

WHO PUBLIC INSPECTION REPORT**(WHOPIR)****Active Pharmaceutical Ingredient Manufacturer****Part 1: General information about the inspection**

Name of manufacturer	Macleods Pharmaceuticals Limited
Physical address	Plot No. 2209, GIDC Industrial Area, Sarigam, District: Valsad, Gujarat 396 155, India
Unit	Unit V
Manufacturing block	Block A, Module IV
Postal address	As above
Telephone number	HQ: +91-22-6676 2800 Site: +91-260-278110, 2781102, 2781103
Fax number	+91 260 2781104
Summary of the activities performed by the manufacturer	Production and quality control of intermediates and finished APIs
Active Pharmaceutical Ingredient(s) included in the inspection	Tenofovir Disoproxil Fumarate
Type of inspection	Routine inspection, covering aspects of GMP
Date of inspection:	12-14 June 2012

Part 2: Summary

Background information

Macleods Pharmaceuticals Ltd (further referred to as Macleods) has the following manufacturing sites:

(Formulations)

- Plot No 23-28, Premiere Industrial Estate, Kachigam, Daman (U.T.)
- Plot No 8, Ganesh Industrial Estate, Daman (U.T.)
- Plot No 367/7, Kabra Industrial Estate, Daman (U.T.)
- Plot No 1, Mahim Road, Palghar, Maharashtra
- Theda Village, Nalagarh, Himachal Pradesh

and API manufacturing site at: Plot No 2209, GIDC, Sarigam, Gujarat.

The total number of employees engaged on the site for Production, Engineering, QC/QA, Stores and Distribution was about 228 employees.

History of WHO or regulatory agencies inspections

The last routine WHO inspection at this site for APIs was carried out on 14-19 March 2008. The site was also inspected by USFDA on 14 to 17 February 2011.

Focus of the inspection

The inspection focused on the production and control procedures of Tenofovir Disoproxil Fumarate API. The inspection covered several sections of WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, production and quality control.

Inspected Areas

- Quality Management
- Qualification and validation
- Complaints and Recalls
- Self-inspection
- Personnel Training
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

2.1 QUALITY MANAGEMENT

In general, a system for managing quality was established. The quality department was independent of the production department.

Product quality review

The “Product Quality Review” (PQR) SOP (Annual product review) was reviewed. 12 batches of Tenofovir Disoproxil Fumarate were manufactured and released during the review period.

Change control

The SOP “Change control” was reviewed. Changes were related to:

- Facility
- Documentation

Changes were classified as:

- Major
- Moderate
- Minor

Change Control logs for 2011 and 2012 and six monthly review of changes were presented to the inspectors.

Deviations

The SOP “Handling of deviations” and log books for 2011 were reviewed. Deviations were specified as:

- Planned
- Unplanned

Deviations were classified as:

- Major
- Minor

Trending of deviations was carried out once per year. Trend analysis – 2011 were presented to the inspectors.

According to the SOP Planned deviations trending should be done for:

- Process
- Facility
- Raw material
- Equipment
- Specification
- Packaging
- Others

According to the SOP Unplanned deviations trending should be done for:

- Process
- Equipment/instrument
- Analysis
- Utility
- Others

- Total unplanned deviations

Corrective action and preventive action

The SOP “Corrective Actions and Preventive Actions” was reviewed. The SOP was applicable for continual assessment of compliance with:

- Audits
- Deviations
- Out of Specification
- Non-conformances
- Product recall
- Product Quality Review
- Failure investigation
- Returned goods
- Market complaint
- Quality risk analysis
- Self-inspection

CAPA assessment tracking logs 2011 and 2012 were presented to the inspectors.

Responsibilities of the quality and production units

Not inspected.

Internal audits (self-inspection)

The SOP “Self-inspection” was reviewed. Self-inspection plan was prepared yearly. Self-inspection was carried out once in six months for each department. Approved auditors list was presented to the inspectors. Audits were carried out according to the check lists for each department. After the audit observations were recorded and given to the head of audited department and CAPAs were requested. CAPAs were evaluated by the QA head, if necessary follow up audit should be carried out to evaluate effectiveness of the CAPAs.

Supplier approval

The SOP “Vendor qualification” was reviewed. Questionnaire to the vendor was sent before the audit. Questionnaire was evaluated by the plant QA Head. Audits were carried out according to the check list. Observations were listed in the audit report and CAPAs were requested. CAPAs were evaluated by the plant QA head. If CAPAs were found to be appropriate the vendor was certified, if not the vendor was dis-certified. Audits mostly were carried out by the plant QA head and the second line manager.

Key Starting Material (KSM) vendor audit plan & status for October to December 2011 and KSM vendor audit plan & status for the year 2012 were presented to the inspectors.

2.2 PERSONNEL**Personnel qualifications**

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs.

The SOP “Training” was reviewed. There were following types of training listed in the SOP:

- Induction training
- Induction training on QA system
- Training for operators
- Training for executives/supervisor
- Training for managerial staff
- cGMP training
- On job training
- Safety training
- training by external faculty
- External training.

Training effectiveness was evaluated through multiple choice questionnaires (true or false). Training for contract workers were given in local language. Training effectiveness for contract workers was evaluated orally.

The company had ten GMP training modules for the staff members and three training modules for contract labor. Training schedule on GMP modules for 2012 (for staff members and contract labor) as well as training matrix for 2012 was presented to the inspectors.

Training record / log for housekeeping staff and contract workers was spot checked.

Personnel hygiene

Specific attention was not paid to personal hygiene. Direct contact with intermediates or APIs was avoided.

Consultants

The company did not make use of any consultants.

2.3 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 SOP “Environmental monitoring of class 100 000 areas in A block” was reviewed. Area classification was monitored by settle plates and air sampling once per week. Settle plates were exposed for 4 hours. Alert and action limits were specified based upon trend data.

Utilities

Not inspected.

Water

Not inspected.

Containment

Highly sensitizing materials were not manufactured on site.

Lighting

Lighting was adequate.

Sewage and refuse

Not inspected.

Sanitation and maintenance

Specific attention was not paid to the sanitization and maintenance.

2.4 PROCESS EQUIPMENT**Design and construction**

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 SOP “Process for operation of Sparkler filter” was spot checked.

Equipment maintenance and cleaning**Preventive maintenance (PM)**

The SOP “Preventive maintenance of equipment” was reviewed. The SOP was applicable for all equipment in:

- Production area
- Utility area
- AHUs
- Dust collection system
- Ventilation and exhaust unit
- Air preparation units
- Filter cleaning area

Annual PM Schedule for all equipment in production department, warehouse, AHU
PM procedure for each piece of equipment was part of the PM SOP.

Annual PM Schedule of manufacturing equipment’s – year 2012 and PM check lists for SS reactor and centrifuge were spot checked.

Equipment History card was available for all equipment’s where equipment break down was recorded.

Written procedures were established for cleaning of equipment.

The SOP “Type I and Type II cleaning process of SS reactors capacity 1KL” was reviewed.

Calibration

Some equipment calibration certificates were spot checked and found in order.

Computerized systems

It was said that GMP-related computerized system (ERP) was validated; however validation protocol/report was not checked during the inspection.

2.5 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 and finished API. Acceptance criteria were established and documented for in-process controls.

Equipment cleaning and use record

The SOP “Operation and cleaning of dispensing booth” and the SOP “Cleaning and sanitization of areas in warehouse” were reviewed.

Records of raw materials, intermediates, API labeling and packaging materials

Some records inspected were found in order.

Master production instructions

Master production instructions had been established and appropriately approved.

Batch production records

Batch production records were prepared for intermediates and finished APIs. Batches and process operations were traceable.

Laboratory control records

The SOP “Handling of out of specification (OOS) results” and log books for raw materials and intermediate products and finished products for 2011 and 2012 were reviewed. Separate log books were kept for:

- Raw materials
- Intermediate products and finished products

The relevant investigation report was reviewed.

Batch production record review

Written procedures were established for the review and approval of batch production and laboratory control records.

2.6 MATERIALS MANAGEMENT

General controls

In the warehouse, materials were managed using the Enterprise Resource planning (ERP) 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.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Inspectors inspected the Tenofovir Disoproxil Fumarate manufacturing facilities - Block A, Module IV. Raw materials for manufacturing of intermediates and APIs were dispensed in the warehouse under LAF.

In-process sampling and controls

In-process controls were carried out in the Quality control laboratory.

Blending batches of intermediates or APIs

According to the company explanation blending of batches was not carried out.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Not inspected.

Packaging materials

Packaging materials were stored in locked rooms.

Label issuance and control

Labels were stored securely in the locked cabinets.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures

Inspectors made a tour to the warehouses – main warehouse and solvents warehouse as well as to the solvent farm. Facilities were available for the storage of all materials. Released and rejected materials were stored separately. Quarantine areas were identified.

The following documents were reviewed:

- Handling of rejected raw materials
- Raw material inward register
- Rejected raw material register.

Distribution procedures

APIs were released for sale after QA approval.

2.10 LABORATORY CONTROLS

The SOP “Handling of out of specification (OOS) results” and log books for raw materials and intermediate products and finished products for 2011 and 2012 were reviewed. Separate log books were kept for:

- Raw materials
- Intermediate products and finished products

The SOP “Handling and qualification of standards” were reviewed. Assay and Impurities standards were available for Tenofovir Disoproxil Fumerate API. Those standards were prepared in the R&D and supplied to the company. Expiry date for standards was 1 year. Standards were packed in 13 vials (one each for one month’s use). Standards prepared on site were dispensed in the warehouse under LAF.

Microbiological laboratory

Not inspected.

Testing of intermediates and APIs

Laboratory tests were performed for all intermediates in the QCL. Instrumentation and facilities were adequate to conduct the tests required. Impurity profiles were established

Certificates of analysis

Certificates of analysis (CoA) were issued for each batch of API.

Stability monitoring of APIs

The SOP “Stability study for Tenofovir Disoproxil Fumarate” was reviewed. Window period for charging the samples was specified 30 days from the batch release, analytical time frame was also specified.

Tenofovir stability study results for validation batches were presented to the inspectors.

Tenofovir Disoproxil Fumarate stage I holding time study protocol and report were reviewed. Hold time studies were carried out for 6 months. All test parameters were within the specifications.

Expiry and retest dating

Supporting stability information was available for expiry date assigned. The SOP “Re-testing of raw material and intermediates” was reviewed.

Reserve/retention samples

Appropriately identified reserve samples of each batch of API were stored in the same packaging system in which the bulk APIs were stored. Retention samples were stored under appropriate conditions for 6 years.

2.11 VALIDATION

Qualification

Vacuum dry IQ, OQ and PQ reports were reviewed. T mapping study was part of OQ.

Process validation programme

Tenofovir Disoproxil Fumarate Process validation protocol and report were reviewed. Critical process parameters were specified for the first and second stage of the production.

Cleaning validation

The SOP “Cleaning validation policy” was review. There were two types of cleaning:

- Type I batch to batch cleaning (visual cleaning)
- Type II product change over cleaning (10 ppm therapeutic daily dosage criteria), if required toxicology criteria.

Cleaning validation was done together with process validation for each product. Swab and rinse samples were used of the cleaning validation. A list of products manufactured in the Module IV was presented to the inspectors.

Swab and rinse samples were taken for analysis to verify cleaning effectiveness after product changeover.

Validation of analytical methods

Analytical method used for the cleaning validation was spot checked and found to be acceptable.

2.12 REJECTION AND RE-USE OF MATERIALS

Rejection

Intermediates and APIs failing to meet established specifications were rejected.

Reprocessing and reworking

The SOP “Reprocess and rework” was reviewed.

Recovery of materials and solvents

The SOP “Procedure for usage of recovered solvents in the manufacturing process” was reviewed. Batch Manufacturing Records were used to record recovery of solvents.

Returns and rejects

The SOP “Handling of returned goods” and the SOP “Handling of market returned finished products” were reviewed.

2.13 COMPLAINTS AND RECALLS

Quality-related complaints were recorded and investigated according to a written procedure. Records of complaints were retained. The SOP “Handling of complaints” was reviewed. There were no complaints registered in 2011 and 2012. According to the SOP complaints should be reviewed monthly and trending should be carried out once per year.

The SOP “Product Recall” was reviewed.

There was no recall in the history of the company. Recalls were specified as:

- Voluntary recall
- Forced recall

The SOP stated: “To check effectiveness of the procedure mock recall should be carried out once in two years”. Last mock recall was carried out 24.01.2011 and report was presented to the inspectors.

2.14 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

N/A

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, as well as the corrective actions taken and planned Report Macleods Pharmaceuticals Limited Plot No. 2209, GIDC Industrial Area, Sarigam, District: Valsad, Gujarat 396 155, India the Tenofovir Disoproxil Fumarate API is considered to be manufactured in compliance with WHO GMPs 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.