

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1	General information
Manufacturers details	
Name of manufacturer	Mylan Laboratories Limited
Corporate address of manufacturer	Plot No. 564/A/22, Road No.92, Jubilee Hills, Hyderabad-500096, Telangana, India.
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Mylan Laboratories Limited, Pithampur, Plot No 11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase II, Sector III, Pithampur, District Dhar, Madhya Pradesh, 454 775, India GPS Coordinates: 22. 63. 3914N 75. 61.9405E
Inspection details	
Dates of inspection	23 – 25 May 2018
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	The site manufactured Oral Solid Dosage Formulations (Tablets & Hard Gelatin Capsules).
General information about the company and site	Mylan Laboratories Limited is the Indian Subsidiary of Mylan Laboratories Inc., USA which is specialty Pharma company. Mylan Pithampur facilities are located at an industrial area in Indore Special Economic Zone and were originally owned by Unichem Laboratories Limited. The site was constructed in March 2012 and it was acquired by Mylan Laboratories Limited in 2013. Block A - Construction of additional warehouse, manufacturing and packaging areas along with required utilities were completed as a part of strategic capacity expansion plan. Adequate manufacturing and packaging equipment were installed in expanded area. This capacity expansion was initiated through change control. Similarly, a new area for quality control laboratories was established Part of Manufacturing Block A was separated and was transformed to Block B for manufacturing of OEB4 products. Block B was completed in 2017

History	This was the third WHO inspection. The site was inspected by WHO in October 2013 and in October 2014 respectively. The site was also inspected by the following authorities in the last three years		
	No	Authority	Date
	1	Medicines and Healthcare Products Regulatory Agency (MHRA)	August 2015
	2	Medicines Control Council (MCC), South Africa	September 2015
	3	The Licensing Authority, Food & Drug Administration, Madhya Pradesh, INDIA	November 2015
	4	United States Food and Drug Administration (USFDA)	February 2016
	5	Pharmacy, Medicines and Poisons Board (PMPB) Ministry of Health, Government of Malawi	March 2016
	6	Taiwan Food and Drug Administration (TFDA)	April 2016
	7	Central Drugs Standard Control Organization (CDSCO) & State Food and Drug Administration (FDA), MP State	August 2016
	8	ANVISA (BRAZIL)	August 2016
	9	Central Drugs Standard Control Organization (CDSCO) INDIA	September 2016
	10	National Drug Services Organization (NDSO) LESOTHO	October 2016
	11	ZAZIBONA [Collaboration between National Medicines Regulatory Authorities (NMRAs) in Botswana, Namibia, Zambia and Zimbabwe]	January 2017
	12	Pharmacy and Poisons Board (Kenya)	April 2017
	13	National Agency for Food and Drug Administration and Control (NAFDAG) Nigeria	April 2017
	14	Food and Drug Authority (FDA) Ghana	May 2017
	15	Central Drugs Standard Control Organization (CDSCO) & State Food and Drug Administration (FDA), MP State	January 2018
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 • Data integrity • Sampling and testing of materials • Batch processing records • Materials management system • Purified water system • HVAC system Site visited: • Starting material warehouse Rife Production operations • QC laboratories including chemical and microbiological
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 products covered by the inspection	Protionamide Tablet, Film-coated 250mg Lamivudine/Zidovudine Tablet, Film-coated 150mg/300mg Efavirenz Tablet, Film-coated 600mg Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 200mg/300mg Lamivudine/Nevirapine/Zidovudine Tablet, Film-coated 150mg/200mg/300mg Lamivudine/Nevirapine/Zidovudine Tablet, Dispersible 30mg/50mg/60mg Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 600mg/200mg/300mg Efavirenz/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 600mg/300mg/300mg Lamivudine/Zidovudine Tablet, Dispersible 30mg/60mg
Abbreviations	Meaning
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate

API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
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
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
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	Brief summary of the findings and comments (where applicable)
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1. Pharmaceutical quality system

A pharmaceutical quality system (PQS) was established, with Quality Manual, Policies and written procedures covering essential GMP principles for the site. The Quality Manual was prepared based on global company policies. Management Review meetings were held monthly in accordance with the relevant procedure. QA was responsible for compiling all data and information; and organize and maintain minutes of the meetings. PQS included both corporate and site-specific procedures. Procedures that were reviewed and discussed during the inspection were generally presented promptly, however a few of these procedures were not sufficiently detailed or satisfactorily implemented, and in some procedures both content and level of implementation had to be improved.

Product quality review (PQR)

Annual product quality reviews were performed according to a corporate SOP. PQRs were conducted annually on a rolling basis and QA was responsible approving the reports and monitoring the process which had to be completed within two calendar months from end of product review period. Ten WHO prequalified products were registered but only three products were manufactured. The PQRs were reviewed over two annual periods. The APR indicated an increase of laboratory deviations. The majority of OOS, were due to analysts' practices. These were addressed by analyst training and if required by re-qualification. Training was not regarded as CAPA.

Quality Risk Management (QRM)

A QRM procedure was available. It described in detail the principles for identifying different risks pertaining to product/ specific process, system, equipment and evaluate the impact on product quality, service and patient health. QRM was widely applied on all manufacturing operations including but not limited to change control and deviation management, production and complaints.

Change and deviation management

The company had a procedure in place for change management. The procedure adequately described the process for initiating temporary and permanent changes, defined roles, responsibilities and requirements for management of changes and tracking their effectiveness. Changes were registered and managed using a software program. An initial impact assessment had to be performed to evaluate the criticality of the

change and for critical and major changes a risk assessment was performed. Changes relating to new expansion area including new equipment and new AHU were reviewed

Deviations were categorized as planned and unplanned and they were categorized based on their criticality. Root-cause investigations were conducted and relevant CAPA were identified and implemented. Deviations were managed using a software program.

CAPA management

The same software was used to monitor CAPA implementation and assist in the assessment of CAPA effectiveness.

Investigation of Out of Specification

OOS investigations were performed according to a written procedure. Investigations were conducted in three phases. Phase 1 included evaluation and verification of test process and results. Phase 2 included evaluation of product through analytical testing as well as the process by which the product was manufactured. Phase 3 evaluated the sampling process as a mode of possible failure. OOS investigations were checked in detail 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 adequately defined and documented in BMRs and BPRs. Required resources were available, including adequate premises, equipment and utilities. Appropriately qualified personnel were employed. Similarly, to the previous WHO inspection all areas visited were generally clean, tidy and well-maintained. There were procedures in place for:

- Entry and exit from the warehouse,
- Operation and cleaning of the compression machine,
- Issue, cleaning and storage of tablet tooling,
- Handling of returned raw and packaging materials from production.

3. Sanitation and hygiene

Premises and equipment were generally cleaned according to established procedures. Change rooms were well maintained and authorized instructions displayed the steps and dress code. Cleaning records of manufacturing rooms and equipment were in place. Spot checks on rodent traps and insecticutors were made. Human resources were responsible for monitoring and controlling the third party providing pest control services.

4. Qualification and validation

The key principles of qualification and validation program were defined and documented in the Validation Master Plan. The VMP of the site addressed validation/qualification activities including but not limited to equipment, utilities, processes and cleaning, analytical methodology, vendors and computerized systems.

The expanded facility Block A was qualified and inter connected with the existing General Manufacturing Block A. New AHU qualification as well as the PW system qualification were checked. Qualification of the PW system was performed in three phases Phase 1 and Phase 2 included sampling from all user points for 30 days. Phase 3 included daily sampling of supply and return sampling points and the rest of the sampling points on a rotational basis, every 15 days. The duration was defined as one year and it was initiated in September 2017

5. Complaints

The company had in place a procedure on registering, investigating and monitoring complaints as well as on handling and disposal of non-conforming products. Risk assessment was carried out during the investigations and trend analysis was performed periodically to detect recurrence.

6. Product recalls

A product recall procedure was available. Mock recalls were documented and performed in accordance with the Recall SOP. Mock recalls were performed on an annual basis.

7. Contract production, analysis and other activities

The contract between Mylan and the third party installing the PW loop and performing passivation was reviewed.

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

Self-inspection was not reviewed in detail. A vendor management procedure was in place. Vendor evaluation was performed based on a quality questionnaire, evaluation of test results of samples as well as a vendor audit. API vendor audits were performed centrally by Global Operations Audit Team. Annual evaluation of vendors for raw and packaging materials was carried out. API vendors were audited every 3 years.

9. Personnel

Organization charts were available reflecting administrative structure. In general personnel met during the inspection appeared aware of the basic principles of GMP. Job descriptions of the Head of Quality (QA) and Senior Manager of Quality Control.

10. Training

Training of personnel was performed according to a written procedure. Respective head of department was responsible for grouping personnel together according to job profile and training needs. Training sessions were prepared based on a matrix in coordination with the training department. Training material was uploaded in a computerized system. Induction training was provided as well as job specific training. A procedure on training fixed term employees was also available. Training records of a qualified analyst were requested and promptly provided. Records indicated that induction training took place and a written assessment was available. Further to induction training, annual training related to GLP/GMP, good documentation practices, health and hygiene and data integrity was provided. Training and re-certification of analysts took place as part of CAPA following OOS results.

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. For new personnel including contract personnel, medical examinations were foreseen before joining the company and yearly afterwards Spot checks on medical records of personnel were performed.

12. Premises

In Block A construction of additional warehouse, manufacturing and packaging areas along with required utilities were completed as a part of strategic capacity expansion plan. Adequate manufacturing and

packaging equipment were installed in expanded area. Storage areas for warehousing of raw materials and finished product were of sufficient capacity. Temperature and humidity were monitored. Receiving and dispatch bays were separated and were protected from weather conditions. A new area for quality control laboratories was established. Part of Manufacturing Block was separated and was transformed to Block B for manufacturing of OEB4 products. Block B was completed in 2017.

13. Equipment

In general equipment was appropriate for the manufacture of solid dosage forms. Records for calibration, qualification and maintenance were available. Due to a new building extension, a PW distribution system was modified introducing new user points. Qualification of the system was reviewed.

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 SAP. 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.

15. Documentation

A documentation system was in place. 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. Some discrepancies in distribution of documents were identified but appropriate CAPA were applied.

16. Good practices in production

A visit to production areas was made. At the time of inspection there were ongoing production operations. Areas inspected included sampling booths, dispensing areas, granulation, compression rooms, coating rooms and primary and secondary packaging areas. In general production operations and documentation were under control and met GMP standards.

17. Good practices in quality control

Quality control laboratories were separated from production areas. Chemical laboratories as well as the microbiological laboratory were visited. The QC lab was well organized and equipped. Analytical equipment was installed in separate rooms and logbooks for use and maintenance of equipment were presented. Empower 3 software was used to network GC and HPLC equipment. Different roles and access rights were established. Reference and impurities standards were kept and their consumption documented.

Practices in Microbiological laboratory were also reviewed. Procedures and records for preparation of culture media, growth promotion and consumption of materials and reagents were spot checked.

Part 3	Conclusion – Inspection outcome
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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, ***Mylan Laboratories Ltd, Pithampur***, located at ***Plot No 11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase II, Sector III, Pithampur, District Dhar, Madhya Pradesh, 454 775, India*** was considered to be operating at an acceptable level of compliance with WHO GMP 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.

Part 4	List of GMP Guidelines referenced in the inspection report
	- 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 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/ - WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. Short name: WHO TRS No. 957, Annex 2 http://www.who.int/medicines/publications/44threport/en/ - WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2 Short name: WHO TRS No. 970, Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/ - 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 http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1 - Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8 Short name: WHO TRS No. 1010, Annex 8 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/ - 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

http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. 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. 961, 957), Annex 1

<http://www.who.int/medicines/publications/44threport/en/>

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2

Short name: WHO TRS No. 957, Annex 2

<http://www.who.int/medicines/publications/44threport/en/>

9. 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

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

10. 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

11. 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

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

12. 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

http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2

Short name: WHO TRS No. 961, Annex 2

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

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. **Short name: WHO TRS No. 981, Annex 2**
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
Short name: WHO TRS No. 981, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
Short name: WHO TRS No. 992, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
Short name: WHO TRS No. 992, Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5
Short name: WHO TRS No. 992, Annex 5
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
20. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6

Short name: WHO TRS No. 992, Annex 6

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5

Short name: WHO TRS No. 996, Annex 5

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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 TRS No. 996, Annex 10

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf