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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Manufacturers Details	
Company information	
Name of manufacturer and address	**Mylan Laboratories Limited (Unit-8)** G. Chodavaram, Poosapatirega Mandal, Vizianagaram District - 535 204, Andhra Pradesh, India. Latitude: 18°06'51.88" N Longitude: 83°34‘42.68" E D-U-N-S Number: 650438158
Corporate address of manufacturer	MYLAN LABORATORIES LIMITED Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad-500096 Telangana, India. Tel: + 91-40-30866666/23550543 Fax: + 91-40-30866699 Web: www.mylan.in
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Manufacturing blocks	MB-1, MB-2, MB-3, MB-4, MB-5, MB-6 (A and B wings), MB-7, MB-8, MB-9, MB-10, MB-11, MB-15
Manufacturing license number	Site is licensed by the Drugs Control Administration of Government of Andhra Pradesh under license No. 177/VN/AP/96/B/R
Inspection details	
Dates of inspection	3 - 6 October 2017
Type of inspection	Routine
Introduction	
Brief summary of the manufacturing activities	The manufacturer was involved in manufacturing, packaging, labelling, testing and storage of intermediates and active pharmaceutical ingredients (APIs).

General information about the company and site	The site was established in 1993, formerly known as Vera Laboratories Limited, acquired by Matrix Laboratories Limited in 2004; Matrix Laboratories Limited was acquired by Mylan Inc. USA in 2007. The site was renamed as "Mylan Laboratories Limited (Unit-8)" in 2011. The site is engaged in manufacturing of intermediates and APIs for domestic and international markets. APIs classify into various therapeutic categories like anti-retroviral, anti-inflammatory, muscle relaxant, anti-depressant, anti-viral, anti-psychotic, anti-urolithic, anti-arrhythmic, bone resorption inhibition, iron chelator, anti-histamine, anti-pyretic, PDE5-inhibitor, hyperphosphatasaemia, anti-convulsant, anti-hypertensive, osteoporosis, anti-Parkinson, anti-hypolipoproteinaemia, anti-ulcerative, anti-infective, smoking cessation agent. Highly potent drugs or cytotoxic substances were not manufactured at the site. Shared facilities were used (multiproduct manufacturing blocks, multiproduct equipment). The site had 11 manufacturing blocks. "Pharma" areas were used for final stages of production. <u>Main Activities:</u> Intermediates and APIs were produced by chemical synthesis; production processes involved steps of chemical reactions, crystallization, purification, filtration, drying, and, if requested by the customer, powder processing ("pulverization"). Production and in-process controls were organized in three shifts covering 24h.
History	The site has been inspected by the following authorities in the recent years:

Authority	**Date/s of inspection**	**Facility/block/unit covered by inspection**
BGV, Hamburg	January 2013	MB-11 & MB-15
COFEPRIS, Mexico	July/August 2013	All manufacturing blocks
COFEPRIS, Mexico	June 2014	MB-4 MB-9 MB-2 MB-5 & MB-6
WHO	September 2014	MB-1 MB-2 MB-3 MB-4 MB-6B

			MB-7 MB-8B MB-9 MB-10 MB-15
	USFDA	April 2015	MB-1 MB-3 MB-5 MB-10
	AGES, Austria	December 2015	MB-11
	PMDA, Japan	May 2017	MB-11
	ANVISA, Brazil	July 2017	MB-9 MB-4 MB-1
	USFDA	August 2017	MB-6
Brief report of inspection activities undertaken			
Scope and limitations			
Areas inspected	• Pharmaceutical Quality System • Documentation system • Production System • Facilities and Equipment System • Laboratory Control System • Packaging and labeling system		
Restrictions	Inspection was focused at manufacture and quality control of APIs currently under WHO assessment: APIMF 290 Sofosbuvir APIMF 327 Daclatasvir dihydrochloride.		
WHO product numbers covered by the inspection	APIMF 290 Sofosbuvir APIMF 327 Daclatasvir dihydrochloride APIMF 010 Abacavir sulfate APIMF 038 Tenofovir disoproxil fumarate APIMF 039 Emtricitabine for intermediate APIMF 065 Ritonavir Form-II APIMF 069 Lamivudine APIMF 071 Efavirenz APIMF 072 Zidovudine APIMF 095 Atazanavir (sulphate)		

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
AQL	Acceptance quality limit
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
FG	finished goods
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatography
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatography
HVAC	heating, ventilation and air conditioning
ID	identity
IR	infrared spectrophotometer
IPC	In process control
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
NIR	near-infrared spectroscopy
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency

OQ	operational qualification
PHA	preliminary hazard analysis
PM	preventive maintenance
PpK	process performance index
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
RH	relative humidity
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SOP	standard operating procedure
STP	standard test procedure
T	temperature
TAMC	total aerobic microbial count
TFC	total fungal count
TLC	thin layer chromatography
TMC	total microbial count
TOC	Total organic carbon
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
WFI	water for injection
WS	working standard

Part 2	Brief summary of the findings and comments (where applicable)

Brief summary of the findings and comments

1. Pharmaceutical quality system

The quality management system was generally well established, documented and implemented; the system encompassed organizational structure, procedures and processes. QA and QC departments were independent of production. In general, deviations from established procedures were documented and explained. Procedure was in place for notifying responsible management of regulatory inspections, serious GMP deficiencies, product defects and related actions.

Traceability of records and documentation system were satisfactory.

TrackWise system was used for:

- Incidents
- Change controls
- OOS/OOT investigations
- Complaints investigation
- CAPA tracking

Product Quality Review (PQR)

The corporate SOP "Annual product review / product quality review" was discussed. The PQR covered but was not limited to:

- Intermediate / API manufacturing overview
- Review of packaging materials
- Review of API starting materials
- Review of intermediate manufacturing
- Final API review
- Process capability determination
- Review of manufacturing supporting systems
- Review of status on DMF deficiencies
- Review of pending CAPA or other action items from previous PQR
- Final conclusion / recommendations.

PQR was performed annually and according to the SOP should be completed by the end of February of the following year.

Process capability was evaluated by statistical process control (SPC) by Cpk, using Minitab software. According to the SOP, Cpk value 1.33 and above indicates that the process is performing in a good state of control; Cpk between 1.00 and 1.33 indicates a state of control.

Annual product review /product quality review for Sofosbuvir, Daclatasvir dihydrochloride and Abacavir Sulphate were reviewed.

A review on "Equipment Qualification, Supporting System – Water and Compressed Air" was reported in "Annual Review of Manufacturing Supporting Systems".

Quality risk management (QRM)

The corporate SOP "Quality Risk Management" was discussed. The tool used by the Company was FMEA. RPN was based on:

- Severity: Fundamental, High, Moderate, Minor and Insignificant
- Detection: Not aware / No control exists; Nonexistent / Very little chance of detection; Not effective / Likely to be detected; Effective / Very likely to be detected; Very effective / 100% likelihood of detection
- Occurrence: Almost certain, Likely, Possible, Unlikely, Rare

Based on the procedure, the risk assessments were to be reviewed every 3 years and an annual plan was established 'Annual Schedule of Quality Risk Management Reports Year: 2017'.
Risk assessments for Sofosbuvir and Daclatasvir dihydrochloride were conducted based on product manufacturing process and were discussed.

Deviations (Incidents)

The corporate SOP "Handling and investigation of incidents / deviations", its flow chart and register were discussed. According to the SOP incidents / deviations were classified as:

- Minor
- Major
- Critical

and regarding product impact as:

- Severe
- Major
- Medium
- Minor
- Negligible

According to the SOP, the following tools were used to establish root cause:

- 5 Why`s (used for human errors)
- Ishikawa diagram
- Cause / effect diagrams

Incidents / deviations were classified by Quality Assurance Department (QAD) personnel.

A number of deviation investigation reports were discussed. Incidents were trended quarterly, trends for 2017 were presented to inspectors.

Corrective actions and preventive actions (CAPA)

The corporate SOP "Corrective and preventive actions with effectiveness check", flow chart and register for 2017 were discussed. The procedure was applicable but not limited to:

- Deviations
- OOS/OOT
- Validation /qualification
- Complaints
- Recall
- Self-inspection/external inspection
- Risk assessment
- Returns
- Management review

According to the SOP, CAPAs were proposed by cross functional team. CAPA implementation was monitored by QAD personnel.

CAPAs related to the incidents mentioned above were discussed.

Change control (CC)

The corporate SOP "Change management process", change approval flow chart and registers for 2016 and 2017 were discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017) and harmonized in line with Mylan Global Policy. Impact assessment and risk assessment was applied to CC. CCs were classified as:

- Minor
- Major
- Critical
- Temporary
- Permanent

CC effectiveness checks were performed after a defined period of time to ensure implementation was satisfactory. CCs were trended quarterly, trends for 2017 were discussed. No critical CCs were recorded in 2017.

A number of CCs were discussed.

Management review (MR)

The corporate SOP "Management review" was discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017) to include review of data integrity issues during management review. According to the SOP, management reports were prepared monthly. The following items were to be covered:

- Self-inspection
- Audits
- Validation status
    - Process validation
    - Cleaning validation

  - Equipment validation / qualification
  - computer system
- Technical agreements
- Training
- Preventive maintenance of the equipment
  - Production
  - Quality control
- Calibration of equipment
  - Manufacturing
  - Quality control
- Documentation
- Quality incidents
- CAPA
- CC
- Analytical investigation reports
- OOS
- OOT
- Rejections
- Reprocessing
- Stability
- Recalls / withdrawal
- Health authority notifications
- Complaints
- APQR/PQR

According to the SOP, QAD shall forward the summary report to Head Corporate Quality. Head Corporate Quality shall review the summary report and provide guidance when required.

Last management monthly report – site and minutes of meeting were presented to inspectors.

Complaints

The corporate SOP "Handling of customer complaints", its flow chart and register were discussed. Designates person from site QAD was responsible to log the complaint in the TrackWise system. Complaints were classified as:

- Critical
- Major
- Minor

Site Quality Head was responsible for complaint investigations.

Trends for 2016 and 2017 were presented to inspectors. A number of complaint investigation reports were discussed.

Recalls

The corporate SOP "Product recalls" was discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017) to include risk based mock recalls. There were no product recalls in the site history. Recall effectiveness was evaluated by mock recall. Site Quality head was responsible for recall on the site level. Recalls were not classified.

According to the SOP, a mock recall should be performed once in three years.

Self-inspection

The corporate SOP "Internal quality audit" and schedule for 2017 were discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017) to include internal quality audit training, report preparation, categorization of observations. The new version of the SOP was effective from 29.09.2017. The following departments were under self-inspection program:

- Stores
- Manufacturing
- Solvent recovery plant
- Engineering
- Quality control
- Quality assurance
- Personnel & administration
- Information technology

The following new attachments to the SOP were discussed:

- Internal audit (self –inspection) training module
- Department wise check lists
- Internal auditor qualification form for new auditor
- Internal auditor certification form
- Template for internal audit report
- Internal audit summary report
- Template for internal audit response report

Internal audits following the revised procedure were to be executed from October 2017.

Quality Assurance Department internal audit (self-inspection) training module was discussed.

Supplier qualification

The corporate SOP "Vendor approval", its flow chart and vendor audits schedule for 2017 were discussed. Vendors were identified by supply chain management. For new vendors the following procedure was applied:

- Questionnaire – evaluated by the site QA
- Vendor route of synthesis reviewed by R&D and RAD
- Route of synthesis accepted
- 3 different batches sampled, CoA and filled questionnaire
- Testing of samples and documentation evaluation

- Laboratory performance by chemical research and development; if passed, a provisionally approved status was given
- The vendor was approved after successful completion of validation and vendor audit.

According to the SOP, all key starting material (KSM) vendors should be audited once in 3 years. Audits were performed by Corporate QA.

Approved suppliers list was maintained in SAP system. Approved suppliers list for KSM and packaging materials was presented to inspectors. Adding of a new class A suppliers was performed via change control procedure. According to the SOP, class A supplier audits should be performed every two years. Supplier audits were performed by Mylan Corporate, audit schedule for 2016 & 2017 was presented to inspectors.

Profile folders were maintained for each supplier; annual supplier-specific quality reviews were conducted.

Vendor audit report and compliance report of XX was discussed.

Personnel

The current organization chart of the company was available. The company had sufficient number of personnel with responsibilities according to their respective unit and department. Personnel were wearing suitable clothing for the manufacturing activities.

According to the Company presentation, the site employed approximately1072 full time employees.

The SOP “Contract helper management” and “Basic GMP, personal hygiene & clean room practices” training module were discussed. Training module was in English and local language. Helper’s classroom training records were presented to inspectors.

The corporate SOP “Training of employees” and its flow charts were discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017) to include University program introduced for training of employees in Myuniversity.

The corporate SOP “Training work flow in Myunivertity” was discussed. This SOP was introduced after Mylan Unit 9 inspection in July 2017. Myuniversity was an on-line learning program. The program was applicable for employees working in all Mylan API sites. Training effectiveness was evaluated.

Myuniversity training of Mr. XX was discussed.

The corporate SOP “Qualification of analysts” and its flow chart were discussed. According to the SOP, an analyst shall be qualified after joining, as per allotted job role(s) and prior to performing new techniques. Re-qualification of analysts was done once in three years. Analysts were given a previously approved sample to analyze, results were compared. RSD values for triplicate tests were specified.

Mr. XX re-qualification for residual solvents by GC raw data was discussed.

Job description of Mr. XX, executive QA was discussed and Mr. YY, deputy manager QC were discussed.

2. Documentation system

Documentation system was generally well established.
Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved and distributed according to written procedures. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories. Electronic document management system was maintained by Corporate.

Production, control and distribution records were retained for one year after the expiry date of the batch. For APIs with retest dates, records were retained for three years after the batch was completely distributed. Specifications were established for raw materials, intermediates and APIs. The Company had a policy to archive logbooks and other documents.

The corporate SOP "Preparation, issue, review and archival of MBPRs" "Handling of Returned Goods" were discussed.

3. Production system

In general, production operations followed defined procedures. Process flows (with IPCs) and routes of synthesis were available. Deviations from procedures were recorded; major deviations were investigated. Access to production premises was restricted to authorized personnel. Weighing and measuring devices were of suitable accuracy for the intended use.

Inspection was focused at facilities and equipment used for manufacture of Sofosbuvir and Daclatasvir dihydrochloride APIs (currently under WHO assessment).

Closed systems were used for material transfers from reactors to centrifuges. Manual operations were also applied, e.g. uploading materials from centrifuges, drying and packaging.

The corporate SOP "Batch numbering system" was discussed. A register was kept for the issuance of Master Batch Production Records.

SAP was used to track the history of final batch (e.g. reprocessed batch number might not be the final batch number, in case powder processing/pulverisation was performed after reprocessing).

Blending of finished API batches was not performed as stated by the Company. Mylan Corporate level SOP on blending was available.

<u>Reprocessing and Reworking</u>

The corporate SOP "Reprocess" was discussed. The reprocessing was to be conducted only once and initiated through Change Control. Reprocessed batch records were created.

The corporate SOP "Rework" was discussed. Based on the procedure, for any decision for reworking, the changes in the manufacturing process should be validated. Rework log register was maintained.

The corporate SOP "Management of recovered solvents CMUs (contract manufacturing unit)" and "Recovery of solvent management" were discussed. CMUs were audited annually by Corporate QA. Corporate QA also performed monthly visits to CMUs to ensure ongoing activities are performed in cGMP compliant manner. According to the procedure, recovered solvents were used in the same stage of synthesis or previous stage.

Contracts

Quality agreement for contract manufacturer XX and audit report were discussed. The agreement was for recovery, packaging, testing, storage and release of solvents.

Material management

Materials were managed by SAP system. SAP system was re-validated globally every two years. There were two raw material warehouses. Raw materials were sampled under RLAF. Separate warehouses were provided for storage of primary, secondary packaging materials, solvents in drums, carbon, toxic materials and corrosive materials. There were two tank farms: for explosive and for non-explosive solvents.

Samples were taken from tankers; after release solvents were transferred to the storage tanks. New solvent was mixed with solvent in the tank and samples were again analysed.

Solvents in drums were sampled in dedicated rooms. Sampling rooms were supplied with 100% fresh air, filtered via F9 filter.

Sampling of starting materials was performed by QC according to a documented sampling plan.

Process Validation

Process validation and process verification were covered by Mylan Corporate documents "Process Validation" and "Validation Master Plan". Based on the VMP, equipment routine requalification was to be conducted every 5 years for direct contact equipment.

Hold time studies for intermediates were initiated within the validation.

Continuous process verification was addressed in the "Process Validation" SOP. Verification reports were drawn quarterly.

Cleaning Validation

Cleaning procedures were established on the site level. The site had created matrices of equipment trains and APIs / intermediates, and had assessed solubility.

Centrifuge bags were stated to be disposable, discarded upon the end of production campaign.
Cleaning of process pipelines had been addressed.

4. Facilities and equipment system

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups and contamination.

Permanently installed pipework was appropriately identified. Solvent pipelines had different colour codes.

Equipment status boards indicated calibration status with due dates and preventive maintenance due dates. Equipment was identified as to its contents and cleanliness status. On spot checks in MB-6B, process pipelines were labelled.

Calibration and preventive maintenance schedule was managed in SAP. Calibration schedule of calibration master instruments was maintained separately (as a legacy system). Check-lists were available for preventive maintenance; the Company stated that change control was applied for changing check-lists.

The corporate SOP "Temperature mapping study" was discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017).

T mapping of cold storage room (2 °C to 8 °C) was discussed.

Utilities

PW was used for production and for cleaning of equipment and tools. The system had 3 distribution tanks and 8 loops. Storage tanks and loops were made from stainless steel 316 L. PW was in continuous circulation. Conductivity and flow rate on the return loops were checked on-line. Designed flow rate NLT 1.2 m/sec. PW storage tank and loops were sanitized every 15 days using 80 – 85 °C water for 30 minutes. PW system appeared to be well maintained. Samples form return loops were analysed daily. Action and alert levels for total aerobic microbial counts were specified.

MB-6 "pharma" rooms were serviced by XX air handling units. Air was re-circulated, apart from the washing room which was stated to be supplied by 100 % fresh air.Filter cascade: G3 → G4 →F9; HEPA filters H13 were installed terminally. Pressure differentials between G3 and G4 and G4 and H13 were monitored. Technical areas for AHUs were in an acceptable state.

Nitrogen was produced on-site and stored in the compressed gas form. Oxygen monitoring was done on-line. Nitrogen production was not followed up during this inspection.

Oil free compressed air was used in contact with product. Final filter: 0.01 micron. Compressed air production was not followed up during this inspection.

Chemical and microbiological tests on compressed air and nitrogen were performed every six months by contractors.

Environmental monitoring (EM)

Settle plates were used to monitor "pharma" rooms. Trending of results was arranged. 4 hour exposure time was recently validated.

Laboratory premises
Laboratory areas and operations were separated from production areas.

3 quality control laboratories were operating on site:
- QC I – analysis of raw materials, intermediates and in-process samples
- QC II – analysis of finished products and stability samples
- QC III – dedicated to in process analysis for manufacturing block MB X and MB XI

Computer System
Empower 3 validation had been discussed during Unit 9 inspection in July 2017. The same procedure was applicable for all Mylan Units.

Risk assessment was conducted unto the system based on severity impact tools, which were further categorized as:
- Likelihood of impact
- Severity of impact
- Mitigation Control

The corporate SOP "Empower-3 Chromatography operation" was discussed. Privileges were assigned to the five user types.

Back up data
All on-line laboratory data through the Empower 3 system was to be backed up daily, weekly and annually. The corporate "Empower 3 Data Backup, Restoration and Verification" was discussed. Hot (daily) back up and cold back up (weekly) was performed automatically. Monthly back up was taken on external storage media by IT personnel.

5. Laboratory control system

Quality control appeared to be adequately organized and equipped.

In process control (IPC) tests were performed in Quality control laboratory by dedicated analyst group working in 3 shifts.

All HPLC and GC workstations were equipped with Empower 3 software and networked.

The corporate SOP "Release of intermediates and active pharmaceutical ingredient (API) to customer" was discussed. Check-list was used for product release. Batch production records review check-list was discussed. Analytical raw data e.g. injection sequence was reviewed in LIMS by QC reviewers. All analysis system audit trials and project audit trails were reviewed by QA reviewers once in a month.

The corporate SOP "Quality control of raw materials and packaging materials" was discussed. 100 % identity test was performed for all KSM. Identity tests were performed in the QCL using NIR. The SOP "Procedure for operation, calibration and data management of near infrared spectrophotometer" was discussed.

Primary packaging materials were sampled according to the AQL inspection level II. Defects were classified as:

- Critical (AQL 0.025)
- Major (AQL 0.4)
- Minor (AQL 1.0)

OOS (out of specification) results were covered by Mylan Corporate procedures "Investigation of out of specification (OOS) results" and "Investigation of out of trends (OOT) analytical results". UK MHRA guide had been taken as a basis for OOS investigations.

A number of OOS cases were reviewed during the inspection.

TrackWise was used to track individual OOS cases, with indication to the stage of investigation.

The corporate SOP "Management of reference and working standards (WS)" and its flow charts were discussed. The SOP had been revised after Mylan Unit 9 inspection (July 2017) to include procedure for intermediate working standard storage and handling. According to the SOP, WS were qualified against pharmacopeia reference standards (RS). Purity of the candidate substance should be NLT 99.0%. WS were dispensed in 14 amber vials; one vial was for one month use. Dispensing was performed under LAF. In case RS were not available, in-house reference standards were prepared.

Excel sheets were used for assay and impurities calculations. The procedure corporate SOP "Preparation, validation and use of Ms-Excel calculation sheets" was discussed. Validated Ms-Excel sheets were verified once in three years; verification schedule was presented to inspectors.

Certification of Ms-Excel calculation sheet validation protocol and report XX for residual solvents was discussed.

API reserve samples were retained for one year after the expiry date and stored in the same packaging system in which the API was stored. Reserve samples for APIs with retest dates were retained for three years after the batch was completely distributed.

The corporate SOP "Procedure for Stability study of Drug substance (API)" was discussed. Four types of stability studies were specified and performed for products under prequalification:

- Accelerated 40 °C ± 2 °C / 75 % RH ± 5%
- Intermediate 30 °C ± 2 °C / 65 % RH ± 5%
- Long term 25 °C ± 2 °C / 60 % RH ± 5%
- Alternative long term 30 °C ± 2 °C / 75 % RH ± 5%

One batch per year was placed on on-going stability studies. According to the procedure, stability samples should be tested within + 15 calendar days for accelerated stability testing and within + 30 calendar days for intermediate and long term and on-going stability testing from the scheduled date. Stability samples inward CUM planned register was checked. Cross-checks showed that the stability schedule was followed. In the QC there was a separate group who managed stability studies.

The corporate SOP "Skip/reduced testing" was discussed. The procedure was applicable to raw materials, packaging materials, intermediates, mixed solvents, recovered solvents and API individual batches.

Abacavir sulfate, batch XX analytical data raw sheets were cross checked with analytical metadata, instruments usage log books, standards usage log books and instrument calibration records. No discrepancies were observed during the cross checks.

6. Packaging and labelling system

Packaging and labelling operations were not carried out during the inspection. APIs were said to be labelled in finished good warehouse by production personnel in the presence of QA personnel.

The corporate SOP "Generation of labels through SAP" and SOP "Release of intermediates and active pharmaceutical ingredient (API) to customer" were discussed. Finished product labels were printed by designated QA personnel using dedicated computer and label printer.

PART 3

CONCLUSION

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection including the observations listed in the Inspection Report, Mylan Laboratories Limited (Unit-8, manufacturing blocks MB I, MB II, MB III, MB IV, MB V, MB VI, MB VII, MB VIII, MB IX, MB X, MB XI & MB XV) G. Chodavaram, Poosapatirega Mandal, Vizianagaram District - 535 204, Andhra Pradesh, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for active pharmaceutical ingredients 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 used for assessing compliance

1. 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/

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
   Short name: WHO TRS No. 986, Annex 2

3. 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

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six 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/

5. 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

6. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   Short name: WHO TRS No. 961, Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

7. 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

8. WHO Good Practices for Pharmaceutical 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
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