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Prequalification Unit Inspection services
PUBLIC WHO INSPECTION REPORT
Remote Real Time Inspection
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Lupin Ltd
Corporate address of manufacturer	Kalpataru Inspire 3rd Floor, Off Western Express Highway Santacruz (East) Mumbai 400055, India (+91) 22-66402323 Fax number: (+91) 22-6640-2051
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Lupin Ltd, Nagpur Lupin Limited, Plot No. 6A1, 6A2, Sector-17, Sez Mihan Notified Area, Nagpur, Maharashtra, 441 108, India North Latitude: 21°2'36.67"N (21.043518) East Longitude: 79°1'53.29"E (79.031473) D-U-N-S: 650759348
Unit / Block / workshop number	Unit 1 • Block 1 • Block 2
Manufacturing license number	ND/59-In Form 25 (Other than specified in Schedule C, C1 and X) ND/58-In Form 28 (specified in Schedule C, C1)
Dates of inspection	17 - 21 January 2022
Type of inspection	**Remote Real Time Inspection**
Introduction	
Brief description of the manufacturing activities	Manufacture, quality control and release of Solid Oral Dosage Forms: Tablets and capsules
General information about the company and site	Lupin Limited has its headquarters in Mumbai, India, Lupin Limited is a pharmaceutical company producing a wide range of generic and branded formulations and APIs for the developed and developing markets of the world. Lupin Limited is multidivisional and multi locational organization. The company was founded in 1968 and is currently engaged in the manufacturing of Formulations, API and Biotechnology based products. Lupin has its R & D Facilities, Lupin Research Park (LRP) at Pune and Aurangabad. Lupin has bulk drug manufacturing (API) facilities at: • Ankleshwar (Gujarat) • Baroda (Gujarat), • Mandideep (Madhya Pradesh) • Indore (Madhya Pradesh) • Tarapur (Maharashtra) • Vizag (Andhra Pradesh)

	Lupin has formulation facilities at: • Aurangabad (Maharashtra) • Indore (Madhya Pradesh) • Jammu (Jammu & Kashmir) • Mandideep (Madhya Pradesh) • Nagpur (Maharashtra) • Pune (Maharashtra) • Sikkim (Sikkim) • Verna (Goa) The facility at Nagpur (Unit 1) was engaged in the manufacturing of Solid Oral Dosage Forms: Tablets and capsules
Major changes since last WHO inspection	• Additional OSD manufacturing facility (Block 2) commissioned for the manufacturing of OSD. The facility is being used for the manufacturing, packing, storage, holding, testing and distribution of drug products for oral solid dosage form. • Area qualification of QC laboratory of new OSD manufacturing Block-2 carried out followed by qualification of analytical instruments and equipment. • Blister packing room (Room No. 150) modified to Inspection – ll and Blister packing machine (PR-BPM-003) with line machine transferred to existing bottle cleaning area (Proposed Blister Packing Area). • Packing air lock (Room No. 151) modified to packing corridor and connected to process corridor with air handling unit (EN-AHU-002). • Bulk packing 1 (Room no. 152) and Spare room I (Room No. 151A) merged to wet granulation V. • Inclusion of new equipment, "Tertiary Serialization Labelling Machine" in the production facility of Lupin Ltd. Nagpur, Block 1, Unit 1, for shipper to pallet aggregation with following details: Make: ACG Inspection Systems Pvt. Ltd. Model: Voyager – N037 Sr. No.: VFTH0918028 • Inclusion of new equipment, "Serialization Track and Trace system" in the production facility of Lupin Ltd. Nagpur, Block 1, Unit 1, for carton to shipper aggregation with following details: Make: ACG Inspection Systems Pvt. Ltd. Model: HAWKEYE – N048 Sr. No.: PCCH0818018 • Tablet automated Visual Inspection system (PR-AIS-002) is transferred from Block 2 production facility to Block 1 production facility Unit I, Lupin Limited, Nagpur. Details of equipment is given below, Equipment ID. PR-AIS-002 Make: ACG Pam Pharma Technologies Pvt. Ltd Model Type: Visitab 2PL Serial number: PM 75 • Multi- Functional Rotor Processor is introduced in manufacturing facility Unit-1 (Block – 1), Lupin LTD. Nagpur. Details of Equipment are given below, Equipment ID – PR-MRP-001 Make – Freud-Vector corporation Model – VFC-60M FLO-COATER Multipurpose Fluid Bed System Serial No.- FL-863 Area name – Wet Granulation 5 Equipment ID – PR-MRP-001

<table>
<tr><td>History</td><td>This was the second PQT inspection of this site. Last inspection by the PQT was performed 19/09/2018 to 21/09/2018.

The site has been inspected by the following authorities (last 5 years):

<table>
<tr><th>Authority</th><th>Date/s of inspection</th><th>Facility/Block/ Unit covered by inspection</th></tr>
<tr><td>CDSCO (India)</td><td>27/09/2021 to 28/09/2021</td><td>Block 1 and Block 2, Unit 1</td></tr>
<tr><td>Ethiopian Food and Drug Authority (EFDA) Ethiopia</td><td>18/08/2021 to 20/08/2021</td><td>Block 1 and Block 2, Unit 1</td></tr>
<tr><td>USFDA, USA</td><td>06/01/2020 to 10/01/2020</td><td>Block 1 and Block 2, Unit 1</td></tr>
<tr><td>Medicines Control Authority of Zimbabwe</td><td>09/09/2019 to 11/09/2019</td><td>Block 1 and Block 2, Unit 1</td></tr>
<tr><td>USFDA, USA</td><td>05/08/2019 to 08/08/2019</td><td>Block 1, Unit 1</td></tr>
<tr><td>National Drug Authority Uganda</td><td>17/09/2018 to 18/09/2018</td><td>Block 1, Unit 1</td></tr>
<tr><td>USFDA, USA</td><td>10/09/2018 to 12/09/2018</td><td>Block 1, Unit 1</td></tr>
<tr><td>CDSCO (India)</td><td>26/04/2018 to 27/04/2018</td><td>Block 1, Unit 1</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>
<table>
<tr><th>FPP</th></tr>
<tr><td>Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg</td></tr>
<tr><td>Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 200mg/300mg</td></tr>
<tr><td>Atazanavir (sulfate)/Ritonavir Tablet, Film-coated 300mg/100mg</td></tr>
<tr><td>Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg</td></tr>
</table></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>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>
</table>

CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
CD	Compact disk
CV	Curriculum vitae
DQ	Design qualification
DVD	Digital versatile disk
EDI	Electronic deionization
EHS	Environment, health, safety
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GC	Gas chromatography (or gas chromatography equipment)
GMP	Good manufacturing practices
GPT	Growth promotion test
GxP	Good "variable" practices The variable "x" depends on the application of the standards. The "x" can be C for "Clinical", D for 'Distribution", L" for Laboratory" or M for 'Manufacturing"
GQCSC	Global quality council steering committee
HEPA	High efficiency particulate air
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation, and air conditioning
IC	Ion chromatography (or ion chromatography equipment)
IQ	Installation qualification
LAF	Laminar air flow
LCL	Lower control limit
LIMS	Laboratory information management system
LoD	Loss in drying
MACO	Maximum allowable carryover
MB	Microbiology
MBL	Microbiology laboratory
MET	Microbial enumeration test
MF	Master formulae
MR	Management review
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOC	Out of calibration
OOS	Out of specification
OQ	Operational qualification
OOT	Out of trend
NMT	Not more than
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
QAMS	Quality assurance management system
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
RPN	Risk priority number
SQCM	Site Quality Council Meeting
SMF	Site master file
SOP	Standard operating procedure
UCL	Upper control limit
UHPLC	Ultra-high-performance liquid chromatography (or ultra-high performance liquid chromatography equipment)
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

NOTE: CORPORATE AND SITE-SPECIFIC SOPs WERE SUBMITED WELL BEFORE INSPECTION DATES AND CHECKED BY INSPECTORS IN ADVANCE

Inspection was focused on general Quality Management System and procedures

1. Quality system

Principle

Production and control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were specified in written job descriptions. Product and processes were monitored, and the results were checked 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.

Quality Assurance Management System (QAMS) is an electronic system and was used for the initiation, execution, review, and approval of quality management documents, for example deviations, CAPAs, etc.

Data integrity policy

Data integrity policy was in place. Corporate SOP "Data Governance" was checked. SOP defined the main components of a data governance intended to ensure the accuracy, consistency, and completeness of data throughout its lifecycle when such data is generated to support the product quality, safety, and efficacy. The scope of the SOP covered operational activities that have direct impact on the integrity of data. SOP was applicable to all Lupin sites that are manufacturing and distributing healthcare products for human consumption and to all data generated manually or electronically.

Electronic data

The following corporate SOPs were available and checked:

- "Back up, Restoration and Archival of Computerized system".
- "Disaster Management & Business Continuity Plan for Computer Software System".
- "Standalone Computer Software System Administration".

The following site-specific SOPs were available and checked:

- "User Management of Electronic Data in Standalone Software". SOP NGP 1 PR 008868 (1.0) "User Management"
- "Periodic Review of Electronic Data in Manufacturing System".
- "Periodic Review of Laboratory Software".

Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 200mg/300mg Batch no XX test Assay (HPLC) meta data was checked. Sequence audit trail, injection audit trail, system audit trail, method audit trial was presented. Users/privileges: lab manager, reviewer/administrator/analyst were checked. Delete function was deactivated.

Check list for review of manufacturing software audit trails and administrative software audit trails for FBD as checked.

Product Quality Review (PQR)

Corporate SOP) "Annuals Product Quality Review of drug products" was checked.

The review period for preparation was considered either January to December or one anniversary year starting from regulatory approval month or last 12 months as per the planner thereby distributing the products over a year. Annual Product Quality Review (APQR) was prepared, checked, and approved within 30 working days from the scheduled date for the product.

Statistical evaluation to determine the maximum, minimum, mean was carried out for batch yield, relevant in process and finished product test parameters. Process capability index (CpK) value was calculated for batch yield and key quantitative analytical results like Assay and Related Substances.

APQR for Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 200mg/300mg and Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg were checked.

Management review (MR)

Corporate SOP "Management review of Quality Metrics" was checked. Management review was performed monthly.

Site Quality Council Meeting (SQCM) was held once every month at respective site. SQCM was organized for the review and discussion on monthly report with all functional departments at site.

Quality Council meeting (QCM) was held at corporate minimum six times per year to review the Quality performance of each site.

Global Quality Council Steering Committee (GQCSC) Meeting was held at Corporate once in a Quarter to review the Quality performance of each site.

Minutes of XX QCM and presentation (all Lupin sites) and Site (Nagpur) Quality Council meeting May 2021 presentation and meeting minutes were checked. Presentation was very comprehensive.

Complaints

Corporate "Handling of Market Complaints for drug products" and complaints register for 2021 were checked. Site QA and Quality Assurance or Contract Manufacturing QA were responsible for complaints investigation. Complaints were categorized:

- Category I: Critical
- Category II: Major
- Category III: Minor
- Category IV: Adverse Drug Event. ADRs were handled by Lupin Drugs Safety Department

A number of complaint files were checked.

Recalls

Corporate "Recall/Market Withdrawal of Drug Products" and List of market withdrawal 2021 was checked. SOP was applicable to drug products marketed in India and overseas.

Recalls were voluntary and statuary and were classified as:

- Class I
- Class II
- Class III

There were three recall levels specified:

- Consumer or user level
- Retail level
- Wholesale level

The recall /market withdrawal of the product/batch should be completed within 30 working days of the receipt of product recall intimation unless until justified. Mock recall was carried out annually.

Rejection/returns

SOP "Handling of returned Finished Products" and rejected batched register for 2021 checked.

SOP "Handling of Data loggers" was checked. According to the SOP two data loggers shall be installed in two different pallets for each consignment. If different customers are there, then two data logger per customer in each dispatch for the purpose of ongoing recording and monitoring of temperature excursion.

Quality Risk Management
Corporate SOP "Quality Risk Management" and Risk Assessment protocol/report for Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets were checked. SOP provided the principles and examples of tools for quality risk management that was applied to different aspects of pharmaceutical quality.

The following was reviewed:
- QRMP/Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50mg, 300mg and 300 mg/18/01 (Protocol)
- QRMR/Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50mg, 300mg and 300 mg/18/01 (Report)

Change control
Corporate SOP "Change Control" and list of CCs for WHO products were checked. SOP was applicable to changes related to Manufacturing Facilities, Procurement, Warehousing, Distribution, Equipment, Utilities, Manufacturing Processes, Materials/Products, Systems and Instruments, Document Management Systems such as Specifications, Test Methods and Operating Procedures. Quality Unit was responsible for the oversight of the change control system.

Trending of change control was done by the nature of change type as Permanent Change and Temporary Change and further categorized based on the impact of change as Major Change and Minor Change.
Subsequently, the change controls were further categorized into Products, Materials, System, Equipment, Instrument, Document and Others based on the applicability of changes.

A number of Change Controls were checked.

Deviation management
Corporate SOP "Handling of Deviations" and deviations register for WHO products were checked. Deviations were classified as:
- Critical
- Major
- Minor

A Quality Risk Assessment was required for all Critical and Major deviations and as needed for Minor deviations.

Deviation trends were prepared and evaluated quarterly by QA within 30 days of the quarter end to determine if there were any trends developing which could be indicative of systemic problems.

Trends July 2021 - September 2021 and a number of deviation files were checked.

Corrective and preventive actions (CAPAs)
Corporate SOP "Corrective Action and Preventive action" and register for 2021 were checked.

The effectiveness/monitoring of implemented CAPAs was carried out by the initiator of respective department.

Self-inspection
SOP "Self-inspection" and self-inspection schedule 2021 were checked. SOP was applicable to all the departments at Lupin Ltd Nagpur, namely Production (Manufacturing & Packing), Quality Assurance, Quality Control, Validation, Technical Training, Warehouse, Engineering, Process Development, Packaging Development, Environment Health Safety (EHS), Information Technology, HR, and Administration. Self-inspection team and Quality Assurance were responsible for conducting the self-inspection. Non-conformances were classified as:

- Critical
- Major
- Minor/ recommendations

Self-inspection audit summary report QC and audit summary report QA were checked.

Supplier approval
Corporate) "Vendor Qualification" was checked. -

On-site audits and approval of vendors was carried out by corporate QA. Approved suppliers list was managed by SAP system.

According to the SOP each calendar year, site QA shall evaluate the performance of all the approved vendors. Annual evaluation was completed by the end of March, every year.

Vendor disapproval procedure was explained.

Technical agreement with manufacturer of raw materials was checked.
Documentation
SOP "Document Control" and SOP "Preparation, Review, Issuance and Control of Test Data Sheet" were checked. In case additional pages were issued request, forms were maintained by Head QC/designee.

Batch release
Site specific SOP "Batch Release of Drug Products" and batch release register 2021 were checked. Responsibilities were specified.

Batch numbering
Corporate SOP "Assignment of Batch Number, Manufacturing Date and Retest/Expiry Date" was checked. Batch numbers were automatically generated during process order creation in SAP system. In case one semi-finished batch was packed into multiple different packs; each different pack was assigned a unique batch number.

BMR/BPR
Corporate SOP "Preparation, Review and Approval of Batch Manufacturing and Batch Packaging Records" and BMR for Tenofovir Granules for Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (50mg/300mg/300mg) were checked.

Contract laboratories
SOP "Qualification of Contract Testing Laboratories" was checked.
According to the SMF no contract manufacturing was carried out.
According to the SMF ten (10) contract testing laboratories were used. Laboratories audits were performed by site QA/DQA.

Personnel

Number of personnel according to the SMF:

Department	No. of employees
Location Head	1
Accounts	1
Human Resource	6
Administration	2
IT	9
Engineering	46
Process Development	33
Production	325
Quality Assurance	81
Quality Control	192
Regulatory Affairs	10
Technical Training	3
Validation	7
Warehouse	51
Purchase	3
EHS	6
GSCO	3
Total	779

Corporate SOP "Training of Personnel" was checked. SOP was applicable to initial and ongoing technical training of new and existing employees at manufacturing and research sites of Lupin Limited. It covers both permanent and contractual staff. It is also applicable to the corporate employees who are involved in GxP activities.

Corporate "Analyst Qualification" was checked. According to the SOP, the Analyst Qualification is a process to evaluate proficiency of the analyst to satisfactorily perform analysis using specific analytical technique with desired precision. A qualification program was designed based on the job responsibilities.

Corporate SOP "Microbiologist Qualification" was checked. According to the SOP, the Microbiologist Qualification is a process to evaluate proficiency of the microbiologist to satisfactorily perform analysis using specific microbiological technique with desired precision.

Personnel Hygiene

SOP "Personnel Hygiene" was checked.

2. Production system

A virtual tour of the site was conducted, which included both Block 1 and Block 2.

The following areas were covered:

- Warehouse
- Manufacturing
- Utilities (Purified Water system and HVAC)
- Quality control laboratories

Process validation
Corporate SOP "Process Validation for Drug Products" was checked.
SOP explained following steps:

- Stage 1 – Process design
- Stage 2 – Process qualification
- Stage 3 – Continued process verification

Process Validation Protocol/Report for Tenofovir Granules for Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 50mg/300mg/300mg was checked.

Hold time studies
Corporate SOP "Hold Time Studies for Drug Products" and Hold Time Protocol for Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 200mg/300mg was checked.
Cleaning validation
Corporate SOP "Cleaning Validation for Drug Products" was checked. Cleaning validation approach:

- Cleaning validation using a bracketing
- Identification of worst-case molecule
- Establishment of MACO

Sampling methods:

- Swab
- Rinse

Cleaning verification can be done by visual inspection or visual inspection along with analytical verification.

The following was checked:

- "Cleaning Validation Master Plan of Nagpur, Unit-1, Block-1"
- "Dirty Equipment Hold Time Protocol and Report"
- "Cleaning Validation Protocol and Report of Tadalafil Tablets"

3. Facilities and equipment system
Equipment qualification/maintenance
The following SOPs were checked:

- Corporate SOP "Qualification Procedure for Analytical Instrument & Equipment"
- Corporate SOP "Qualification of Equipment. System and Facility for manufacturing/Packaging of Drug Products
- Corporate SOP "Validation of Computerized Software System"
- SOP "Calibration of Measuring Instruments"
- SOP "Calibration of Equipment/Instruments"
- SOP "Equipment Maintenance Program"
- SOP "Equipment Maintenance and Handling of Breakdown Maintenance of Instruments/Equipment

The following equipment qualifications were checked:

- "Periodic Requalification Protocol and Report - Equipment Fluid Bed Dryer
- "Installation and Operational Qualification Protocol/Report - Tablet Compression Machine
- "Requalification Protocol and Report - Metal Detector and De-duster
- "Periodic Requalification Protocol and Report - Equipment Blister Pack Machine

Utilities
HVAC
SOP "Environmental Monitoring (EM) of Production Premises by Settle Plate method" and EM trends checked. Frequency of plate exposure for 1 hour in production area was specified once in a month ± 5 working days.

Action and alert limits were specified.

EM trend data of production premises Block I and II for period January to June 2021 were checked.

SOP "Qualification/requalification of HVAC systems was checked. SOP was applicable to HVAC Qualification/requalification for AHU's, LAF's/ RLAF's and APU equipment's of Production, Warehouse, packing and QC/ Micro area and HEPA filters replacement procedure. HVAC systems qualification was performed by 3rd party.

Periodic Qualification Protocol of HVAC system and Periodic Qualification Report of HVAC system XX were checked.

Purified water system
Qualification (Block 2)

- Phase I 09/02/19 to 26/02/19
- Phase II 27/02/19 to 16/03/19
- Phase III 01 /04/2019) to 31 /03/2020

Summary reports of PW return loops A and B trends for December 2021 and were checked. All results were within specifications and below specified microbiological alert level.

Laboratory premises
A virtual tour of the laboratories was conducted, which included both the Chemistry and Microbiology laboratories.

4. Laboratory control system
OOS investigation records
Corporate SOP "Handling of Out of Specification Test Results", site specific SOP "Investigation of Out of Specification Results in Microbiology tests" and OOS registers chemistry and microbiology were checked. Phase I and Phase II investigations were applied.

In the event an OOS result is confirmed, and an assignable root cause is identified during investigation, the risk assessment impact was performed on other manufactured batches.

Trends July 2021 – September 2021 was checked.
A number of OOS investigation files were checked.

Out of Trends (OOT)
Corporate SOP "Trend Analysis of Quality Parameters and Out of Trend Investigation", OOT register 2021 were checked.

A number of OOTs were checked.

Trends JAN 2020 – December 2020 were checked.

Laboratory investigations

Corporate SOP "Handling of Laboratory Incidents" was checked.

A number pf laboratory investigation files were cjecked.

Chromatography

Corporate SOP "Good Chromatographic Practices and Documentation" was checked. SOP was applicable for good chromatographic practices and documentation of chromatographic data i.e., HPLC, UPLC, IC and GC in Quality Control Laboratories of Lupin Limited. Injection sequence was explained in detail. Manual integration was allowed only with prior approval from Manager/designee.

Reference materials

Corporate SOP "Procurement, Storage, Qualification and Handling of Analytical Standards was checked.. In-house reference standards were dispensed/filled in amber coloured glass bottles or vials and then stoppered/crimped (i.e., single-use vials).

Retention samples

Corporate SOP "Retention Sample Management" was checked. According to the SOP, retention samples were stored in their marketable packs or in the simulated market pack or more protective packaging than the marketed packaging system. The samples were stored in a secured area with limited access. Retention samples were stored for one-year after expiry or as per country specific regulatory agency guideline, whichever is the greater.

Analytical test sheets

Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg batch No XX, the following were checked:

- CoA (QA) Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg
- Sampling advice sheet of finished product
- CoA Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg
- Check list for verification of analytical data
- Finished product test data sheet
- Check list for review of analytical data of microbial enumeration tests and test for specified microorganisms in MB lab
- Balance print out sheets
- TLC scans
- Check lists for the review of analytical data from Chromeleon data base
- Injection sequence
- Chromatograms
- Dissolution calculation sheet
- pH test report
- Miscellaneous test data sheet
- Calculation sheet for related substances
- Column usage log
- HPLC usage log
- Instruments usage log
    - ✓ Analytical balance
    - ✓ Working & Impurity standard

SOP "Preparation, Review, Issuance and Control of Test Data Sheet" was checked. SOP was applicable for preparation, approval, issuance, and control of e-test data sheet (e-TDS) for those Materials/Products whose inspection lot are generated through SAP and issuance of Test data sheet (Manual) for recording of analytical raw data.

SOP "Quality Control Sample Management" and SOP "Receipt, Issuance & Usage of HPLC, GC and IC Columns" were checked.

Microbiology laboratory

The Microbiology Laboratory ran a 24-hour operation. Laboratory activities included the following:

- Media preparation (prepared in-house) and growth promotion testing
- Equipment preparation
- Calibration and qualification of equipment
- Handling and testing of samples
- Enumeration of micro-organisms
- Identification of micro-organisms
- Handling of reference cultures
- Calibration and qualification of equipment

The following SOPs were checked:

- SOP "Handling, Control and Qualification of Microbial Culture Media"
- SOP "Identification of Microorganisms
- SOP "SOP for Operation of HPHV Steam Sterilizer"
- Corporate SOP "Procedure for Handling of Ready to Use Lyophilized Form of Microbial Strains"
- Corporate SOP "Procurement and Maintenance of Microbial Cultures"

The following protocol reports were checked:

- "Temperature Mapping of Incubators"
- "Report for Periodic Revalidation of LAF Units and Bio Safety Cabinets"
- "Periodic validation report of HPHV Steam Sterilizer"

5. Materials system

A virtual tour of the warehouses was conducted.

The following documents were checked:

- Corporate SOP "Transportation study of Drugs Products"
- SOP "Receipt of Material in Warehouse"
- SOP "Storage, Traceability and Bin Codification in Warehouse Management System"
- SOP "Sampling, Release and Rejection of Raw Material". 100 % identity tests were performed for APIs and excipients, however in case of excipient, if there is information that manufacturer has "dedicated" facility for manufacturing of excipient and the manufacture's quality system checked by QA and found acceptable, in those cases the specification of respective excipients shall be revised to mentioned sampling plan as per $\sqrt{n}+1$ container for conducting both identification and rest of chemical test
- SOP "Dispensing of Packaging Materials"
- SOP "Dispensing of Raw Materials"
- SOP "Temperature/Relative Humidity Distribution Study of an Area"
- Transportation study report (via road and air) TSR/NGPl/002/00 Ethacrynic Acid Tablets USP 25 mg

6. Packaging and labelling system

The following documents were checked:

- SOP "Batch Reconciliation and Calculation of Yield"
- SOP "Sampling, Visual Inspection, Testing and Release of Packaging Materials". Sampling was carried out in accordance with AQL, general inspection level III. Defects were classified: Critical, Major and Minor

Part 3	Inspection outcome

Based on the areas inspected, the people met and the documents checked, and considering the findings of the inspection, including the observations listed in the Inspection Report ***Lupin Ltd (Nagpur) Buildings I and II, located at Plot No. 6A1, 6A2, Sector-17, Special Economic Zone, MIHAN, Nagpur, Maharashtra, 441 108, 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 an other 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/

3. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
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4. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4. ***Short name: WHO TRS No. 937, Annex 4***
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5. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3. ***Short name: WHO TRS No. 943, Annex 3***
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6. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1. ***Short name: WHO TRS No. 957, Annex 1***
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   http://www.who.int/medicines/publications/44threport/en/

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***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. Model guidance for the storage and transport of time-and temperature-sensitive 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 9. ***Short name: WHO TRS No. 961, Annex 9***
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http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10. ***Short name: WHO Multisource guidance*** or ***WHO TRS No. 996, Annex 10***
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