packaging materials. It was the responsibility of

the site QA to conduct vendor audits. It involved vendor identification, evaluation and certification.

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

2.7 PRODUCTION AND IN-PROCESS CONTROLS

At the time of inspection, Valsartan was running in SS reactor. The solvent lines (IPA, Ethyl acetate and Acetone) were identified through colour coding (yellow, green and red respectively). Dipstick was used to measure and verify the volume before adding in the reactors.

It has been noted that cleaning of various production equipment done through Type I or Type II cleaning process. Type I is cleaned after next batch was taken and this was recorded. Type II cleaning is recorded directly in respective Equipment Cleaning Record (ECR) after product changeover. Samples collected after Type II cleaning were sent to QC for testing before moving to next step.

Procedure for using hose pipes, procedure for operation of centrifuge and procedure for cleaning of centrifuge were briefly sighted during inspection.

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

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Primary packaging materials were stored in the raw materials warehouse in good order. Labels applied to the containers were printed by shift manager, label samples were attached to the BPRs. In general, packaging and labelling of APIs and intermediates was found acceptable.

2.9 STORAGE AND DISTRIBUTION

Facilities were provided for storage of raw materials; packaging materials and intermediates. There were demarked areas for quarantine and released materials and a secure area for rejects. Materials were labelled with their status. Raw materials and intermediates were stored in a warehouse under different conditions.

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

2.10 LABORATORY CONTROLS

The quality control was independent from manufacturing.

Procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Laboratory records were maintained. Appropriate specifications were established for APIs and intermediates. Specifications included testing of impurities - organic impurities and residual solvents. Reagents and standard test solutions were prepared and labelled following written procedures and current GMP guidelines.

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

2.11 VALIDATION

The site had an overall validation policy document and procedures on manufacturing process, cleaning validation and analytical method validation. Cleaning validation policy was applicable to reactors, centrifuges, dryers, sifters, multi-mill, blender, jet mill. The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.12 CHANGE CONTROL

Change control was handled according to SOP. Changes were classified as major, moderate and minor with examples given for each. The need to notify regulatory authorities was included in the procedure.

2.13 REJECTION AND RE-USE OF MATERIALS

Intermediates and APIs failing to meet established specifications were rejected.

SOP Reprocess and Rework was reviewed and noted that in case of reworked batches, first three reworked batches shall be put up for stability study.. It was also stated in SOP that reprocessed/reworked batches can be dispatched to regulated market if it is already covered in DMF. If it is not mentioned, only after obtaining clearance from RA, dispatch can be made.

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

2.14 COMPLAINTS AND RECALLS

The handling of customer complaints was described in SOP. The procedure including the flow chart was reviewed together with a complaint. The procedure described responsibility, allocation of complaint number, classification of complaints into critical, major & minor/other and formal risk analysis using a separate SOP. Upon

reviewing the product quality of Ethionamide, it was noted that there was no complaint or recall received in 2013.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Production activities were not contracted out as confirmed by the site. Specific analyses were contracted out to other laboratories. This section was not inspected.

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, APIs manufactured at **Macleods Pharmaceutical Limited, Unit-V, Block C, Block B & Block A, Plot No 2209, GIDC Industrial Area, Sarigram, Valsad, Gujarat, India** were 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.