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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Macleods Pharmaceuticals Limited (Pithampur)
Corporate address of manufacturer	Macleods Pharmaceuticals Limited Atlanta Arcade, Marol Church Road, Andheri (E), Mumbai: 400059, India Tel: +91 22 66762800 *Fax: +91 22 29256229/ 29256599*
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Macleods Pharmaceuticals Limited (Pithampur) Plot No. M-50 to M-54-A, Indore Special Economic Zone, Phase II, Pithampur, Distt. Dhar 454774 (MP), India GPS coordinates: North latitude: 22°37′57.09″N East longitude: 75°38′03.0″E D-U-N-S: 854247775
Unit	XI
Unit / block / workshop number	Block G1
Manufacturing license number	28/52/2020 25/88/2020
Dates of inspection	15 – 19 November 2021
Type of inspection	Initial
Introduction	
Brief description of the manufacturing activities	Manufacture, quality control and release of tablets
General information about the company and site	Macleods Pharmaceuticals Limited is a global pharmaceutical company having a vision to provide quality healthcare to humanity with special focus on essential and difficult to make medicines. Macleods Pharmaceuticals Limited, was established in 1986 by Dr. Rajendra Agrawal. The corporate headquarter is located at Andheri (E), Mumbai. Macleods Pharmaceuticals Limited has ten manufacturing facilities in India. The Pithampur site construction started 04/05/2019, construction finished date which comprise of facility qualification completion was 18/02/2020 and operation startup date was 25/02/2020. The Pithampur site, accessible by Air, Road as well as by Railway, is about 41.7 km south west of Indore, on Indore – Dhar highway. The nearest railway station is Indore. The nearest domestic and international airport is Indore. The site is located in special economic zone, surrounded by industrial units that are of non-chemical nature and do not let out any emissions in the form of soot, vapor, or any other gases.

<table>
<tr><td>History</td><td>This was the first PQT inspection of this site.
The site has been inspected by the following authorities:
<table>
<tr><th>Authority</th><th>Date/s of inspection</th><th>Scope of inspection/outcome</th></tr>
<tr><td>Food and Drug Administration, Madhya Pradesh, India.</td><td>17th JAN 2020</td><td>Facility approval Certificate Received</td></tr>
<tr><td>Food and Drug Administration, Madhya Pradesh, India.</td><td>08th SEP 2020</td><td>Schedule M Certificate Received</td></tr>
<tr><td>Central Drugs Standard Control Organization (CDSCO) & Food and Drug Administration, Madhya Pradesh, India.</td><td>19th – 20th JAN 2021</td><td>Local GMP and COPP certification Certificate Received</td></tr>
<tr><td>Ethiopia Food and Drug Administration, Ethiopia.</td><td>07th - 10th of AUG 2021</td><td>Facility approval Certificate received on 08th Nov 2021</td></tr>
<tr><td>Medicines & Healthcare products Regulatory Agency, UK.
Remote inspection</td><td>19th – 22nd OCT 2021</td><td>Facility approval and product Tenofovir Disoproxil 245 mg Tablets
CAPAs submitted</td></tr>
</table></td></tr>
<tr><td colspan="2">Brief report of inspection activities undertaken – Scope and limitations</td></tr>
<tr><td>Areas inspected</td><td>See Part 2 below</td></tr>
<tr><td>Restrictions</td><td>N/A</td></tr>
<tr><td>Out of scope</td><td>Products out of scope of WHO PQ</td></tr>
<tr><td>WHO products covered by the inspection</td><td>• Tenofovir disoproxil fumarate Tablet, Film-coated 300mg
• Flucytosine Tablet 500mg
• Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg
• Linezolid 150 mg Dispersible Tablets</td></tr>
<tr><td>Abbreviations</td><td>Meaning</td></tr>
<tr><td>ADE</td><td>Acceptable daily exposure</td></tr>
<tr><td>ADR</td><td>Adverse drug reaction</td></tr>
<tr><td>AHU</td><td>Air handling unit</td></tr>
<tr><td>ALCOA</td><td>Attributable, legible, contemporaneous, original and accurate</td></tr>
<tr><td>API</td><td>Active pharmaceutical ingredient</td></tr>
<tr><td>APQR</td><td>Annual product quality review</td></tr>
<tr><td>APS</td><td>Aseptic process simulation</td></tr>
<tr><td>AQL</td><td>Acceptance quality limit</td></tr>
<tr><td>BMR</td><td>Batch manufacturing record</td></tr>
<tr><td>BPR</td><td>Batch production record</td></tr>
<tr><td>CC</td><td>Change control</td></tr>
<tr><td>CCEA</td><td>Complete, consistent, enduring, available</td></tr>
<tr><td>CFU</td><td>Colony-forming unit</td></tr>
<tr><td>CIP</td><td>Cleaning in place</td></tr>
</table>

CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
LoD	Loss in drying
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OQ	Operational qualification
PDE	Permitted daily exposure
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications

UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments**

1. Quality system

Principle

Production and quality control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were specified in written job descriptions. Products and processes were monitored, and the results were reviewed as part of the approval process for batch release. Regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

Computerized (TrackWise) system was used for handling and documentation of:

- Complaints
- CC
- Events
- CAPAs
- OOS/OOT
- Lab incidents / atypical results

Data integrity policy

The general data integrity and documentation policy was available and discussed. The procedures covered the electronic, hydride and the paper-based documents.

Separate SOPs were in place for the paper-based documents of different type e.g. SOPs, validation documents. Amongst other measures (e.g. as detailed in the QRM case discussed) the following procedures were discussed related to the good documentation practices and data integrity.

The paper-based documents of any type generated in the GMP environment were stored and archived in the QA Department.

Procedures explained document management system as well as data integrity principles based on ALCOA plus principle.

The following SOPs were discussed:

- Good Documentation Practices & Data integrity
- Guideline for Data Integrity
- Documentation Control
- Issuance, Control, Retrieval, Retention and Disposal of Documents, Formats and Logbooks
- Code of Conduct on Data Integrity and Management of GMP Violations

Product Quality Review (PQR)

Corporate guideline “Guideline for Annual Product Quality Review of Drug Product” was discussed.

Products under PQ were not commercially manufactured, PQRs for 2020 was discussed.

- Tenofovir disoproxil fumarate tablet 300 mg
- Flucytosine tablet 500 mg
- Linezolid dispersible tablet 150 mg
- Dolutegravir sodium 50mg/Lamivudine 300mg/Tenofovir disoproxil fumarate 300mg tablet

Management review (MR)

Procedure for Quality Management review" was discussed. Head QA or designee and Head Production or designee were responsible to organize Quality Review Meetings (QRM). Head QA or designee and Head Production or designee were assigned as a QMR coordinators and chairpersons. According to the SOP QRM shall be conducted second week of the month. Quality Operations and Regulators compliance indicators were used to evaluate site performance.

Quality management system, Quality operation and Regulatory compliance indicators were specified.

Change control (CC)

Corporate "Change Management System" and CC registers for 2020 and 2021 were discussed. The SOP was applicable for changes related to:

- Manufacturing,
- Validation / testing
- Holding
- Sampling
- Storage
- Handling
- Packaging
- Release
- Destitution
- Regulatory / non-regulatory impact

A number of CC were discussed.

Deviation management

Corporate "Event management" and event register for 2020 and 2021 were discussed. SOP was applicable to all non-compliance and failures reported during manufacturing, validation/testing, holding, sampling, storage, handling, packaging, release and distribution of the drug products and drug substances e.g. unplanned events. In the company terminology deviations were called "events".

Full risk assessment was carried out for Critical and Major events and formal risk analysis was carried out for Minor events. FMEA and HACCP were used for risk assessment.

According to the SOP the following tools could be used for Root Cause investigation:

- 5 Why`s
- GEMBA (Go and See)
- Fishbone diagram

A number of events were discussed.

Quality Risk Management

According to the following topics were considered for the QRM:

- Change controls
- New product
- New equipment
- Events
- Data integrity
- Cross contamination
- Customer complaint
- Cleaning validation
- Process validation
- Audits/inspections.

A number of RA were discussed.

Corrective and preventive actions (CAPAs)

Corporate "Handling of Corrective and Preventive Actions" and registers for 2020 and 2021 were discussed. SOP was applicable to events such as:

- OOS/OOT/Incidents/Complaints/Recall
- APQR/PQR
- Regulatory inspection
- Customer audits
- Infernal audits
- Process or system improvement
- Trend analysis
- Validation/qualification
- Quality review meeting
- Quality risk management

CAPAs effectiveness should be checked within 60 days, if extension was required, it should be approved by site Operation Head and Site Quality / CQA.

Complaints

A system was in place to review complaints and other information concerning potentially defective products. SOP "Handling of customer complains in TrackWise" was discussed. SOP explained actions to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect. Complaints concerning a product defect were recorded with original details and investigated. SOP was applicable for Pharmacovigilance complaints product quality related complaints. Till the date of inspection, no complaints were recorded.

Recalls

A system was in place to recall from the market, promptly and effectively, products known or suspected to be defective. Recall SOP was regularly discussed and updated. SOP "Procedure for Product Recall – Overseas Market" was discussed. There was also SOP for recall – domestic market which was not discussed. Head Corporate QA in consultation with recall comity was responsible for recalls form all sites. There were two types of recalls specified:

- Voluntarily
- Statutory

Recalls were classified as:

- Class I
- Class II
- Class III
- Class IV

Recall effectiveness was evaluated by Mock recall. Mock recall should be performed annually. SOP specified that Mock recall should be initiated in shortest possible time.

Till the date of inspection, no recalls were executed.

Self-inspection

System for self-inspection was in place and provided a minimum and uniform standard of requirements. SOP "Self-inspection", schedule self-inspection and self-inspection report were discussed.

Self-inspection should cover the following departments, but not limited to:

- QA
- QC & Microbiology
- Production: manufacturing / packaging
- Engineering: utilities & EHS
- Human resources
- Stores
- IT

Auditing tools were specified and explained. Department wise check-list were used.

Head QA was responsible to nominate independent self-inspection team consisting of experts in their respective fields and familiar with GxPs. Criteria for qualification of auditors was specified.

Audit report was reviewed and approved by lead auditor, audit team and Head QA. CAPAs were proposed by user department. CAPAs implementation / effectiveness was verified by self-inspection team members and QA. If required follow-up audit was performed. Self-inspection trends were prepared on half yearly basis.

Suppliers approval

A system was in place for supplier's approval. Before suppliers were approved and included in the approved suppliers' list they were evaluated. Corporate SOP "Vendor qualification and approval", audit schedule for 2021 and approved suppliers list for starting materials and packaging materials were discussed. Approval of suppliers was done at corporate level. Approved suppliers list was revised every month. SOP also explained procedure for de-listing /rejection/ black-listing of suppliers.

Because of Covid 19 restrictions in 2021 many suppliers' audits were remote audits.

Technical agreements (TA)

TA between Macleods Pharmaceuticals Limited and manufacturer of Tenofovir Disoproxil Fumarate API was discussed. Contract giver and acceptor responsibilities were clearly specified.

Corporate SOP "Procedure for Qualification of Contract Laboratories" was discussed. Qualification of contract laboratories was carried out by corporate QA. Qualification was performed using check-list. According to the SOP re-qualification of contract laboratories has to be done after every three years. Procedure was in place for de-listing of contract laboratories.

TA between Macleods Pharmaceuticals Limited and laboratory used for microbiology tests was presented and discussed.

Reprocessing-rework

SOP "Reprocessing, recovery, reworking and repackaging" was discussed. According to the SOP:

- Reprocessing: no re-processing is allowed
- Recovery: there shell be no recovery addition from one batch to another
- Reworking of non-conforming intermediate or finished product shall not be permitted
- Re-packaging: allowed only for bulk packs (containers). De-blistering was not allowed.

Returned products

SOP "Handling of Market Returned Finished Goods" was discussed. According to the SOP no goods were returned back to India from overseas markets.

Batch numbering system / BMR / BPR

SOP "Allotment of Batch Number" and SOP "Preparation, Review, Revision, Approval, Control, Issuance, Retrieval and archival of Batch Manufacturing and Batch Packaging Records" and manual issuance register were discussed. BMR/BPR issuance register was maintained by QA. The same register was used for batch number allocation.

Batch release

SOP "Batch Release Procedure" was discussed. As an example, analytical raw data of Amlodipine Besilate 10 mg tablets was discussed. The file contained following documents:

- Review record for analytical data, categories of discrepancies (Critical/Major/Minor), reviewed by QA
- Routine check points: compression
- Analytical raw data sheets for each test, discussed by QC reviewer

Personnel

Company employed sufficient number of qualified personnel to carry the tasks for which the manufacturer was responsible. Individual responsibilities were defined and recorded as written descriptions. Company employed adequate number of personnel with necessary qualifications and practical experience:

Corporate SOP "Training Program through Pharmaceutical Learning Management System /e-Learning Management System & Manual System" and annually training plan for 2021 were discussed.

SOP "Analyst Qualification", analysts qualification matrix and signature specimens were discussed. SOP was applicable for newly recruited analysts and existing analysts. According to the SOP re-qualification was based on error trending. Analyst were given to analyze already approved batch and results were compared. Acceptance criteria was specified for different tests.

A number of training files were discussed.

The following SOPs were discussed:
- "Personal Hygiene"
- "Procedure for Medical Check-up"
- "Handling of Garments"
- "Operation of Washing Machine, Garment Dryer and Flat Bed Press Equipment"

2. Production system

Production operations followed defined procedures. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and CAPAs were implemented where necessary. Checks on yields and reconciliation of quantities were carried out. Access to production premises was restricted to authorized personnel.

During inspection Paracetamol tablets 500 mg was under granulation in Granulation room X and Amlodipine Besilate 10 mg under granulation in Granulation room Y. To avoid possible cross-contamination operators in Granulation rooms were wearing "kitchen" aprons, which were removed before exit of the rooms.

During inspection Paracetamol tablets 500 mg was under compression in Compression room X and Amlodipine Besilate 10 mg under compression in Compression room Y. Metal detectors were provided for all compression machines and challenged before start of compression, every 4 hours and at the end of compression by using ferrous, non-ferrous, stainless steel and dumb pieces.

Punched/dies, FBD finger bags and screens were stored in separate room in SS locked cabinets. Punches and dies rotation was ensured and checks were performed before and after use according to the check list. Punches and dies drawings were available. Finger bags were visually discussed for damage. Checks on screens were done according to the check list. Sieves integrity checker was provided.

The manufacturing parameters captured during the compression were recorded by the SCADA system, printed out and attached to the BMR.

The following batch manufacturing records were discussed.
- Batch Manufacturing record of Dolutegravir Sodium, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50/300/300 mg
- Batch Manufacturing record of Dolutegravir Sodium, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50/300/300 mg

<u>Process validation</u>

The general policy regarding process validation was described in the validation master plan. Manufacturing processes were validated before commercializing the product with at least 3 consecutive bathes. The following documents were discussed.
- Process Performance Qualification
- Process validation Protocol and Report of Product Linezolid Tablets 150mg
- Process validation Protocol and Report of Product Tenofovir Tablets 300mg
- Process validation Protocol and Report of Product Flucytosine tablets 500mg
- Process validation Protocol and Report of Product Dolutegravir Sodium, Lamivudine and Tenofovir
- Disoproxil Fumarate Tablets 50/300/300 mg

According the SOP "Simulated Hold Time Study" the hold time of the intermediates were investigated for a time period recommended by the Corporate PDR (Product Development and Research). The target was 30 days as indicated in the SOP.

Cleaning validation
The cleaning procedures were defined, and their effectivity proven by cleaning validation.
The equipment chain was identified for the products tally with the process validation and the corresponding BMR. Worst case products were defined based on the solubility and PDE of API. MACO calculations considered the criteria of "10ppm", "dose" and "PDE". The PDE values were provided by the toxicologist working for the Corporate R and D.

The cleaning validation was always based on the worst-case product of the chain.
In case of introducing a new API into the plant the verification study was done. The decision, whether re-validation is required, is made upon the result of the verification. The last verification was performed with pretomanid.

The following documents were discussed.

- SOP Procedure for Cleaning Validation Program
- Cleaning validation Protocol Master
- Equipment list, Equipment design, Sampling points, Product vs. Equipment chain, Product grouping, Product Matrix, PDE Values, Worst case based on MACO, Worst case establishment of MACO calculations, Establishment of worst case
- Cleaning verification pretomanid tablets 200 mg
- Cleaning validation Linezolid Tablets 150 mg

3. Facilities and equipment system
The facility was spread around 28.14 acres of land and currently consisting of 1 block for manufacturing activities, identified as 'G1' block. G1 block was spread in a Lower ground floor, Ground floor and First floor with built up area of approximately 8400 m^2 for manufacturing of solid dosage forms which was distributed as 4181.43 m^2 for Production and Warehouse area, 824 m^2 for QC Area I and II with passage and 111.88 m^2 for Microbiology. G1 Block was under expansion for a second and third floor. It had cubicles for manufacturing of solid orals along with one bulk packing line, two blister packing line and one strip packing line. First floor consisted of Quality control area and microbiological laboratory.

Admin block was also under construction for Finished Goods store, Reject/Recall area, RM/PM receiving area at lower ground floor and Admin, Human Resources, Accounts, Information Technology and Quality Assurance department at ground floor. Soft gelatin capsules manufacturing facility was under construction at third and fourth floor of Admin Block.

Production premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. Premises were cleaned and disinfected according to detailed written procedures, records were maintained. Where dust was generated measures were in place to avoid cross-contamination and facilitate cleaning. Premises carefully maintained and cleaned according to written procedures. Records were maintained. Production rooms appeared to be well maintained and clean. Stainless steel bins and containers were used for production and storage of in process products.

The garment washing and drying facilities were located in a separate building with rooms for used linen reception, washing-drying (with an automated washing and drying machine), ironing and washed linen store. The procedure was described in SOP Operation of washing machine, dryer and flat-bed press.

The personnel entrance to the storage and warehousing areas was controlled by biometric identification (fingerprint reader).

The production equipment had equipment logbook where the main data of the equipment usage were recorded. The equipment qualification consisted of DQ/IQ/OQ/PQ based on the Traceability Matrix and the general policy of SOP "Performing of Equipment validation/equipment qualification" and "Process Performance Qualification".

The Qualification Documents of the Compression Machine were discussed. The IQ and OQ documents were provided by the vendor and approved by the local professionals. The validation of the Scada connected to the equipment covered: initial risk assessment, URS, validation plan, functional risk assessment, IQ/OQ/PQ.

The measuring devices of the equipment were calibrated regularly. The calibration records of the pressure gauge attached to the compression machine were discussed. The calibration was performed by an accredited laboratory.

Utilities, HVAC
The HVAC system consisted of XX AHU units supplying the controlled areas qualified as ISO 8.
The layout, construction qualification and monitoring documents of AHU X were discussed.

The qualification and the regular monitoring covered the air velocity, system leakage, air pressure differentials, non-viable particles, viable (settle plate), temperature, relative humidity, air flow pattern, air velocity, recovery. The requalification was due in every 6 months.

The filters were cleaned at the filter dedusting, cleaning, drying and storage rooms in the technical area.

Utilities, Purified water system
Soft water was used for bin washing (automatic washing machine) filter cleaning, utility (chilled water and steam) and purified water generation.

The purified water system (including purification from soft water, storage and distribution) was located in the technical area of the building.

The conductivity, flow, TOC and temperature was monitored on-line. The test results were printed out in every hour. In case of out of the limit result, the water is drained by an automatic valve, but it never happened since the system was approved and operational.

The maintenance of PW system was scheduled quarterly upon a checklist.

Documents discussed:
- Qualification Document of Pretreatment Water System
- Qualification Document of Purified water generation system
- Qualification Document of Purified water storage and distribution system
- Specification of PW
- Specification of soft water
- Sampling and analysis of water with

SOP "Environmental Monitoring (EM) in Manufacturing Area" and EM trends for were discussed. Production rooms EM was performed using settle plate method. Action and alert limits were established.

Laboratory premises
Microbiological laboratory (MBL) was separated for OC laboratory. MBL was not visited during site tour. MBL layout was checked. Work with Master cultures was done in Bio Safety Cabinet, microbiological analysis was performed in RLAF.

SOP "Receipt, Handling, Preparation and Storage of Media" was discussed, Media Preparation and Sterilization Record log book was checked.

Computerized systems
The validation policy of the computerized systems was summarized in the validation master plan. Additionally, there was an SOP in place on computerized system validation covering the entire site and all the departments Annex provided the list of the systems, together with the periodic review planner. List of computerizes systems was available. Access levels were specified.

4. Laboratory control system
Samples arriving into the laboratory were recorded in sample inward record (samples of process validation, FP, RM, PM, IPC, cleaning validation) and given analytical number (AR number). All the products had approved specification and corresponding description of the standard test procedures which made the basis of the sampling (number and location of the sample, pooling, composite sample preparation) and sample distribution.

The test results were recorded in predefined form of Analytical Data Sheet.

The test records of Tenofovir FP were checked.

The working standard of Tenofovir was received from the Macleods Sarigam site where the working standards are prepared and qualified. The storage conditions were 2-8 ^{0}C.

The chromatography followed the good chromatography practices defined in an SOP. The HPLC columns were dedicated for a certain product.

The qualification and maintenance of the HPLC XX was performed according to the SOP and protocol tally with the defined schedule.

Chromatographs were connected to a network running Chromeleon software.

The audit trail and user management were described in SOP. The list of system users was available together with their user group and privileges. The monthly audit trail review was recorded in the checklist.

The control samples were stored in the Control Sample Room, Laboratory section 1 below 25 ^{0}C and recorded in the Control Sample Register. The control samples of the inspected products were available.

The analytical test methods which were validated in another site (R&D in Sarigam) were transferred (upon technical transfer protocol) or verified in case of compendial methods.

The stability samples were stored at:

- 25 ^{0}C/60%
- 40 ^{0}C/75%
- 30 ^{0}C/65%
- 30 ^{0}C/75%

The conditions were continuously recorded, and the data backed up daily. Audit trail addressed door openings.

Stability testing was performed upon defined stability program. In case of commercial production, the on-going stability is tested with the first batch of a calendar year.

The following documents were discussed.

- In process and Finished product Specification of product Flucytosine tablets 500mg
- "Sample Receipt & Testing of Finished Product and In-Process Samples
- Sample inward record RM
- RM sampling checklist
- Raw material identification individual container
- Raw material composite sample details
- "Sampling, Testing, Review, Release and Rejection of Raw Materials"
- AR number generation record
- "Assigning of Analytical Reference Number"
- Raw material COA (Tenofovir)
- Raw material Tenofovir specification and STP
- Tenofovir tablets Finished product COA
- Finished product Tenofovir tablets specification and Sampling, Testing, Releasing and Rejection of Packaging Materials
- Qualification document of HPLC
- "Performing of equipment qualification"
- Calibration record of HPLC
- "Audit Trail Review of Electronically Generated Data"
- Column Management in Quality Control Laboratory
- User privilege of Chromeleon software
- "User Management for Chromeleon Chromatographic Data Management System (CDMS)
- Analytical method transfers
- Analytical Method Verification for Drug Substance and Drug Product
- Stability program Tenofovir tablets stability summary report

<u>OOS investigation records:</u>
It was noted that various OOS were related to the stability studies:

The OOS/OOT/atypical results and laboratory events were recorded, investigated following a predefined procedure, process flow, responsibility matrix in the TrackWise system according to the SOP Handling of OOS/OOT/Atypical results and laboratory investigations.

A number of OOS investigations were discussed.

Sampling of starting and packaging materials

"Sampling, Testing, Review, Release and Rejection of Raw materials" and "Sampling, Testing, Releasing and Rejection of Packaging Materials" were discussed. 100% sampling was performed for APIs and excipients. Primary and Secondary packaging materials sampling was performed according to the AQL, normal inspection, level II. AQL for critical and major deficiencies and minor deficiencies was specified, explanation of defects was given for all types of primary and secondary packaging materials,

The site was using a number of contract laboratories.

5. Materials system

Incoming materials and finished products were quarantined after receipt or processing, until they were released for use or distribution. Materials and products were stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation. Starting materials and packaging materials were purchased from approved suppliers, approved suppliers list was available in warehouses. Containers were checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels. Procedures were in place to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn were identified. All products and packaging materials to be used were discussed on delivery. An identity test was conducted on a sample from each container of starting material. Inspectors were told that Raman IR spectrophotometer was qualified, library was under validation. Identity tests were performed in QC using IR. Enterprise Resource Planning system (ERP) system was used for materials management. The material codes were defined and recorded in the List of Identification Code of Products.

Sampling and dispensing were carried out under RLAF. Sampling and dispensing log books were checked. Dispensing procedure of starting materials for the batch:

- Cleaning
- API
- Excipients
- Cleaning
- Colored materials

In stores T & RH was recorded twice per day with minimum and maximum recorded.

Tenofovir disoproxil fumarate API was stored in cold chamber at T 2 – 8 ℃. T in the chamber was recorded online every hour by 8 sensors. Print out was taken and discussed daily. In case of T excursions sound alarm system was in place: stores and security.

Roll labels were stored in locked rooms, access was controlled.

Finished products had approved product specification and standard test procedures. The following documents were discussed:

- Finished product Specification of product Tenofovir
- In process and Finished product Specification of product Flucytosine tablets 500mg

Temperature and RH mapping

"Temperature Mapping" was discussed. SOP was applicable to all storage areas where product is stored in production, QC and QA departments. Initial T&RH mapping studies for storage areas were done for 3 seasons: summer, winter and rainy. Periodic validation for storage areas was performed every three years during summer season. Periodic validation of refrigeration equipment was performed annually.

A number of T & RH mapping studies were discussed.

6. Packaging and labelling system

"Dispensing of Packaging Materials" and "Receipt of Excess Packaging Material from Production". were discussed. Dispensing of PVC, PVC-PVDC, Plain & Printed AL foils was done on weight basis. Dispensing of Roll labels: complete roll of labels was issued to the packaging. All labels had sequence numbers.

Part 3	Inspection outcome

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 ***Macleods Pharmaceuticals Limited (Pithampur) Unit XI, Block G1, located at Plot No. M-50 to M-54-A, Indore Special Economic Zone, Phase II, Pithampur, Distt. Dhar 454774 (MP), India*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products 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.

DEFINITIONS

Critical deficiency

A critical deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

Major deficiency

A major deficiency may be defined as a non-critical observation that:

- has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
- indicates a major deviation from the GMP guide;
- indicates a failure to carry out satisfactory procedures for release of batches;
- indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

Other deficiency
A deficiency may be classified as other if it cannot be classified as either critical or major, but indicates a departure from GMP. A deficiency may be other either because it is judged to be minor or because there is insufficient information to classify it as major or critical.

Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.

Part 4	List of GMP Guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
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   http://www.who.int/medicines/publications/44threport/en/

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8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6. ***Short name: WHO TRS No. 961, Annex 6***
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9. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7. ***Short name: WHO TRS No. 961, Annex 7***
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