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Prequalification Team Inspection services
WHO INSPECTION REPORT
of the FPP manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Lupin Limited
Corporate address of manufacturer	Kalpataru Inspire, 3rd FLR, Santacruz (E), Mumbai 400055. (Maharashtra) India
Contact person	Mr. Gautam Pareek gautampareek@lupinpharma.com
Inspected site	
Address of inspected manufacturing site if different from that given above	A-28/1, MIDC, Industrial Area, Chikalthana, Jalna Road, Aurangabad 431 210, India
Unit/block/ workshop number	Rifa and Non-Rifa facilities Blocks 1, 2 and 3
Inspection details	
Dates of inspection	7-10 November 2017
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	The facility at Aurangabad was engaged in manufacturing of oral solid dosage forms, liquids, nasal solutions and powders for oral suspension.
General information about the company and site	The company was established in 1968 and its headquarters were located in Mumbai. It had 18 manufacturing facilities globally, including 5 API sites and 8 FPP sites in India. The Aurangabad facilities started their operations in 1978 and were located approximately 2 Km from Aurangabad airport. There were 3 manufacturing blocks on site. WHO prequalification products were manufactured in all 3 blocks.
History	This was the seventh WHO inspection since 2007. The last WHO inspection was carried out in June 2014. According to the company the site was inspected by US FDA in April and July 2017.

Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	**Document reviewed including but not limited** • Organization Chart • Job descriptions for key personnel • Personnel training and hygiene • Product Quality Review • Quality Risk Management • Responsibilities of the quality units and production • Complaints and Recalls • Deviation control and change control • CAPA procedure • OOS and investigation • Material release • Self-inspection and vendor qualification • Validation and qualification • Equipment calibration • HVAC and PW system • Data integrity • Sampling and testing of materials • Batch processing records • Materials management system • Purified water system **Site visited:** • Starting material warehouse • OSD Production operations (Blocks 1, 2, 3) • QC laboratories including chemical and microbiological • Controlled samples and Documentation area • Stability chambers area
Restrictions	The focus of the inspection included storage, production quality control areas where WHO prequalification products were manufactured
Out of scope	Products not submitted to WHO for Prequalification
WHO product numbers covered by the inspection	Dosage forms inspected included capsules and tablets

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
QA	quality assurance
QC	quality control
QCL	quality control laboratory

QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

PART 2

Brief summary of the findings and comments

Pharmaceutical quality system

A pharmaceutical quality system (PQS) was established, with Quality Manual, Policies and written procedures covering essential GMP principles for the site. A Corporate Quality Manual was available and was briefly reviewed during the inspection. PQS included both corporate and site specific procedures (operational procedures). Procedures that were reviewed and discussed during the inspection were generally presented promptly, however not all of these procedures were sufficiently detailed or satisfactorily implemented, and both procedure content and implementation had to be improved.

Product quality review (PQR)

A PQR procedure was in place describing the steps to verify consistency of existing processes, appropriateness of established specifications for starting materials, in process and finished products as well as monitoring trends. According to the procedure an annual program was issued and PQR had to be completed within 30 days from the date specified in the plan. Nevertheless it was noted that CAPA effectiveness was not adequately monitored and certain quality attributes were not appropriately trended and statistically analyzed.

Quality Risk Management (QRM)

A QRM procedure was presented. Fault Tree Analysis (FTA) was used for risk identification and FMEA was identified as the main tool for risk assessment. QRM was widely applied on all manufacturing operations including but not limited to change control and deviation management, production and complaints. The company had performed risk assessments on all WHO prequalified products. Risk assessment protocols and reports for several products were reviewed.

Change and deviation management

The company had procedures in place for change and deviation management. Deviations and changes were registered and managed in Quality Assurance Management System (QAMS). Changes were classified as permanent or temporary and as minor, or major. Deadlines for implementation of changes were monitored through the electronic system. Extensions were registered and approved electronically while effectiveness of the change was also assessed. Changes implemented in 2016 and 2017 were reviewed.

Deviations were categorized as major or minor followed by root cause investigations and relevant CAPA. According to the procedure deviations had to be closed out within 30 working days from the day of registration. Extensions were documented and could be granted upon justification. Whenever contractual agreements were in place the contract giver was notified and his approval was needed for major deviations. 2016 and 2017 deviation registers were presented and reviewed.

CAPA management

A CAPA management procedure was presented. CAPAs relating to deviations were registered and managed in QAMS. CAPAs relating to 2016 and 2017 deviations reported above were checked.

Investigation of Out Of Specification

OOS investigations were performed according to a written procedure which was used for both chemical and microbiological testing. OOS investigations were checked during PQR review and during the laboratory visit.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were generally described, and implemented. Manufacturing processes were defined and documented, though in certain cases with inadequate detail in BMRs and BPRs. Required resources were generally provided, including adequate premises, equipment and utilities. Appropriately qualified personnel were employed. Similarly to previous WHO inspections all areas visited during the inspection were generally clean, tidy and well-maintained.

3. Sanitation and hygiene

Premises and equipment were generally maintained at an acceptable level of cleanliness and they were appropriately labelled.

4. Qualification and validation

The key principles of qualification and validation program were defined and documented in the Validation Master Plan. This was a standalone document containing details on all validation/qualification activities including but not limited to equipment, utilities, processes and cleaning. It was noted that equipment re-qualification had to take place within six months of the due date. Re-qualification of mill and tablet compression machine and initial validation of new Capsule filling machine were reviewed. It was noted that standard equipment used in qualification was not always documented.

5. Complaints

The company had in place a procedure on registering, investigating and monitoring complaints. The 2016 and 2017 complaints were spot-checked

6. Product recalls

A procedure on product recall was available. The most recent mock recall was reviewed.

7. Contract production, analysis and other activities

The company had contracts in place with external laboratories for performing certain tests on APIs, excipients and FPPs. However according to the company all WHO prequalified FPPs and raw materials used in WHO prequalified products were tested by Lupin laboratories.

8. Self-inspection, quality audits and suppliers' audits and approval

A procedure for self-inspection, as well as an audit plan for 2017 was available. It was noted that the procedure became effective one day after it was approved not allowing sufficient time to train concerned personnel. The criteria for qualifying auditors were not detailed.

A vendor qualification procedure and a vendor audit management procedure were in place and critical excipient suppliers were audited every three years. An annual review of purchased and rejected batches was performed. Audit frequency could be shortened based on quality defects or regulatory authority actions (e.g. GMP non-compliance). However, under certain circumstances audits could be waived without sufficient justification or application of alternative measures to check GMP compliance of vendors.

9. Personnel

Organization charts were available though they reflected administrative structure rather than the workflow structure. In general personnel met during the inspection appeared aware of the basic principles of GMP. Job descriptions of the production manager and senior executives in Block 2, QC manager and warehouse head were reviewed during the inspection.

10. Training

A training procedure was in place and training records were maintained. Training sessions were evaluated. An annual training plan was presented

11. Personal hygiene

Personnel gowning procedure was appropriate and was generally followed. Instructions and pictorials to be followed were sufficiently clear when it came to personal hygiene. Spot checks on medical records of personnel were performed. It was noted that contract personnel was not undergoing the same extent of medical examinations as permanent personnel.

12. Premises

Storage areas for the warehousing of raw materials and finished product were of sufficient capacity. Temperature and humidity were monitored. However temperature mapping exercise was incomplete. Receiving and dispatch bays were separated and were protected from weather conditions. The warehouse was connected with the 3 manufacturing blocks through a corridor. Electronic and physical segregation were provided for the storage of rejected, recalled, and returned materials or products. Quality control laboratories were separated from production areas. There were also separate and dedicated areas for retained samples and for stability chambers.

13. Equipment

In general equipment was appropriate for the manufacture of solid dosage forms. It was noted that software on certain PLCs was old and it had limitations in terms of assigning individual access rights to operators and maintaining audit trails. However the company had carried out a risk assessment on concerned equipment and had implemented measures. Records for calibration, qualification and maintenance were available. Qualification of the PW system was reviewed as well as the monitoring report. Some discrepancies regarding passivation and sampling operations were identified.

14. Materials

There was a procedure in place describing receipt and storage of raw materials. A check list was used for receipt of raw materials. Material stock and status were managed via an electronic inventory system. A unique material code was assigned to each material in the system. Procedures for material sampling and dispensing were available. Temperature and Relative Humidity were monitored and controlled. A cold room was available.

15. Documentation

A documentation system was in place. The Quality Manual acted as an umbrella describing the basic quality principles and corporate as well as site procedures defined and supported manufacturing and quality control operations. In general documents were approved, signed and dated by appropriate responsible persons, reviewed and kept up to date. Specifications and testing procedures were available.

16. Good practices in production

A visit to production areas in Blocks 1, 2 and 3 was made. At the time of inspection there was production of tablets ongoing. Areas inspected included the dispensing areas, granulation, compression rooms, coating rooms and primary and secondary packaging areas. Product dedicated FBD filter bags were used and they were appropriately marked and stored. BMRs and BPRs of batches being manufactured during the tour were spot checked as well as maintenance and calibration of equipment. It was noted that certain challenge tests on equipment were not appropriately documented. These observations are included in Part 3

17. Good practices in quality control

Quality control laboratories were separated from production areas. Both chemical and microbiological laboratories were visited as well as the separate areas where stability chambers were installed. Receipt and allocation and reconciliation of samples followed established procedures and were appropriately documented. Data management was briefly reviewed, appropriate procedures were in place. GC and HPLC equipment was connected to a server and appropriate software was used. The primary server was located on site and a backup server was available off site. HPLC columns were stored in a dedicated cabinet and use was recorded. A list of standalone equipment was presented and it included UV-VIS as well as FT-IR. Retained samples were stored in a separate building where temperature was controlled. A separate area was dedicated to host 9 stability chambers and a cooling cabinet. Backup power supply was available and an alarm system in case of malfunction was installed. Stability protocols and results were reviewed.

Miscellaneous	
Samples taken	Nil
Assessment of the site master file	SMF was provided before the inspection and it did not give rise to any observations
Annexes attached	Nil

PART 3
Conclusion – inspection outcome

Based on the areas inspected, the personnel met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as the Corrective Actions taken and planned**, Lupin Limited Chikalthana**, **India** was considered to be operating at an acceptable level for compliance with WHO GMP guidelines.

All the non-conformances observed during the inspection that were listed in the full inspection report as well as those reflected in the WHO Public Inspection Report (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.