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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Mylan Laboratories Limited (Viatris)**
Corporate address of the manufacturer	**Head office:** Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad - 500096, India. Phone: + 91- 40-308-66666, + 91- 40-235-50543 Fax: +91-40-308 66699 *E-Mail: mylan.india@mylan.in*
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Plot No 20 & 21, Pharmez, Sarkhej-Bavla, National Highway No. 8A, Near Village Matoda, Taluka: Sanad, Dist: Ahmedabad 382213, India Geographical coordinates: The latitude of Mylan is 22.874 N° The longitude of Mylan is 72.402 E° D.U.N.S. Number: 677604150
Unit/block/ workshop number	Filling lines 1 and 2
Inspection details	
Dates of inspection	14-18 November 2022
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Mylan Laboratories Limited, Ahmedabad is engaged in the manufacturing of medicinal products solid orals [Hormonal and Non-Hormonal Tablets] and Injectable hormonal formulations (Terminal sterilised suspension). The facility was commissioned in 2009 as part of Famy Care Limited. In May 2015, Famy Care has demerged its female contraceptive business into "Jai Pharma Limited". Mylan acquired Famy Care's female contraceptive business in November 2015. On 20th November 2015, Jai Pharma Limited became part of "Mylan Laboratories Limited". Presently, Mylan Laboratories Limited, Ahmedabad is supplying medicines to the Government of India, for its National Family Welfare program and is exporting its products to countries in North America, South America, Europe, Africa, Asia and Australia. The unit is located in Pharmez, (The Pharmaceutical Special Economic Zone) with surrounding units engaged in manufacturing only Pharmaceuticals Formulations Units which do not emit

	excessive soot, chemical and biological emissions.
General information about the company and site	Mylan Laboratories Limited is the Indian Subsidiary of Mylan Inc., USA, which is one of the world's largest generics and speciality Pharma Companies. Mylan Inc., USA was founded in 1961 and has Corporate Headquarters in Pittsburgh, Pennsylvania, United States. Mylan Inc., USA has primary businesses in the following areas: - Generic Pharmaceuticals and Branded Generic Formulations - Specialty and Brand Pharmaceuticals - Active Pharmaceutical Ingredients
History	The Ahmedabad manufacturing site for injectables has been periodically inspected by the WHO PQ Inspection Services. The last on-site inspection was performed in April 2016. In addition, the manufacturing site was inspected by the USFDA in August 2017 and September 2019 for the same MPA injection. The FDA Gujarat inspected the site in July and October 2022 and issued a GMP certificate until 08/11/2025
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The following areas were inspected: - Pharmaceutical quality system - Personnel and training - Documentation - Hygiene and sanitization - Process and computerized system validation - Equipment and materials - Production and packaging - Quality control including microbiology laboratory - Utilities
Restrictions	None
Out of scope	The scope of this inspection was limited to the injectable. The OSD products will be covered during a separate inspection.
WHO products covered by the inspection	RH074 (Medroxyprogesterone acetate Suspension for injection 150mg)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability

DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High-efficiency particulate air
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar airflow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non-conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	Summary of the findings and comments (where applicable)

1. Pharmaceutical quality system

A formal documented quality system was established, with procedures covering all expected key quality elements being in place. QA department was independent of production. Operations were specified in written form and GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Product and processes were monitored, and these results were considered during batch release. Regular monitoring and reviews of the quality of APIs and FPPs were being conducted according to documented schedules and procedures.

From the opening meeting presentation, it was noted that TrackWise was used at the site for the change management system (permanent/temporary), investigations (manufacturing investigation/laboratory investigation, trending assessment, CAPA, notice of rejection and pre-market supply incidents) and market complaints. Documentum for Life Science solution suite (D2) was used for preparation, review, approval and revision of standard operating procedure. A learning management system was being used for online training of employees along with manual training. Other software-based Quality Management Systems implemented at the site include Laboratory Information Management System (LIMS), Empower (Chromatography Data Management) and SAP for Material Management.

Annual product review/product quality review was discussed. The QA was responsible for collecting the data and feeding it into Minitab before analysis was performed. The annual product review included a trend analysis of the critical quality attributes of all the batches of the concerned commercial product manufactured throughout the year. The product quality review included critical material attributes, critical quality attributes, critical process parameters, Yield Data, Quality Control data, Environmental monitoring data and Stability summary. A minimum of 25 batches were required to demonstrate process capability. Critical events like batch deviations, rejections, OOS, customer complaints or recalls and any change controls related to products were reviewed.

Medroxyprogesterone Acetate (MPA) injection (150mg/ml) PQR was reviewed. The review period was Jan-Sept 2021. The product shelf life is 3 years and no part of the manufacturing was outsourced as informed. During the review period, 116 batches were produced wherein 92 batches were packed together with 3 batches from the previous year. A total of 9 campaigns were taken. It was noted that Type B cleaning was carried out after every batch of the campaign.

Handling of the incident investigation was discussed and noted that the procedure applies to investigations into incidents concerning API, excipients, raw materials, packaging components, in-process materials, cleaning validation, environmental monitoring and finished product, including when a deviation is identified as related to batches that have been distributed or were on stability. It was noted from the flowchart that any events other than manufacturing incidents were categorised as "operational incidents". The incidents were categorised as minor, major and critical based on the answers to be given in the TrackWise system. Incident trend analysis for the year 2022 was performed quarterly covering sterile and non-sterile products produced on the site. In general, the trend analysis was found adequate.

Data integrity risk assessment (DIRA)
The site QA performed an assessment report of GMP/regulatory guidance documents (against the WHO requirement (TRS 1033 Annex-4). It was concluded that no further actions were required as existing controls meet the current requirement as published in the WHO DI guide. The contamination control strategy gap assessment in the form of a presentation was available. The purpose of this gap assessment was to identify any gaps between the existing facility, systems, and processes used for the manufacture of Medroxyprogesterone Acetate (MPA) injection manufactured by Mylan's Ahmedabad facility against the revised EU GMP Annex-1 (WHO GMP for sterile medicinal products). As MPA injection is terminally sterilized, the company believes that the risk is low as compared to products manufactured.

Risk Assessment
The risk assessment related to the handling of hazardous substances was performed following the WHO Technical Report Series, No. 957, 2010 (WHO GMP for pharmaceutical products containing hazardous substances).

Waste Streams
The SOP Management of Solid and Hazardous Waste was reviewed. Waste streams were defined in Production, QC, R&D Laboratories, Process Development, Stores, Effluent and Solvent Recovery Plants.

Deactivation Process
For the qualification of the deactivation process, 4% sodium Hypochlorite was added for a 4 hours-time period. Filled vials were not deactivated and were sent for thermal destruction. Common Hazardous Waste Treatment Storage and Disposal Facilities (CHWTSDF) documents were reviewed with the procedure for disposal of Chemicals, Laboratory Waste and Left-Over Samples. Deactivation was described here as 4 % Sodium Hypochlorite for 24 hrs. The SOP on the management of solid and hazardous waste details that deactivated waste was collected from respective locations and bags were tied up. It details that the waste was deactivated for 4 hrs at 4%.

Disposal Vendor
The audit report included: Environmental Clearance, Consent for Establishment, Consent of Operation, Agreements, Factory Licence, Waste transportation, Storage facilities, Leachate system, Containment, Inspection, Disposal, and Treatment Systems.

The deficiencies noted from the pharmaceutical quality system section have been addressed satisfactorily and the same will be verified during future PQ inspections.

2. Good manufacturing practices for pharmaceutical products

In general, production operations followed defined procedures. Manufacturing processes were adequately defined and documented in BMRs and BPRs. Required resources were available, including adequate premises, equipment and utilities. Appropriately qualified personnel were employed. Qualifications and validations were performed according to the prepared protocols.

The MPA injection has been regularly produced in Line 1 for WHO and other markets. The site has expanded the production of MPA injection onto a newly built line 2, currently producing the same MPA

injection for the Rest of the World (RoW) markets. The company confirmed that there were some differences in the formulation of WHO Prequalified and RoW markets. The MPA injection is produced on dedicated lines (1 & 2) as there were no other products manufactured on these two lines.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

3. Sanitation and hygiene

The cleaning and disinfectant procedures were in place along with the disinfectant programme.

4. Qualification and validation

The company had in place procedures for performing qualification, calibration and validation of equipment and processes.

The system development life cycle procedure provided a validation philosophy in line with 21 CFR Part 11, defining the template used for validation and management of the computerized system. In general, the procedure adequately defined the life cycle approach for computer systems. The company is required to verify each equipment, instrument, and software against the DI requirement and confirm that there were no gaps against the ALCOA+ principles. If there are gaps identified, appropriate corrective and preventive actions should be implemented within the stipulated timeline.

Process validation program procedure was in place. The processes were validated for a new product, changes in the existing product, changes in the API, changes in batch size, and changes in facilities. The concept of three-stage validation was defined in the validation master plan wherein Stage 1 was carried out in the R&D (process development laboratory located in Hyderabad) and based on the nature of the product, a number of batches were recommended for process validation at the site. Stage 2 was carried out at the site taking three batches and process validation was governed through this procedure. Stage 2 was defined as “Process Performance Qualification” i.e., process validation.

The cleaning validation procedure was discussed. The product risk ranking was performed based on toxicity (ADE band/rating), solubility in water and potency (lowest therapeutic dose or strength). The MACO was calculated using ADE values which were calculated by company staff based out of Mylan Pharmaceuticals, Morgantown, WV.

Visual inspections
The inspectors visited the visual inspection area. The MPA injection batch number was being inspected. The vials were inspected using inspection booths with white and black backgrounds.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

5. Complaints

The handling of complaints procedure was discussed. The complaints were logged into TrackWise as well as in the logbook depending on the receipt of the complaints. An initial classification was performed based on the complaint receipt. The acknowledgement was done and assigned to a manufacturing site. Potentially critical and non-critical classification and accordingly health authorities were informed. Should there be a need to recall the affected product, a final classification was performed based on the outcome of the investigation (critical, major, minor, and adverse drug reaction). In 2021, two complaints were received whereas no other complaint was received by the company since the commercialization of the MPA injection.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

6. Product recalls

Product recalls were handled as per the procedure ("Product Recall and withdrawal"). The procedure described the sequence of actions to be taken and recall levels were decided considering the seriousness of the complaint and the regulatory requirement. The recall procedure provided the details related to the communication channels to be used, the access to distribution records, the names and addresses of concerned persons involved in the distribution chain and the effectiveness of the recall. The mock recall was performed on commercial batches distributed in the market annually and whenever there was a change in recall methodology.

7. Contract production, analysis and other activities

The activities related to the production and packaging of the said product were not contracted out. Contract testing facilities were utilized in a few instances, in case of no availability of required instrument/technique or breakdown of existing instrument etc. Apart from this, a few contract services were used for supporting functions like calibration, transportation, pest control, medical check-ups, etc.

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

Self-inspections were carried out as per the annual self-inspection program as per procedure "Procedure for self-inspection") to ensure that the quality management system exists and that they were implemented properly and effectively. The self-inspections were carried out by the persons who were not directly responsible for that area but have sufficient knowledge and expertise in that area. Self-inspection was conducted twice a year for each department.

The deficiencies noted in this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

9. Personnel

From the opening meeting presentation, it was noted that the organization chart showed arrangements for quality assurance, production and quality control. The total number of employees as of 31 October 2022 was 522. In addition, contracted staff were employed in various manufacturing areas less critical in nature.

10. Training

The training was managed using a learning management system (LMS).

11. Personal hygiene

All personnel, before and during employment, had to undergo an initial health examination. hereafter regular health examinations were carried out every year. Personnel conducting visual inspections had to undergo periodic eye examinations every six months. The personnel gowning procedure was appropriate and was generally followed. Instructions and pictorials to be followed were sufficiently clear when it came to personal hygiene. Operators working in the aseptic filling area were qualified periodically.

12. Premises

The premises of the plant included areas of manufacturing, warehouse, quality control, quality assurance, administrative, utility area, and service/ technical floor. The entrance to the warehouse was via WO 43, which had an air curtain and a strip curtain. Street footwear was removed, and the process included washing and drying of hands, collecting primary gowns and sanitizing after gowning.

The manufacturing area includes the Hormone Tablet manufacturing area, Non-Hormone Tablet manufacturing area and Terminal sterilize Hormone Injectable manufacturing area and their respective packaging lines. The entire manufacturing activities were divided into three floors (the ground floor for manufacturing activities, the first floor for utilities and the second floor for quality control including the microbiology section). The layout of the ground floor was discussed. The manufacturing site is divided into OSD and injectable sections. The OSD was not covered during this inspection. The injectable section was comprised of two filling lines. The first-floor site plan was discussed. A separate water system was provided for hormone, non-hormone and injectable products. The compressed air and nitrogen gas were produced on-site whereas generation is common and distributed separately. The second floor has utilities and quality control laboratories including microbiology, stability and retention samples.

<u>Water system:</u>
Water pre-treatment comprises of raw water storage tank, multi-grade sand filter, CSRO (Chemical Sanitizable Reverse osmosis system) with the dosing arrangement. The purified water was comprised of HSRO (Hot water Sanitizable Reverse Osmosis system) + Electro de-ionization system with an Ultraviolet system. It was noted that there were three independent purified water distribution systems loops in continuous circulation with velocity check (through flow monitoring), online UV, conductivity and TOC monitoring. The multicolumn distilled water system is comprised of multiple columns, a heat exchanger & water cooler to generate distilled water. The WFI distribution system loops were in

continuous circulation with water velocity check (through flow monitoring) Online Conductivity, temperature and TOC monitoring.

Pure Steam

Specifications included: pH 5-7, TMC Alert: 5 CFU/100 ml, Action 8 CFU/100 ml, Speciation: 10 CFU/100 ml. TOC- Alert: 350 ppm, Action: 400 ppm, Specifications: 500 ppm. The conductivity limit was set at 1.3 micro-siemens at 25 ℃. All results including BET were within specification.

Heating, ventilation, and air-conditioning (HVAC) systems

AHUs were the re-circulatory type with a minimum of 20 ACPH and corridors were negatively pressurized for process rooms.

AHU

The AHU that supplied Line 1, was MI-AHU-G41. Requalification was performed yearly and included a fresh air and bleed air flow test, supply airflow and ACPH test, return airflow test, NVPC, airflow pattern, micro-bioburden, temperature /RH, and pressure differential. There were 7 HEPA EU 13 and 8 Risers. The placement of the particle counter was defined as 6 locations based on area and ISO guidelines concerning area. The data set for the area at rest was available.

HEPA integrity

Acceptance of Penetration NMT 0.01 % of upstream concentration was defined. The aerosol concentration was defined as 20- 80 %.

Nitrogen

A nitrogen plant for the generation of nitrogen as per requirement was reviewed. For nitrogen, the allowable limits were oxygen 0.01 % and nitrogen 99.99 %. Requalification parameters included nitrogen, CO, CO_2, oxygen, particle count, and micro-bioburden at generation and user points.

Compressed Air

Compressed air was also generated for pneumatic operations as well as cleaning. All product contact gases were filtered through dual 0.1-micron filters. There were 5 units and 2 were run at any one time. Testing parameters included Dew point, Oil content, Moisture, NVPC and Extraneous gasses. This was performed yearly. Microbial testing was performed at 3 monthly intervals. There was a 0,1-micron filter at the generation point and a POU filter.

The deficiencies noted in this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

13. Equipment

The filling line 1 was dedicated to the manufacture of MPA injections for WHO and other markets. The filling line is also dedicated to the MPA injection which supplies finished products to the RoW markets. The following key equipment were used in the manufacture of MPA injection:

1. Autoclave
2. Vial washing and depyrogenation

3. Vial filling and stoppering line
4. Terminal sterilization
5. Visual inspection

The deficiencies noted in this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

14. Materials

There was a procedure in place describing the receipt and storage of raw materials. A checklist was used for the receipt of raw materials. Material stock and status were managed via an SAP system. A unique material code was assigned to each material in the system. Procedures for material sampling and dispensing were available. Temperature and relative humidity were monitored and controlled. In general, starting materials and packaging materials were maintained at ambient temperature (15-25°C) in the warehouse whereas MPA was stored inside the production area at ambient temperature. Quarantine was applied until the materials were appropriately sampled, tested and released. At receipt, the source of materials was checked against an approved supplier list. An SAP system was used to manage material stock.

Handling and storage of raw and packing materials was reviewed. The SOP "Storage and dispensing of Hormones in the warehouse" mentioned that all hormones were received in an aluminium pouch. The hormone APIs were received in the warehouse and transferred to the production area in a storeroom for sampling and dispensing. Non-hormone materials were sampled in the warehouse. The hormones were sampled/dispensed in an isolator. Separate MAL/PAL was provided for manufacturing areas. An air shower was provided upon a way out or exiting the hormone area. Dedicated personnel were deployed for ferrous fumarate and hormone areas. Misoprostol required cold storage at 2-8°C. The MPA injection was sterilised using terminal sterilization. The primary packaging of hormone and ferrous fumarate tablets was in the common area.

Since the same manufacturing site also manufactures oral solid dosage forms for the WHO PQ programme as well as for other markets, several of the hormone APIs were handled on-site.

<u>Sampling</u>
There was an area dedicated to hormone and non-hormonal sampling. The dirty hold was 24 hours and the clean hold times were 48 hours for sampling utensils. It was noted in the non-hormonal sampling area, the area under the dispensing hood was not defined where the operator should work from and where bulk material should be placed.

<u>Containment Studies</u>
The complete process was not subject to determining the residues of hormonal products. Examples include incoming containers in terms of hormonal residue, common dedusting tunnel, "clean" corridor residues, hormonal residues on vials, and scrubber outlet containment.

The deficiencies have been addressed satisfactorily and the same will be verified during future PQ inspections.

15. Documentation

The documentation system was managed through enterprise document management (EDMD2). The documentation system was described in the standard operating procedure for preparation, checking, authorization, and issue of quality-related documentation in the procedure "Preparation, review, approval, distribution, control, revision, archival and destruction of documents". The documentation system comprises specifications, master formula card (MFC), master packaging configuration (MPC), batch manufacturing record and batch packing record. Document control at the site was managed manually.

The deficiencies noted in this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

16. Good practices in production

Manufacturing of injectables was carried out in individual rooms for solution preparation, filtration, vial de-cartooning, vial washing & depyrogenation, vial filling & stoppering, vial sealing, terminal sterilization, visual inspection and packaging activity.

The inspectors visited the manufacturing area and observed Line 1 (MPA injection). The components were sterilized in-house via the autoclave process. The vial process included de-cartooning in the Grade D area. The vials then passed through the wall aperture to grade C. Air visualization for the direction of air moving from C to D or D to C was not performed. Stoppers were autoclaved. It was noted that there was a residue in the bottom of the stopper bowl base. Filling, stoppering, loading and unloading activities were carried out under LAF. A mobile LAF cart was used to transfer sterile components from A through non-A areas. It was observed that during the movement, the LAF was on battery power, and was not considered within the qualification. Residues were observed on the wheel of trollies and LAF. The background for the filling, stoppering, washer and tunnel was carried out under the Grade C. MPA injection is terminally sterilized. It was noted that the garments were sterilized in-house. The wash and sterilization cycles were set to 70 sterilization and wash cycles. The study to confirm this was not performed. The product after manufacturing was transferred to a homogenization tank in pressure then from the homogenization tank to the header tank and via manifold to filling. The tank was not over-pressurized, and a risk that non-A air could enter the tank. An assessment of this risk was not performed. There was a nut missing on the tank below the vent filter. The electrical cord of the tank was taped rather than properly repaired.

A bio-breathable paper of cellulose type was used to wrap change parts instead of the usual Tyvek. The manufacturer should review the use of such paper in light of the risk of particle shedding and a study for this was not completed. It was noted that the wrapping was damaged and torn with the components exposed. At the time of filling activities, environmental monitoring (settle plates) was carried out for 4 hours. It was observed that the settle plates were placed next to the return riser. Non-viable continuous particle monitoring (CPM) was performed throughout the batch-filling activity. It was highlighted that the CPM should comply with DIRA. The disinfectant 70% IPA was used which was filtered through 0.22um. The Line 1 has 6 filling nozzles. Nitrogen gas was used to flush the filling line during pre-, during, and post-filling activities. There were 6 purging needles, 6 filling needles and 6 post-filling nitrogen overlay needles. Polyplex material was used for panels that appeared to be poorly maintained

and discoloured. The company should look into the quality of the materials which should be periodically replaced via a PM program. The filling is carried out using a peristaltic pump and the solution is recirculated. Liquid-borne particle counts (sub-visible particles) were performed for 10um and 25um. Bioburden is performed on the last vial of the last lot and an offline in-process test (extractable volume check) was performed every 30 minutes from the start of the batch which was offline. In terms of this IPC there was no clarity provided as to how vials were separated should there be a failure at the next time point. The 100 vials were discarded after the initial set-up of the machine. Rejected vials were first deactivated before incineration.

Line 2 is a new line currently used for ROW markets. Based on a quick visit to line 2, it was noted that the new line is well-designed and has more capacity.

The deficiencies noted in this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

17. Good practices in quality control

The quality control was responsible for physical, chemical and microbiological testing/monitoring wherever applicable of starting materials, packaging materials, semi-finished products and finished products, environment, services and utilities. The quality control laboratory served both the non-sterile and sterile formulation on the Matoda, Ahmedabad site and was designed with separate sections for wet chemistry, instrumental and microbiology analysis. A laboratory information management system (LIMS) was implemented for sample management and approval for all raw materials and packaging materials in the quality control laboratory.

The sterility testing was carried out under the horizontal LAF with background Grade B. 40 vials from every lot were collected for the sterility testing using Soyabean Casein Digest Medium and Fluid Thioglycolate medium. The sterility testing was not performed using the steritest apparatus due to the nature of the MPA suspension injection. One lot was tested at one point in time before another lot was taken for testing. The company confirmed that the sterility testing method had been validated.

The laboratory information report/LIR procedure was discussed and was supported with a process flowchart. The LIRs were handed through TrackWise, and the investigation was performed in phases (Phase 1 preliminary investigation, Phase 2 further divided into 2A (manufacturing) and 2B (extended lab investigation). The repeat analysis was performed by two analysts in triplicate (total 6 sets) and relative standard deviation was calculated (below 2% for assay and below 15% for related substances). If a root cause is attributed to human error, it is handled by dividing the errors into self-influencing and external influencing factors. Further, a human error assessment was performed. The procedure also covered OOT, atypical (e.g., extraneous peaks), quality impact assessment (lab deviations), invalid (lab incidents) and other LIR (system suitability failure). The procedure also stated that once the sample is injected, it will be handled as OOS, not as an atypical result. In general, the procedure was found adequate and covered all possible laboratory scenarios as possible in one procedure.

Out of specifications (OOS)
A separate procedure for handling OOS related to microbiological test results was discussed. The procedure was applied to BET, MLT, bioburden, sterility and TOC. Another procedure (investigation

procedure for microbiological data deviation) was in place related to environmental monitoring out-of-level results. These were handled through TrackWise. It was noted that there have not been any OOS related to sterility, MLT, bioburden and BET. In 2019, there was an excursion related to environmental monitoring due to the out-of-action level result observed in settle plate location SP-1 of the injection area in changeroom-I. Trend analysis of OOS was performed quarterly and performed separately for injectables and OSD.

Stability studies

The stability section was supported with 8 stability chambers (for different storage conditions such as 25/60%, 30/65%, 30/75%, 40/75%, photostability and deep freezer. The MPA injection was stored in an inverted condition and two batches.

Retention samples

The control sample of Dimple (Medroxyprogesterone Acetate Suspension for injection 150mg/ml) was verified and the WHO reference number RH074 was imprinted on the carton/box. The leaflet or patient information leaflet (September 2017) was verified against the published leaflet on the WHO website (November 2019).

Master Specifications

Specification Medroxyprogesterone Acetate Injectable Suspension USP Specification Number was reviewed. This included tests for Description, ID, SG, pH, Sedimentation value, Resuspendability, Syringability, , Viscosity, and Osmolality as described below.

Water System

A Milli Q system was used to produce water used in the laboratory. It was noted that the work surfaces around the water system were wet. The qualification of the system did not include the HMI DIRA, Microbiological testing was not performed.

Column-management

The column qualification was reviewed which included details of Column Application, Column registration, Column Performance, Column assignment, Column Qualification, and Column usage. The column for the assay test was reviewed. The process was to assign the column into LIMS with acceptance criteria of Tailing factor NMT 2.0 and Plate Count NLT 1000. The company used the SST parameters to qualify the column. The qualification of the column was performed as part of the product testing process and the SOP did not enable a pre-qualified column to be used by the analyst.

Verification report

Method Equivalency Report for Assay of MPA by HPLC for Medroxyprogesterone Acetate Injectable Suspension was reviewed. This was performed in 2016 and included the Methodology, Instruments and Standards, Summary of Method equivalency, Method Precision USP, and Method Precision (in-house).

Analytical Method Validation

MPA Injectable Suspension USP was reviewed. Parameters included Specificity, (ID and Interference Study) as well as forced degradation study, Linearity and Range, Accuracy, Precision (System Precision, Method Precision, Intermediate Precision), Robustness, Stability of Analytical Solution, Stability of Mobile Phase and SST summary, LOD, and LOQ.

Data Management

Empower 3 Chromatography Data Software Operation was reviewed. There were 6 User types including Administrator, QA Administrator, Reviewer, Analyst, Guest, and Service. The company confirmed that Reviewers did not perform an analysis. The steps in data management included sequence run by the analyst, acquisition of data, reviewing of data, processing results and final sign-off. The reviewer had access to all injections, initial sample set, instrument parameters, sample set method report, SST requirements, chromatography, results, calibration curve, sample set, audit trail, project audit trail (monthly), and system audit trail (monthly). The backup occurred daily on an online and scheduled basis. Restoration of data occurred monthly. During the inspection, the testing data of Dissolution for one batch was verified and no anomalies were observed.

Entry into Microbiological Laboratory

The entrance was via a gowning room where the process was to put on an overcoat, overshoes and safety glasses. The biometric access was used to enter the microbiology laboratory as per the SOP Entry and Exit Procedure for Micro Laboratory.

Sterility Test Method Validation

The sterility Test MV Validation Protocol was reviewed. The test was performed by Direct Inoculation, by using a 100 ml medium. The rationale as to why direct inoculation was used and not filtration, was that it was a suspension. The objective was that the sterility test method was applied to the product and that the product did not have any bacteriostatic and fungi-stasis in sterile MPA. Frequency: The validation study was performed on 3 batches. 200 samples were utilized. Requirements were FP vials, Culture suspension, SCDM, FTM, Forceps, Scissors, Equipment and accessories, Autoclave, Incubators, LAF, BSC, vial openers, Microbial cultures, including for FTM: Clostridium, Pseudomonas, Staph, and SCDM- Bacillus, Candida, Aspergillus. Validation test methodology included Product control/Sterility test, Bacteriostatic and fungi-stasis test, Product positive control and Media Negative control.

Autoclave Chamber

The holder channels through under which the sensor wires were fed, were not flush. The drain was not checked before and after each load. Loading patterns were not displayed. The autoclave seal was checked manually daily, for obvious damage. It was lubricated as well monthly. Unloading from the autoclave was under class A.

Steam quality

Steam quality checks were performed 6 monthly. This included Superheat: NMT 25 °C, Dryness: NLT 0.95 and NCG ≤ 35 %. It was noted that the condensed steam was not tested to pure stream standards.

The deficiencies noted in this section have been addressed satisfactorily and the same will be verified during future PQ inspections.

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, located at ***Matoda, Ahmedabad, India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	**List of WHO Guidelines referenced in the inspection report**

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***

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***

3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3

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

5. 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**

6. 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

7. 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 3.
   Short name: WHO TRS No. 957, Annex 3

8. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Sixth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 2.
   Short name: WHO TRS No. 1044, Annex 2

9. WHO guidelines on technology transfer in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
   Short name: WHO TRS No. 1044, Annex 4

10. 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***

11. 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***

12. 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

13. 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

14. 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

15. 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

16. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***

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***

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***

19. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6

20. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS No. 1033, Annex 4***

21. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10

22. Stability testing of active pharmaceutical ingredients and finished 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 10.
Short name: WHO TRS No. 1010, Annex 10

23. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**

24. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**

25. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6**

26. Production of water for injection by means other than distillation. WHO Expert Committee on

Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3. ***Short name: WHO TRS No. 1025, Annex 3***

27. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4. ***Short name: WHO TRS No. 1025, Annex 4***