

**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 Limited-Specialty Formulation Facility
Address	Mylan Laboratories Limited-Specialty Formulation Facility No. 19A, Plot No. 284/B1, Bommasandra - Jigani Link Road, Industrial Area, Anekal Taluk, Bangalore-560 105, India GPS details Latitude: 12.8168 Longitude: 77.6793 Data Universal Numbering System (DUNS): 677605290
Corporate address of manufacturer	Mylan Laboratories Limited Plot No. 564/A/22, Jubilee Hills, Hyderabad - 500 034, Telangana, India Telephone Number: +91-40-30866666, 23550543 Fax Number: 30866699 Site: www.mylanlabs.in
Inspected site	
Address of inspected manufacturing site if different from that given above	As above
Unit / block / plant number	Specialty Formulation Facility (SFF), manufacturing suite 4
Manufacturing license number	The site is approved by “Drug Controller and Licensing Authority, Karnataka, India” for commercial manufacturing of “Small Volume Parenterals and Large Volume Parenterals” • License No: KTK/28/384/2009 - Small Volume Parenterals • License No: KTK/28D/18/2016 - Large Volume Parenterals
Inspection details	
Dates of inspection	10 - 19 September 2018
Type of inspection	Initial

Introduction																																									
Brief summary of the manufacturing activities	The main activity is the manufacturing, packaging, labelling, testing and storage of: • Sterile liquid parenterals in vials (aseptically filled) • Sterile liquid parenterals in vials (terminally sterilized) • Sterile lyophilized parenterals in vials • Sterile liquid parenterals in mini bags (terminally sterilized)																																								
General information about the company and site	Specialty Formulation Facility (SFF) commenced manufacturing operations in May 2009 (as Strides Arcolab Limited and later as Agila Specialties Private Limited prior to Mylan acquisition). Acquired by Mylan in December 2013 and operating as Mylan Laboratories Limited, effective from December 2014. SFF started commercialization of sterile injectable products in 2011. No outsourcing and subcontracting activities is carried out from other manufacturing units which are directly related to products supplied by SFF. Mylan has five injectable manufacturing sites located in and around Bangalore, India including SFF site.																																								
History	This was the first WHO inspection. <table border="1" data-bbox="416 1061 1366 1832"> <thead> <tr> <th>Date</th><th>Name of competent authority</th></tr> </thead> <tbody> <tr><td>USFDA-US</td><td>17 Jun 13 to 27 Jun 13</td></tr> <tr><td>CDSCO- INDIA</td><td>12 Aug 13 to 13 Aug 13</td></tr> <tr><td>CDSCO-INDIA</td><td>12 Nov 13 to 13 Nov 13</td></tr> <tr><td>ANVISA-BRAZIL</td><td>08 Sep 14 to 12 Sep 14</td></tr> <tr><td>CDSCO-INDIA</td><td>16 Sep 14 to 19 Sep 14</td></tr> <tr><td>USFDA-US</td><td>23 Sep 14 to 03 Oct 14</td></tr> <tr><td>TGA-AUSTRALIA</td><td>06 Oct 14 to 10 Oct 14</td></tr> <tr><td>MCC-SA</td><td>17 Nov 14 to 19 Nov 14</td></tr> <tr><td>CDSCO- INDIA</td><td>03 Nov 15 to 04 Nov 15</td></tr> <tr><td>ZAZIBONA</td><td>03 Dec 15 to 05 Dec 15</td></tr> <tr><td>CDSCO-INDIA</td><td>24 Mar 16</td></tr> <tr><td>USFDA-US</td><td>04 Apr 16 to 13 Apr 16</td></tr> <tr><td>CDSCO-INDIA</td><td>08 Sep 16</td></tr> <tr><td>TGA-AUSTRALIA</td><td>21 Nov 16 to 26 Nov 16</td></tr> <tr><td>USFDA-US</td><td>10 Apr 17 to 18 Apr 17</td></tr> <tr><td>Tanzania FDA</td><td>17 Jul 17 to 18 Jul 17</td></tr> <tr><td>LIBYAN Ministry of Health</td><td>09 Sep 17 to 12 Sep 17</td></tr> <tr><td>CDSCO-INDIA</td><td>27 Nov 17 to 28 Nov 17</td></tr> <tr><td>USFDA-US</td><td>22 Feb 18 to 02 Mar 18</td></tr> </tbody> </table>	Date	Name of competent authority	USFDA-US	17 Jun 13 to 27 Jun 13	CDSCO- INDIA	12 Aug 13 to 13 Aug 13	CDSCO-INDIA	12 Nov 13 to 13 Nov 13	ANVISA-BRAZIL	08 Sep 14 to 12 Sep 14	CDSCO-INDIA	16 Sep 14 to 19 Sep 14	USFDA-US	23 Sep 14 to 03 Oct 14	TGA-AUSTRALIA	06 Oct 14 to 10 Oct 14	MCC-SA	17 Nov 14 to 19 Nov 14	CDSCO- INDIA	03 Nov 15 to 04 Nov 15	ZAZIBONA	03 Dec 15 to 05 Dec 15	CDSCO-INDIA	24 Mar 16	USFDA-US	04 Apr 16 to 13 Apr 16	CDSCO-INDIA	08 Sep 16	TGA-AUSTRALIA	21 Nov 16 to 26 Nov 16	USFDA-US	10 Apr 17 to 18 Apr 17	Tanzania FDA	17 Jul 17 to 18 Jul 17	LIBYAN Ministry of Health	09 Sep 17 to 12 Sep 17	CDSCO-INDIA	27 Nov 17 to 28 Nov 17	USFDA-US	22 Feb 18 to 02 Mar 18
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Scope and limitations	
Areas inspected	See Part two below
Restrictions	N/A
WHO product numbers covered by the inspection	Solutions for Injection for tuberculosis treatment

Abbreviations	ADE	acceptable daily exposure
	AHU	air handling unit
	ALCOA	attributable, legible, contemporaneous, original and accurate
	API	active pharmaceutical ingredient
	APQR	annual product quality review
	AQL	acceptance quality limit
	BET	bacterial endotoxin test
	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
	EU	endotoxin unit
	FAT	factory acceptance test
	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
M	meter
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
Ph. Eur	European Pharmacopoeia
PHA	preliminary hazard analysis
PM	preventive maintenance
Ppk	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
PRC	product release certificate
PW	purified water
QA	quality assurance
QC	quality control
QCL	quality control laboratory
QMS	quality management system
QRM	quality risk management
RA	risk assessment
RABS	restricted access barrier system
RCA	root cause analysis
RH	relative humidity
RM	raw materials
RS	reference standard
SAP	system applications products for data processing
SFG	semi-finished goods
SMS	short message service
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
UPS	uninterruptible power supply
URS	user requirements specifications
USP	United States Pharmacopoeia

	UV	ultraviolet-visible spectrophotometer
	VMP	Validation Master Plan
	WFI	water for injections
	WS	working standard

Part 2	Brief summary of the findings and comments
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Brief summary of the findings and comments

1. Pharmaceutical quality system (PQS)

Principle

Production and control operations were specified in written form and GMP requirements were essentially being met. Managerial responsibilities were specified in written job-descriptions. Product and processes were monitored, and the results taken into account during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

TrackWise system was used for QMS:

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

Management review (MR)

The SOP “Management review process of site quality council” was briefly discussed. According to the SOP, the Site Quality Council meeting should be conducted monthly. Standard agenda was specified as well as key events, review of previous action items, follow up actions, escalations etc. Annual trends for investigations, CAPAs, change controls, OOS/OOT, complaints and the key elements of the Quality System should be prepared for the period of January to December and should be finalized by the first quarter of the next year. Minutes of Site Quality Council meeting from 7 September 2018 were briefly discussed.

Quality Risk Management (QRM)

The SOP “Quality risk management” was briefly discussed. RA log book for 2017 and 2018 and risk-based prioritization plan for 2018, were briefly discussed. According to the SOP, FMEA was used as the tool for the risk assessments. Several quality risk assessment & managements were briefly discussed:

Product Quality Review (PQR)

The SOP “Annual product review/product quality review” and annual product quality review planner were briefly discussed. According to the SOP, the review period for non-US market and rest of the world market was specified as January to December.

Statistical tools (histogram, control charts, capability analysis) were used to evaluate the process performance. Process capability (Cp/Cpk and Pp/Ppk) was used for all critical in-process testing and/or finished product testing parameters; Cpk target was equal or greater than 1.33.

As an example, PQR for XX Injection USP (10 mg/ml), review period June 2017 - May 2018, was briefly discussed.

Deviations/incidents

The SOP “Incident and investigation management” was briefly discussed. The SOP was applicable to incidents & investigations related to manufacturing, packaging, storage, holding, testing, release and dispatch of products (scale up and commercial manufacturing) and was applicable only to unplanned deviations.

Planned deviations were handled per SOP “Change Management System”.

Investigation reference numbers were reflected in the BMR/BPR. Root cause analysis was explained, and tools used for investigations were specified.

Incidents were classified as:

- Critical
- Minor
- Major

Product impact was classified as:

- Severe
- Major
- Minor
- Negligible

Incidents register for 2018 and trends for the 1st and 2nd quarter were presented to the inspectors; no critical incidents were reported. Trends were performed quarterly and annually. Trends discussed were found to be well organized and detailed.

Several incidents were briefly discussed.

The SOP “Microbiological trend analysis” and number of incidents were briefly discussed

Corrective actions and preventive action (CAPA)

The SOP “Corrective/preventive actions (CAPAs) with effectiveness check” and critical CAPA register 2017 were briefly discussed. CAPAs were classified as:

- Critical
- Non-critical

The SOP was applicable all QMS elements.

Change control (CC)

The SOP “Change management system”, its flow chart and registers for 2017 and 2018 were briefly discussed. Changes were classified as:

- Critical
- Major
- Minor

and

- Permanent
- Temporary

Several major CCs were briefly discussed

Data integrity

The following SOPs were briefly discussed:

- “Data governance program” was briefly discussed. The SOP was applicable to all GxP data
- “Data integrity - Chromatographic data management system”
- “Backup and archival of standalone GMP/GxP systems”, external memory like pen drives were used for weekly/fortnightly and monthly back-ups. Back up data was transferred to the file server located at the site. Online daily, weekly, monthly and yearly automatic backups were transferred to the server located in Hyderabad. Backup registers were presented to the inspectors.
- “System administration of CDMS-Chromeleon”
- “Data restoration of computerized systems”. The SOP was applicable to standalone and network connected systems.
- “Disaster recovery of critical computerized systems”.

- Self-inspection

The SOP “Self-inspection” and SOP “Selection criteria for self-inspection auditors” and self-inspection planner - 2018 were briefly discussed. Self-inspection was based on 6 systems and was divided in sub-system-based audits. Laboratory control system, subsystem “Cultures, reagents, media and lot management” were briefly discussed.

Supplier’s qualification

The “Selection and evaluation of vendor”, its flow chart and vendor (APIs and primary packaging materials) audit schedule for 2018 were briefly discussed. SOP was applicable to raw material and packaging material vendors. Vendors were identified by supply chain management. Raw material and primary packaging material vendor audits were performed by the Global operation auditing team. Secondary packaging material vendor audits were performed by the Regional Quality Compliance team.

Approved suppliers list was maintained in SAP system. Approved suppliers list for APIs and packaging materials was presented to inspectors.

Complaints

The SOP “Receipt, logging, investigation and closeout of market complaints” and its flow charts and complaints registers for 2017 and 2018 were briefly discussed. Complaints were trended monthly and quarterly. Presented trends were well organized and extensive. Complaints were classified as:

- Critical - Should be closed within 15 calendar days
- Major - Should be closed within 45 calendar days
- Minor - Should be closed within 45 calendar days

Several complaints investigation files were briefly discussed.

Product recalls

The “Product recall” was briefly discussed. Product defects and typical actions were defined. Recalls were classified as:

- Class I
- Class II
- Class III
- Class IV

Mock recall was performed annually to evaluate procedure effectiveness.

Product returns

The SOP “Handling of returned and salvaged drug products” and its flow chart were briefly discussed.

Out of specification results (OOS)

The SOP “Laboratory investigation report (LIR)” and its flow chart were briefly discussed. The SOP was applicable to all kinds of laboratory incidents related to raw materials, intermediates, APIs, drug products, packaging/labeling, stability testing and aberrant and OOS results.

The SOP “Investigation and handling of out of level results in environmental monitoring” was briefly reviewed. The SOP was applicable for investigation and handling out of level results in viable environmental monitoring.

Several OOS investigation reports were briefly discussed.

Batch release

The SOP “Semi-finished and finished goods batch record review and release”, batch review flow chart and the following check lists:

- BMR review
- BPR review
- Analytical reports review
- Batch release check list

were briefly discussed.

According to the SOP, batch release can only be performed by a Science or Pharmacy graduate with 5 years’ experience in injectable manufacturing.

Several batch manufacturing records and analytical records were briefly discussed.

Personnel

According to the presentation, the site employed approximately 751 full time employees.

Personnel were trained in the practices of personal hygiene.

The following SOPs were briefly discussed:

- SOPs “Entry and exit procedure for aseptic processing area” and “Entry and exit of employees into production area”. SOPs were supplemented with detailed gowning procedure photos. Gowning SOP was available in English and Kannada language.

- SOP “Procedure for monitoring of personnel hygiene in production area”. List of qualified personnel for aseptic gowning techniques was presented to the inspectors.
- SOP “Personnel qualification by microbiological methods”. Personnel initial qualification was performed for 3 days within one month; requalification was performed once in a year.
- SOP “Health checkup and monitoring”
- SOP “Management of contract employees”
- SOP “Procedure for health checkup and monitoring”. According to the SOPs, all permanent employees and contract workers should undergo annual medical checkups. According to the SOP, visual inspectors should undergo eye sight tests by ophthalmologist every 6 months.
- SOP “Technical training” and Annual refreshment training planner for Microbiological department. “My University” software was used for training of employees. “My University” was an on-line learning program. Training effectiveness evaluation was by “True” / “False” or multiple-choice questions.
- SOP “Technique Evaluation of an Analyst”. Experienced analysts (having experience before joining), qualification was carried out by analyzing an already approved sample. Analyst had to prepare sample in triplicate. Acceptance criteria were specified. Inexperienced analysts had to prepare 6 replicates of the sample. Acceptance criteria were specified.

Training records of TWO aseptic filling operators were briefly discussed. Training files were maintained by Technical training department. “My University” training of training coordinator in QA was also discussed.

Analyst’s qualification matrix and signature specimens were presented to the inspectors. Signature short and full specimens were available for all employees. Two analyst’s qualification records for HPLC tests were briefly discussed.

2. Documentation system

Documentation system was generally established. Documents related to the manufacture of intermediates and Finished product were prepared, reviewed, approved and distributed according to written procedures. The SOPs were also displayed at appropriate points. The issuance, revision, superseding and withdrawal of documents were controlled with maintenance of revision histories.

Specifications were established for raw materials, packaging materials, intermediates and Finished products. Several specifications were briefly discussed.

3. Production system

Production operations followed defined procedures. Qualifications and validations were performed according to prepared protocols. Significant deviations from the initial protocol were recorded and investigated, root causes were determined and CAPAs were implemented where necessary. Checks on yields and reconciliation of quantities were carried out. Access to production premises was restricted to authorized personnel.

During inspection, XX injection batch No. YY was in progress. Inspectors observed aseptic filling line set up operations and startup of filling operations from the corridor via windows. Open RABS were used for aseptic filling. Environmental monitoring settle plates were exposed for 4 hours during set up of machine and filling process. Active air sampling in grade A was performed once per shift. Particle monitoring was undertaken for the full duration of set up of filling line and filling process. 2 video recording cameras were installed in the manufacturing Suite 4; however, video cameras did not support seeing full process. Before

filling operations started, fill weight checks were automatically carried out for all 8 filling needles. Two types of hand disinfectant bottles were used in grade A and B. Push bottles were used in grade A and spray bottles were used in grade B.

4 types of disinfectants were used for RABS cleaning/disinfection. Disinfectants were changed every 15 days.

The SOP “Operation and cleaning of glove integrity tester within glove box” was briefly discussed. RABS gloves integrity tests - visual and blow test were performed before and after production of each batch. Glove integrity tests were recorded in “Gloves integrity test record logbook” and printouts from auto integrity tester were attached to the product batch manufacturing records.

During site inspection, inspectors visited vial quarantine room No. XX visual inspection area ZZ, secondary packaging area YY and vial automatic inspection room No. AA and media fills incubation walk in chambers.

The SOPs “Operation and calibration of visual inspection table” and “Visual inspection by manual method” were briefly discussed. The filled containers of products were manually inspected for extraneous contamination and other defects. The inspection was carried out under suitable and controlled conditions of illumination. Operators performing the inspection were allowed frequent “eye breaks” (approximately every 1 hour).

All visual inspectors were required to be qualified as per SOP “Qualification and requalification of visual inspectors”. The qualification record for visual inspector AA was checked.

The SOP “Operation and cleaning of labelling and inspection machine” was briefly discussed.

Compounding was carried out in grade C environment. During inspection, XX Injection USP batch No. YY was in-progress. Bulk solution was checked for pH and solution clarity and afterwards released by QC for filtration. Filtration was carried out in grade B environment to avoid bioburden. Solution for bioburden check was collected after the first filtration.

Solution was filtered via two 0.22 µ single use filters. Bubble point test was performed before filtration using WFI and after filtration using the filtered solution. According to the SOP “Cleaning and preparation of air filters and water filters”, air and nitrogen gas were also filtered using 0.22 µ filters.

Hold time studies

The SOP “Hold time establishment and sampling details” was briefly discussed.

4. Facilities and equipment system

Classified clean areas for production of sterile products were designed to minimize potential contamination. Adequate space was provided for orderly placement of equipment and materials to prevent mix-ups.

The company had an SOP as the basis for its approach to personal hygiene and sanitation in its production facilities. Microbial monitoring of clean room personnel was performed as part of routine batch control. Generally, the facilities were noted to be clean and well organized during the inspection.

Adequate warehouses were provided for storage of raw materials, packaging materials and finished goods. During inspection, inspector visited warehouse No. 1 and warehouse No. 2. Raw materials were sampled in separate sampling room under RLAF.

The SOP “Cleaning procedure for stores, sampling and dispensing area” was briefly discussed.

Temperature mapping

The SOP “Temperature mapping of room/area” and temperature mapping study for finished good store room protocol and report were briefly discussed.

The SOP “Qualification of laboratory incubators and other storage equipments” and temperature mapping study (re-qualification) protocol and report for walk-in BOD incubator were briefly discussed.

Calibration

Calibration was performed as per SOP “Procedure for calibration of measuring and testing instruments”. Calibration was controlled in SAP. The calibration status of the instruments/gauges used in Suite 4 was checked. Calibration of the magnehelic gauges was performed by an approved external service provider. The service provider was confirmed on the list of external service providers.

SOP “Cleaning, operation and performance verification of weighing balance and handling of standard weights” was briefly discussed.

Maintenance

Maintenance was the responsibility of the Facilities and Engineering department. The planned preventive maintenance program was carried out as per the schedules stipulated in the applicable procedures.

The SOP “Procedure for replacement of HVAC LAF tunnel filters and cleaning of pre-filters” was briefly discussed.

The Validation Master Plan was briefly discussed and reflected the key elements of the validation program.

The Corporate Validation Group (CVG) was responsible for performing re-qualifications (RQ). Hence, responsible for the following:

- Preparation and review of RQ protocol
- Execution of RQ protocol
- Compilation and review of RQ report

Autoclave validation

The SOP “Procedure for operational qualification, performance qualification and requalification of steam sterilizers and bung processors” was briefly discussed. According to the SOP, autoclave re-qualification was carried out every 6 months using two worst-case loads patterns. All four worst-case loads were covered once in a year.

Re-qualification of steam sterilizer protocol and report were briefly discussed. Steam was tested for non-condensable gases, dryness and superheat before validation. Penetration and distribution temperature sensors

were used. Five pre-vacuum cycles were applied for garments and machine parts sterilisation cycles. 5 in-built T sensors and 16 external (12 penetrations and 4 distributions) sensors were used. Sterilisation cycle for both loads was 121.3 °C for 30 min. T sensors were calibrated before and after validation.

The SOP “Procedure for preventive maintenance (PM) of steam sterilizer” and PM schedule was briefly discussed. PM was performed monthly, quarterly and yearly according to the schedule. PM schedule was presented to the inspectors. Cross checks confirmed that the schedule was followed.

The daily vacuum leak test for the steam sterilizer was performed by production operator as per SOP “Set parameters and load pattern for steam sterilizer”.

Sterilisation tunnel validation

The SOP “Operational qualification, performance qualification and requalification of tunnel sterilizer” and re-qualification of the sterilisation tunnel protocol and report were briefly discussed. According to the SOP, re-qualification was carried out every six months. HEPA filter integrity tests, velocity and non-viable particulate matter were part of the validation. During validation, sterilisation tunnel speed was set up 10mm/minute more than normal speed used by production. T penetration sensors were placed in 10 vials and 10 endotoxin spiked vials were used for beginning, middle and end of the sterilisation run (target 3 log reductions, actual result reports 4 log reductions).

Aseptic process validation

The SOP “Validation of aseptic processing - Media fill” and simulation trial record for a liquid fill process was briefly discussed. Media fills were required to be performed every 6 months ± 30 days. Gamma radiated Soybean Casein Digest medium was used.

Cleaning validation

The SOP “Cleaning validation”, SOP “Sampling procedure during process validation and cleaning validation” and cleaning validation assessment report briefly discussed. Swab and rinse solutions were used for cleaning validation studies. Analytical method was HPLC method. Recovery studies from stainless steel surface were performed before cleaning validation. SOP was based on acceptable daily exposure (ADE) as per EMA guideline.

Computerized system validation

The SOP “Validation of Computerized systems” and Computer System Validation Master Plan” briefly discussed. Computer System Validation followed life cycle approach. Empower validation plan and validation report were briefly discussed.

5. Laboratory control system

The QC function consisted of QC Analytical and QC Microbiology departments.

Sampling

The SOPs “Sampling of non-sterile raw materials - API and Excipient”, “Sampling of miscellaneous materials”, “Sampling of miscellaneous materials” and “Sampling of non-sterile packaging material” were briefly discussed. 100 % sampling was applied for APIs and excipients. Identity tests were performed on each sample. Maximum 10 containers were pooled together for complete analysis.

AQL was applied for vial sampling. Critical, major and minor defects were specified and acceptable AQL levels were applied.

QC Analytical laboratory

During inspection, XX, batch No ZZ, sample No YY analytical raw data was cross checked with equipment log books, standards usage and weighing slips. Assay re-calculations were also done. No discrepancies were observed.

LIMS was used for the collection, processing, recording, reporting, storage and retrieval of test and calibration data.

Analytical balances

According to the company procedure analytical balances were verified daily using 3 standard weights and monthly according to the USP Chapters 41 and 1251. Standard weights and calibration certificates were presented to the inspectors.

HPLC & GC calibration

HPLC and GC calibration was carried out every 6 months by vendor. Calibration schedule was available.

HPLC column usage

A column log was maintained in LIMS.

Reference standards

The SOP “Management of analytical standards” was briefly discussed. Following standard types were specified:

- Pharmacopoeia reference standards
- Manufacturer standards
- In-house standards
- Working standards
- Primary standards

Working standards were qualified against pharmacopoeia reference standards and dispensed in glove box in amber color vials. Depending on substance stability, standards were single used or used within one month. Standards were stored in chambers at room T (below 25 °C), - 20 °C and 2 °C - 8 °C. T in chambers was recorded every 30 minutes, print outs were checked daily. Chambers were equipped with an audible alarm system and connected to the UPS. As a CAPA, chambers will be connected to the Wi-Fi alarm system which generates SMS.

Data integrity

Inspectors requested the Company to export to Excel sheets Chromeleon sequence audit trails for submission batches. The submitted files were reviewed and no data integrity issues noted. Selected actions were cross checked. Laboratory incidents and deviations were recorded and were traceable and legible.

Retention samples

The SOP “Management of control samples” was briefly discussed. According to the SOP retention samples should be visually inspected at least once per year according to the monthly inspection schedule. Reserve sample periodic observation sheet from August 1 – August 31, 2018 was presented to the inspectors.

Retention samples were stored in appropriate conditions and in good order. FPP retention samples were stored expiry dates + 1 year, APIs retention samples were stored for 7 years. Maximum expiry date for FPPs was 36 months.

Stability studies

Walk-in stability chambers were visited during inspection. The stability chambers were housed in a separate building. Stability samples were stored in appropriate conditions and in good order. Access to the stability chambers were password controlled. T and RH in chambers was recorded every 30 minutes, print outs were checked daily. Chambers were equipped with audible alarm and Wi-Fi alarm systems (SMS) and connected to the UPS.

QC Microbiology laboratory

The inspector went to the Microbiology laboratory which was separated from the production areas. The Microbiology laboratory was situated on the ground floor and had a separate entry. Access to the Microbiology laboratory was restricted and gowning was required for entry into the Microbiology laboratory. There was a separate air supply to the Microbiology laboratory.

The Microbiology laboratory was responsible for performing the following activities:

- Environmental monitoring
- Microbial assays
- Sterility testing
- Endotoxin testing
- Bioburden testing of raw materials, semi-finished and final products
- Identification of micro-organisms
- Water analysis
- Media and equipment preparation

Sterility testing was carried out in two different areas:

- Carried out in a grade A unidirectional airflow protected zone which was in a clean room with a grade B background
- Carried out within a barrier isolator

Media was prepared both in-house and was also purchased fully prepared. The performance of the media used in the sterility testing of XX was reviewed.

SOP “Microbial cultures management” was reviewed. The strains of microorganisms used for the growth promotion testing of the media was reviewed.

It was confirmed that the working stocks were not more than five generations (passages) from the original reference strain as stipulated in SOP “Microbial cultures management”.

One steam sterilizer was used for the sterilization of media and equipment (miscellaneous). According to SOP “Requalification”, the sterilizers are required to be re-qualified every 6 months. The 6-monthly requalification report was briefly discussed. There was a dedicated sterilizer for the destruction of contaminated waste.

Environmental monitoring of clean area (EM)

The SOPs “Environmental monitoring program in clean rooms and other controlled environments” and “Microbiological trend analyses were briefly discussed. The Environmental Monitoring Data Review Summary Report for the month of July 2018, which included monthly data for the previous 12 months, was briefly discussed.

Microbiological monitoring of PW and WFI

PW and WFI were sampled and tested by the personnel in the Microbiology laboratory as per the defined schedule stipulated in SOP “Monitoring of water for microbiological quality”. Alert and action limits were specified.

Pure steam

The SOP “Sampling and testing of water - chemical” and SOP “Monitoring of water for microbiological quality” were briefly discussed. The SOPs were applicable also for pure steam condensate sampling and testing.

Contract analysis

Several laboratories were used for contract analysis.

Technical agreements

The SOP “Management of technical-quality agreements” was briefly discussed. Technical/Quality agreement for contract testing was briefly discussed.

6. Packaging and labelling system

During inspection inspectors visited secondary packaging room and observed packaging operations of XX ml batch No. YY. Roll labels were used. Packaging line was equipped with label scanning and rejection system. System was challenged before operations started. System challenge was demonstrated to the inspectors.

Packaging Material Specification for glass vials and for rubber closures were briefly discussed.

PART 3

Conclusion – inspection outcome

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-Specialty Formulation Facility (manufacturing Suite 4), located at No. 19A, Plot No. 284/B1 Bommasandra - Jigani Link Road ,Industrial Area, Anekal Taluk Bangalore-560 105, 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.

PART 4

List of GMP guidelines used for assessing compliance

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

3. 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/>
4. 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/
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. 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/
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
Short name: WHO TRS No. 957, Annex 1
<http://www.who.int/medicines/publications/44threport/en/>
9. 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/>
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](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](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](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](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](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)

17. 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
18. 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
19. 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
20. 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