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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the FPP manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Mylan Laboratories Ltd (Waluj)**
Corporate address of manufacturer	Mylan Laboratories. Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad – 500034 Direct: +91 40 3086 6028 Phone: +91 40 3086 6666 Fax: +91 40 3086 6699
Inspected site	
Address of inspected manufacturing site if different from that given above	Plot No H-12 and H-13, MIDC, Waluj Industrial Area Aurangabad- 431 136 Maharashtra, INDIA latitude - 19.839910200000000000. longitude - 75.236238100000030000. DUNS Number: 863996098
Unit / block / workshop number	Finished dosage form manufacturing unit
Manufacturing license number	License from Food and Drug Administration Maharashtra State, India: • Form 25 No. AD/089 & Form 28 No. AD/064 granted on 28.12.2010 & valid up to 27.12.2020 to manufacture the Tablet and Hard gelatin capsules dosage forms. • Form 25F No. 25F AD/003 granted on 29.03.12 valid up to 25.03.2017 for Schedule X drugs
Inspection details	
Dates of inspection	12 – 15 July 2016
Type of inspection	Routine
Introduction	
Brief summary of the manufacturing activities	Manufacture including production, quality control and release of: • Tablets – uncoated, film coated and dispersible • Capsules hard
General	Mylan Laboratories Limited is the Indian subsidiary of Mylan Inc., USA.

information about the company and site	Mylan Inc., USA was founded in 1961 and has Corporate Headquarters at Pittsburgh, Pennsylvania, USA. Mylan Inc. has primary businesses in following areas: • generic pharmaceuticals and branded generic formulations • specialty and brand pharmaceuticals • active pharmaceutical ingredients (API) Mylan Inc., USA has 4 finished dosage form units and 9 API sites in India. Mylan Laboratories Limited, India was founded in 2007 by acquiring Matrix Laboratories. Mylan Laboratories Limited, India has its Corporate Office located at Jubilee hills, Hyderabad India. R&D center is located at Bollaram, Hyderabad, India. Mylan Aurangabad (Waluj) site manufactures non-sterile unit dosage forms: tablets and capsules. The site consists of: solid dosage forms manufacturing facility; warehouse for raw materials, packaging materials and finished products; building for organic solvents; quality control and quality assurance block; engineering and utility section. The inspected finished dosage form manufacturing unit is located at H-12 & H-13, MIDC Waluj, Aurangabad. This unit was constructed in October 2008 and was purchased by Mylan from M/s. Atra Pharmaceuticals Pvt. Ltd in September 2010. The finished dosage forms (tablets and capsules) manufacturing unit is on a 36,000 sq. meter plot. No mutagenic, immuno-suppressant, teratogenic, toxic or hazardous substances are used / manufactured in this facility.
History	The site was last inspected by WHO in May 2013. The site has also been inspected by the following regulatory authorities: • USFDA o January 2012 o May 2014 • MCA-Zimbabwe - June 2012 • TFDA (Tanzania) – December 2012 • NDA Uganda – March 2013 • PPB Kenya – April 2013 • MHRA-UK o June 2013 o September 2015 • FDA-GHANA – June 2013 • MCC-South Africa – October 2013 • CDSCO India

<table>
<tr><td></td><td>

o December 2014
o January 2014
o March 2016

Congo – May 2014

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<tr><td>Brief report of inspection activities undertaken</td><td></td></tr>
<tr><td>Scope and limitations</td><td></td></tr>
<tr><td>Areas inspected</td><td>Finished dosage form manufacturing unit</td></tr>
<tr><td>Restrictions</td><td>N/A</td></tr>
<tr><td>Out of scope</td><td>N/A</td></tr>
<tr><td>WHO product numbers covered by the inspection</td><td>
<table>
<tr><th>PQP Number</th><th>Product</th><th>Strength</th><th>Dosage Form</th><th>Applicant</th></tr>
<tr><td>IN009</td><td>Oseltamivir (phosphate)</td><td>30mg</td><td>Capsules, hard</td><td rowspan="24">Mylan (R+D Centre Bollaram and Corp</td></tr>
<tr><td>IN010</td><td>Oseltamivir (phosphate)</td><td>45mg</td><td>Capsules, hard</td></tr>
<tr><td>IN011</td><td>Oseltamivir (phosphate)</td><td>75mg</td><td>Capsules, hard</td></tr>
<tr><td>TB285</td><td>Isoniazid (under assessment)</td><td>300mg</td><td>Tablet</td></tr>
<tr><td>TB304</td><td>Cycloserine Capsules (under assessment)</td><td>250mg</td><td>Capsules, hard</td></tr>
<tr><td>HA396</td><td>Nevirapine</td><td>200mg</td><td>Tablet</td></tr>
<tr><td>HA403</td><td>Efavirenz</td><td>600mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA414</td><td>Lamivudine/Tenofovir disoproxil (fumarate)</td><td>300mg/300mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA417</td><td>Emtricitabine/Tenofovir disoproxil (fumarate)</td><td>200mg/300mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA426</td><td>Lamivudine/Nevirapine/Zidovudine</td><td>150mg/200mg/300 mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA444</td><td>Efavirenz/Emtricitabine/Tenofovir disoproxil (fumarate)</td><td>600mg/200mg/300 mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA466</td><td>Efavirenz/Lamivudine/Tenofovir disoproxil (fumarate)</td><td>600mg/300mg/300 mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA477</td><td>Atazanavir (sulfate)</td><td>300mg</td><td>Capsules, hard</td></tr>
<tr><td>HA478</td><td>Atazanavir (sulfate)</td><td>150mg</td><td>Capsules, hard</td></tr>
<tr><td>HA501</td><td>Lamivudine/Tenofovir disoproxil (fumarate) + Nevirapine</td><td>300mg/300mg + 200mg</td><td>Tablet</td></tr>
<tr><td>HA572</td><td>Lamivudine/Zidovudine</td><td>30mg/60mg</td><td>Tablet, Dispersible</td></tr>
<tr><td>HA612</td><td>Fluconazole</td><td>50mg</td><td>Tablet,</td></tr>
<tr><td>HA613</td><td>Fluconazole</td><td>200mg</td><td>Tablet,</td></tr>
<tr><td>HA614</td><td>Clarithromycin</td><td>500mg</td><td>Tablet, Film coated</td></tr>
<tr><td>HA625</td><td>Acyclovir (under assessment)</td><td>200mg</td><td>Tablet</td></tr>
<tr><td>HA626</td><td>Acyclovir (under assessment)</td><td>400mg</td><td>Tablet</td></tr>
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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
FG	finished goods
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
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
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
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer
VMP	Validation Master Plan
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

Principle

In general PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release; regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

QMS system consisted of the following elements:

- Validation and qualification
- Procedures (SOP) / documentation
- Change management
- Self-inspection

- Vendor management
- PQR
- CAPA management
- In-process QA / batch release
- Training development

Quality Risk Management

The SOP "Risk management" was discussed. Cross functional team was responsible to carry out the risk assessment activities:

- Conducting RA
- Identification of potential risks
- Identification of risks which should be controlled
- Recommendations for CAPA and tracking of CAPA
- Impart training to the concerned

Risk management activities were approved by Head QA /designee. FMEA was the main tool used for RA. Rating from 1-5 was used to define risk priority numbers (RPN). Other tools specified in the SOP were:

- FMECA
- FTA
- HACCP
- HAZOP
- PHA
- Risk ranking and filtering
- Supporting statistical tools

Risk numbering log for 2015 and document "Risk management manual" were presented to the inspectors. RAs were process / activity based. Product related RAs were carried out during process development, before process validation and commercial manufacturing operations. According to the "Risk management manual", RA shall be re-evaluated / reassessed every two years or due to regulatory changes / retrospective review.

RA "Efavirenz/Lamivudine/Tenofovir disoproxil (fumarate) 600mg/300mg/300mg Tablet, Film coated" was discussed. RA was carried out starting from shifting process.

RA "Dry granulation" and "Coating" were discussed.

Product Quality Review (PQR)

The SOP "Annual product quality review" was discussed. The SOP was applicable to all products. PQR was carried our as per yearly (month wise) schedule. PQRs were conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. In case products were not manufactured during review period PQRs were performed to cover complaints, stability studies etc.

Analytical results were presented as trends: tabular and graphical.

Process capability was calculated using CpK index.

CpK < 1.00	Process is not capable
CpK between 1.00 and 1.33	Process is marginally capable
CpK > 1.33	Process is capable

Several PQRs were reviewed and were to be comprehensive.

Management review

The SOP "Management review and tracking and trending of data" was discussed. According to the SOP MR shall be performed weekly / monthly / quarterly. MR committee was led by the Site Head and Head QA. MR committee consisted of members of each department. MR meetings outcome was recorded in the MR minutes and signed by committee members.

Deviations

TrackWise software was used to maintain documentation on deviations and incidents. The SOP on "incident reports" covered deviations in production, engineering, warehouse and Quality Assurance. MIR (manufacturing investigation reports) – were opened in Trackwise. Information was stored on Mylan Global level. "Child-reports" could be created for various aspects of a case. Final closing was blocked until child-reports were open. Investigation reports examined during the inspection contained sufficient information for traceability. In a couple of reviewed cases root cause had not been clearly described in the relevant section of documentation, but considering all the information recorded about the case, this did not trigger a GMP deficiency.

Corrective and preventive action

The SOP "Corrective and preventive action with effectiveness check" and flow chart were discussed. CAPAs were managed via TrackWise system. CAPAs were proposed by cross functional team and reviewed / approved by the Head QA / designee. Execution and implementation of CAPAs was also checked and approved by Head QA / designee.

CAPAs register for 2015 was presented to the inspectors. Three CAPA cases were reviewed.

Root cause analysis

The SOP "Root cause analysis" was discussed. The following tools were used:

- Cause and effect diagram (Ishikawa/fish bone diagram)
- Pareto analysis
- Flow charts
- Fault tree diagram
- Control charts

Change control (CC)

TrackWise software was used to trace changes. Information was stored on Mylan Global level.
Other Mylan sites could initiate a change in Trackwise which was to take place at the Aurangabad site (e.g. in case of technology transfer).

A log of changes was printed from TrackWise for inspectors, containing changes initiated by the site (the Company in their daily work did not use paper logs).

Trackwise provided an option for different user levels/roles, including the CC coordinator-approver level.
CC system was applied to planned changes (unplanned were managed as deviations / incidents).
Risk categories were assigned to changes. For several changes the CC log showed a brief description as change in master batch record (type: batch documentation change) but essentially these were changes in the process.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were defined and systematically reviewed. Qualifications and validations were performed. Necessary resources were provided and records were made during manufacture. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

3. Sanitation and hygiene

The company had an SOP as the basis for its approach to personal hygiene and sanitation in its production facilities. Areas were cleaned frequently in accordance with an approved written program and SOPs. Handling and storing of cleaning aids like mops and wipes was discussed, with focus at more practical arrangements for the cleaning personnel. Microbial monitoring was regularly performed.

4. Qualification and validation

Validation Master Plan

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan. VMP was revised annually. VMP (general VMP or activity specific plans e.g. in case of cleaning) was applicable for:

- Area/room qualification
- Utilities qualification
- EM
- Process validation
- Packaging validation
- Cleaning validation
- Method validation
- Stability studies
- Computer system validation
- Discrepancy management

Process validation

A specific product process validation data was discussed.

The site is currently working at procedures and protocols for process validation (statistical tools; commercial software).

Cleaning validation

Separate VMP was available for cleaning validation. Worst case product was defined using the following criteria:

- Solubility in water
- Solubility rating A
- Solubility rating B
- Occupational exposure band (OEB) rating C
- Occupational exposure band rating D
- Minimum potency
- Potency rating E
- Potency rating F
- Final score G

HPLC methods were used for cleaning validation; the Company stated that the methods were validated, and that product specific swab recovery studies had been performed; these topics were not followed up during this inspection.

There were three types of cleaning:

- Type A – batch to batch
- Type B – batch to batch (end of the day)
- Type C – product to product

Analytical method validation

Analytical method validation was carried out as well as compendial method verification.

Computerized systems

SAP system was used for:

- Materials management
- Vendor management
- Materials procurement
- Sale and distribution
- Manufacturing execution and release of materials
- PM schedule and equipment break down
- Instrument calibration schedule

SAP system was designed at the Mylan Global level, validated at the country corporate level and implemented at all Mylan units. Certain challenge tests had been executed by the Aurangabad (Waluj) site.

Hold time studies
A specific product was selected to examine hold time studies.

Temperature mapping
The SOP "Mapping of temperature and relative humidity" was discussed. SOP was applicable for T and RH mapping in storage rooms and equipment (cold storage, hot air oven, vacuum tray dryer).

Initial T mapping studies in storage rooms were carried out for three seasons (summer, winter and rainy season). Summer had been identified as the worst season. According to the SOP, T mapping studies shall be repeated every year ± 1 month.

"Protocol for T mapping in material stores; summer study" was discussed. The study was performed in May 2016. After the study two worst points were identified for T and two for RH.

5. Complaints

The SOP "Handling of complaints" and flow chart were discussed. Complaints were managed by TrackWise system. Head of QA / designee were responsible for handling of complaints. Complaints were classified as:

- Critical quality defects
- Major quality defects
- Minor quality defects
- Adverse drug reaction

Complaints log for 2015 was presented to inspectors.
A specific complaint investigation was reviewed. Fish bone diagram was used for root cause investigation. Investigation was found to be carried out in a good manner.

Complaints were trended quarterly and annually. Quarterly trend for April – June 2016 was reviewed. Trends were presented as:

- Product wise
- Substantiated vs unsubstantiated
- Market wise
- Month wise: received / closed

Annual trends were reported in more detail than quarterly trends.

6. Product recalls

The SOP "Product recall and withdrawal" and flow chart were discussed. Head of QA was responsible for evaluation of need of the recall, informing regulatory authorities and qualified persons (QP)/QA of concerned marketing authorization holders.
Recalls were classified as:

- Class I - recall should be executed within three working days
    - Defective/dangerous/potentially life threatening medicines that predictably or probably could result in serious health risk/adverse events or even death
- Class II - recall should be executed within seven working days
    - Possibly could cause temporary or medically reversible adverse health problem or mistreatment

- Class III - recall should be executed within fifteen working days
- Class IV – execution time was not specified.

Recall effectiveness evaluation was carried out by dummy recalls. According to the SOP dummy recall should be carried out separately for different markets annually. Last dummy recall was executed in November 2015 for Namibia.

7. Contract production, analysis and other activities

Manufacturing operations were not contracted out. Contract laboratories were used for certain chemical tests. Approved list of contract laboratories was presented to the inspectors. Contract laboratories were audited by Mylan Global.

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

The SOP "Self inspection" and schedule for 2016 were discussed. Spot checks showed that the schedule was followed. Self-inspection was carried out according to check lists drawn for each department.

Items for self-inspection

The following departments were subject for self-inspection:

- Solid dosage (manufacturing)
- Solid dosage (packaging)
- Warehouse
- QC
- Engineering
- Personnel &administration
- QA
- Process development laboratory

Self-inspection team

Self-inspection was carried out by a team of certified self-inspection auditors.

Frequency of self-inspection

Self-inspection was carried out every 6 months.

Self-inspection report

Self-inspection report specified findings as:

- Critical
- Major
- Minor

CAPAs were proposed by auditee and evaluated by the QA manager / designee.

Follow-up action

Implementation of CAPAs was evaluated by the QA manager / designee. If required, a follow-up self-inspection was carried out.

Suppliers' audits and approval

The SOP "Vendor approval and evaluation" and flow charts (new product and existing product) were discussed. The SOP was applicable to the manufacturers and suppliers of raw materials (APIs and excipients) and packaging materials. The SOP described the quality system requirements to select, evaluate and approve manufacturer of all materials used for the R&D and commercial product batches. Audits of manufacturers and suppliers were carried out by Mylan Global (APIs) and Mylan India (excipients suppliers and printed packaging material manufacturers). The inspected Aurangabad (Waluj) site did not perform any audits.

9. Personnel

General

The site had an adequate number of personnel with the necessary qualifications and practical experience. Specific duties of responsible staff were recorded in job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

Job descriptions

Job descriptions were available for all personnel. Job description for Head QA was reviewed.

10. Training

Inspection focused at training of temporary contract workers. The training was adequately managed in the Company. Separate SOP for contract workers, current list with assignment of work, training packages, records on training and other relevant information were available.

11. Personal hygiene

Personnel suffering from illness such as skin rashes, colds, and open lesions to the body were required to report the department head and were excluded from working in the clean and critical areas. Smoking, eating, drinking, chewing and the storage of food and personal medicines and smoking was prohibited in the manufacturing areas. Regular medical examination was carried

12. Premises

General

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Premises were cleaned and disinfected according to written procedures.

Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas

Storage areas were of sufficient capacity, apart from the storage of organic solvents. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products

Production areas

The premises were laid out in such a way as to allow the production to take place in areas connected in a mostly logical order, corresponding to the sequence of the operations and to the requisite cleanliness levels. The working and in-process storage space permitted orderly and logical positioning of equipment and materials Interior surfaces (walls, floors and ceilings) were found to be smooth and free from cracks and open joints. Production areas were ventilated, with air-control facilities. These areas were regularly monitored to ensure compliance with their design specifications.

Quality control areas

Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

Brief visit was made to the microbiology laboratory. It was well organized and maintained, adequate segregation of operations was provided.

13. Equipment

General

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis.

Preventive maintenance

Major production and laboratory equipment were subject to planned preventive maintenance.
SAP system was used for scheduling PM of process equipment and utilities (HVAC, PW, compressed air). PM was carried out according to equipment related SOPs and check lists. Spot checks showed that PM schedule was followed.

Calibration/verification

SAP system was used for scheduling calibration of measuring systems and instruments. Spot checks showed that the calibration schedule was followed.

The SOP “Operation and verification of analytical balance” was discussed. Daily verification was carried out using 20 mg and 200 g standard weights.

The SOP “Verification of weighing balance” was discussed. Daily verification was carried out with lower, middle and highest weights.

Heating, ventilation and air conditioning system

HVAC system consisted of 139 AHUs.
As an example a specific AHU was inspected. The AHU was serving granulation room. The filter cascade was following: EU4 → F6 → F9 → HEPA (EU13 – 5 No’s). 10 % fresh air was used. HEPA filters were installed terminally in the room. .

The following documents were available:
- URS
- DQ
- IQ
- OQ
- PQ

The following tests were carried out for PQ by third party:
- Room air velocity and air changes
- Differential pressure
- HEPA filter leakage
- Air flow visualization
- Airborne particle counts
- Recovery / decontamination rate
- T & RH
- Microbial monitoring & air sampling

Tests were carried out according to ISO 14644.

Re-qualification of AHUs was carried out:
- Room air velocity and air changes 12 months
- HEPA filter leakage 12 months
- Airborne particle counts 6 months
- Air flow visualization 24 months
- Recovery / decontamination rate 24 months

It was explained to the inspectors that AHUs are always in operation, even if there is no production in related rooms.

Purified Water

Pre-treatment plant and one of the PW generation plants (one out of two) were visited. Certain part of the pre-treatment system supplied housekeeping facilities which were not related to the production. RO (amongst other purification units) was used both in pre-treatment and final PW generation. During the cursory inspection no major issues were detected in the construction, maintenance and monitoring of the water systems.

Compressed air

The SOP “Periodic revalidation of compressed air system” was discussed. Compressed air revalidation was carried out once in a year for the following tests:
- TMC
- Airborne particle count
- Filter integrity
- Dew point
- Oil content
- Particle size concentration

- Moisture content
- Hydrocarbon

14. Materials

General

Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under appropriate conditions. Food grade oil was used for punches and dies lubrications.

SAP was used for material management and tracking. For manufacturing operations, specific work order codes had been created for process steps (packing order, rework etc.). SAP provided options to put materials on hold (e.g. missing documentation on raw materials) and assign certain other statuses.

Materials in the warehouses were stored in high racks. RM, packaging materials and FG were stored in three T&RH controlled storage rooms, two T controlled storage rooms and one cold storage room (2 – 8 ºC). T and RH distribution studies were carried out. T&RH was recorded continuously every 30 minutes, print outs were checked once in a day. Alarm system was installed to indicate excursions from established T&RH conditions.

Check-lists were used for materials receipt.

Starting materials

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active ingredients and excipients) and packaging materials were available in the SAP system. For each consignment, containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material were recorded and reported to the QA department. Four sampling rooms (separate material and personnel entries) were provided for API sampling and two sampling rooms (the same design) were provided for excipient sampling. Sampling was carried out under LAF. Solvents were stored in a separate building; sampling was carried out in a separate solvent sampling room (separate material and personnel entries).

Finished products

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer.

Rejected, recovered, reprocessed and reworked materials

The SOP “Reprocessing and reworking” was discussed. Rejected materials were stored in a locked cage.

Packaging materials

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure locations. Each delivery of a batch of printed or primary packaging material was given a specific reference number. Two sampling rooms (separate material and personnel entries) were provided for sampling of primary packaging materials. Sampling was carried out under LAF.

Reagents and culture media

Microbiological culture media and other materials used in the microbiology laboratory were appropriately stored.

Reference standards and working standards

The SOPs “Receipt, storage, usage and management of reference and impurity standard” and “Receipt, storage, usage of working standard” were discussed. WS’s were standardized against RS’s and dispensed under LAF in 12 amber vials. After opening, WS’s should be used within 15 days.

15. Documentation

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

Specifications and testing procedures

Testing procedures were validated and were appropriately authorized and dated. Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

Specifications for starting and packaging materials, finished products and intermediates

Specifications for starting and packaging materials, finished products and intermediates were available and contained required information about the materials (including material code).

Master formulae

Master formulae were prepared for each product.

Batch manufacturing records (BMR) / batch packaging records (BPR)

BMRs and BPRs were used for each batch processed. Before any processing begins, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded and were part of the BMR.

Batch numbering system

Batch numbering was established in a relevant SOP.

Standard operating procedures (SOP) and records

Generally various SOPs and records of actions taken were available for all activities carried out on site. Records were kept for major and critical equipment.

16. Good practices in production

General

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel.

In-process controls were carried out in three IPC laboratories.

Dispensing operations

Dispensing of materials was performed by warehouse personnel and checked by QA personnel. Separate rooms were provided for dispensing of APIs and excipients. Balances used for dispensing of materials were of appropriate range and were verified daily and quarterly by calibrated standard weights.

Prevention of cross-contamination and bacterial contamination during production

Precautions were taken to prevent the generation and dissemination of dust by airlocks, pressure differentials, and air supply and extraction systems. Production areas were subject to periodic environmental monitoring.

Processing operations

Before processing operations were started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Time limits for storage of equipment after cleaning and before use were stated and based on validation data. Significant deviations from the expected yields were recorded and investigated. Measuring, weighing, recording, and control equipment and instruments were serviced and calibrated at specified intervals and records were maintained.

Packaging operations

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. Line clearance was performed and recorded in the BPRs. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

17. Good practices in quality control

General

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigations as appropriate. Analyst certification matrix was presented to the inspectors. Instruments usage logs books were maintained.

Control of starting materials and intermediate, bulk and finished products

Tests followed the instructions given in the relevant written test procedure. Tests results were checked independently before the material or product was released. Samples were representative of the batches of material from which they were taken.

Test requirements for starting and packaging materials

Before releasing a starting or packaging material for use, the QC manager ensured that the materials have been tested for conformity with specifications. An identity test with NIR (in the warehouse) was conducted on a sample from each container of starting material; composite samples were analyzed for identity by chemical methods (in the QC lab). Each batch of printed packaging materials was examined following receipt.

Batch record review/batch release procedure

The SOP "Batch release" was discussed. Site Head QA / designee were responsible for review of the Batch Production Control Records (BPCR (BMR / BPR)) and batch release. The SOP was applicable to the finished products release. BPCR review was carried out using the check list. BPCR check list required review of analytical raw data. The SOP "Review of analytical data" was discussed. Review was carried out according to the check list. Analytical raw data was reviewed by designated QC personnel (reviewers).

Stability studies

The SOP "Conducting stability study" was discussed. Stability schedule was maintained in LIMS. The schedule was checked for the time period January 2016 – July 13, 2016.

Stability conditions were as following:

- T 40 ºC ± 2 ºC, RH 75% ± 5%
- T 25 ºC ± 2 ºC, RH 60% ± 5%
- T 30 ºC ± 2 ºC, RH 65% ± 5%
- T 30 ºC ± 2 ºC, RH 75% ± 5%

Stand-by chamber was qualified for all stability conditions. Chambers were connected to power supply with 100 % power back up through UPS and Diesel Generator (DG).

Out of specification results (OOS)

The SOP on "Aberrant results" covered out of specification and out of trend /atypical results in chemical-physical testing. The SOP had been elaborated and improved over the last half year. It followed the Mylan Global policy and UK MHRA guidance, including three phase investigation. LIRs – laboratory investigation reports – were initiated in TrackWise by QC personnel.

A common log of OOS and OOT was printed for inspectors from TrackWise.

Separate SOP covered "Microbiology data deviations" (MDD). Microbial tests also triggered LIR in TrackWise, but during the inspection it did not become clear whether LIRs related to microbial testing could be sorted / filtered in the system.

Retention samples

The SOP "Receipt, storage, maintenance of control samples" was discussed. The samples were stored according to the following schedule:

- API – seven years after registration in LIMS
- FG – one year after expiry date
- Primary packaging materials - seven years after registration in LIMS.

Retention samples were stored in two rooms, records and logs were maintained.

Sampling procedure

The SOP "Sampling of raw materials" was discussed. For many materials NIR was used for 100% identity tests. NIR ID tests were carried out in the materials receiving room (identity yes/no fully provided by the instrument,

no assessment on the warehouse level). Subsequently samples from individual containers were combined in the pool sample and full analysis according to the STP was carried out, including the specific ID test. If material spectrum was not available in the NIR library, 100% ID tests were carried out in the QCL.

The SOP "Sampling of packaging materials" was discussed. According to the SOP, the AQL sampling plan according to the ISO 2859-1 was used. Inspection levels for visual inspection and analysis were defined. For the different types of packaging materials inspection parameters were defined and categorized as critical, major or minor.

The following SOPs were discussed: "Management of data integrity", "Chromatographic data management", "Chromatographic analysis, instructions and documentation", "Assigning user privileges to Empower client server users and assigning system policies".

All HPLCs and GCs were connected to the server and operated by Empower 3 software.

Microbiological laboratory

Media were prepared and sterilized in appropriate manner. Autoclave loads were adequately defined. Master strains were available; the Company explained that "singe shot" units are used and no sub-culturing was done.

The SOP "Microbial monitoring of oral solid dosage areas" was discussed. The following samples were analyzed for EM:

- Active air sampling (monthly)
- Passive air sampling (monthly)
- Surface monitoring (six monthly)

Action and alert limits were established based on historical data. Trending was carried out quarterly. EM trends for April – June 2016 were discussed.

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, a Mylan Laboratories Ltd (Waluj), Finished dosage form manufacturing unit, located at Plot No H-12 and H-13, MIDC, Waluj Industrial Area Aurangabad- 431 136 Maharashtra, INDIA was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

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 as 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

1. 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.
   Short name: WHO TRS No. 986, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. 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/

3. 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/

4. 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

5. 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

6. 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
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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 artemisin is used as a starting material in the prosecution 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. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
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http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

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