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WHO Prequalification Unit (PQT) – Inspection Services Team (INS)
WHO PUBLIC INSPECTION REPORT
WHOPIR
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Lupin Manufacturing Solutions Ltd.
Corporate address of the manufacturer	Kalpataru Inspire, 3rd Floor, Off Western Express Highway Santacruz (East) Mumbai – 400055 India
Inspected site	
Name & Address of inspected manufacturing site, if different from that given above	Lupin Manufacturing Solutions Ltd. Plot No. 130, Road No. 11, J. N. Pharma City Parawada (M), Anakapalli, Andhra Pradesh 531019, India. **D-U-N-S Number:** 65-103-8106 **GPS coordinates:** North latitude: 17.68 East longitude: 83.20
Synthetic Unit /Block/ Workshop	• Multi Production Plant-1 • Multi Production Plant-2 • Multi Production Plant-2A& Hydrogenation Block • Multi Production Plant-4A
Inspection details	
Dates of inspection	from 31 March to 4 April 2025
Type of inspection	Routine onsite GMP inspection
Introduction	
Brief description of the manufacturing activities	Lupin Manufacturing Solutions Limited, Visakhapatnam, is engaged in the manufacture and distribution of synthetic non-sterile APIs and intermediates. No other manufacturing activities, apart from pharmaceutical production, are conducted at the site
General information about the company and site	Lupin Manufacturing Solutions Limited, a wholly owned subsidiary of Lupin Limited, operates as a dedicated entity engaged in API production, contract manufacturing (CMO), and contract development and manufacturing (CDMO) services. The company serves a global customer base, with operations based on two primary platforms: chemical synthesis and microbial fermentation. The Visakhapatnam manufacturing site is dedicated to the production of pharmaceutical products.
History	In the last five years, the site has been inspected by the following authorities:

Name of the Authority	**Dates of inspection**	**Scope of inspections (e.g. block, workshop etc. inspected)**	**Outcome of inspection**

	USFDA	13/01/2020 To 17/01/2020	Pre-Approval Inspection (PAI) of Sacubitril Valsartan Trisodium Complex	EIR received
	CDSCO	08/09/2022 To 09/09/2022	For issue of WHO GMP certificate as per the provisions of WHO-TRS Guideline	Satisfactory
	ANVISA	05/12/2022 To 09/12/2022	Periodical inspection for Good Manufacturing Practices for Pyrazinamide	Certificate received
	USFDA	06/03/2023 To 10/03/2023	GMP and preapproval coverage for Tolvaptan.	EIR received
	CDSCO	11/11/2024 To 12/11/2024	Inspection for grant of 9 API's and for renewal of 9 API's as per EU-WC norms	Satisfactory

Brief report of inspection activities undertaken – Scope and limitations

Areas inspected	**Document reviewed:**
	• Quality management
	• Personnel
	• Buildings and facilities
	• Process equipment
	• Documentation and records
	• Materials management
	• Production and in-process controls
	• Storage and distribution
	• Laboratory controls
	• Validation
	• Change control
	• Rejection and reuse of materials
	• Complaints and returns
	• Contract laboratories
	
	Site area visited:
	• Production plants:
	  o Multi Production Plant-1
	  o Multi Production Plant-2
	  o Multi Production Plant-2A& Hydrogenation Block
	  o Multi Production Plant-4A
	• Warehouses for starting materials, solvents, and finished APIs.
	• QC laboratory—Physical/chemical
	• Microbiological laboratory
	• Water generation facility
	• HVAC utility

Restrictions	The scope of the inspection was restricted to the API in the WHO prequalification program.
Out of scope	APIs and production areas/blocks that are not under the scope of WHO prequalification program.

WHO APIs (including WHO API or APIMF numbers) covered by the inspection	**PQT Number**	**Active Pharmaceutical Ingredient**	**Prequalification status**
	WHOAPI442	Bedaquiline fumarate	Prequalified
	WHOAPI040	Pyrazinamide	Prequalified
	APIMF408	Linezolid	Prequalified
	APIMF384	Dolutegravir Sodium	Prequalified
	APIMF487	Pretomanid	Under assessment
	WHOAPI425	Darunavir Ethanolate	Under assessment
	WHOAPI531	Tenofovir Alafenamide	Under screening

Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
BSE	Bovine spongiform encephalopathy
CC	Change control
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
KF	Karl Fisher
KSM	Key starting material
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Nonconformity
NON-CCOE	Non-chief controller of explosive
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
SMF	Site master file
SOP	Standard operating procedure
TSE	Transmissible spongiform encephalopathy
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	**Summary of the findings and comments**

1. Quality management

Quality-related activities were contemporaneously documented, and deviations from established procedures were recorded and justified, including the investigation of critical deviations. ALCOA principles were implemented. A Quality Unit, independent of production, was established. Authorized personnel for the release of intermediates and APIs were designated. Materials were neither released nor used prior to the satisfactory completion of evaluation by the Quality Unit.

The facility maintained an organogram outlining both the corporate and site organizational structures. It was observed that production and quality assurance functions operated independently. The Head of Production reported directly to the Site Head, who reported to the Chief Operating Officer, and subsequently to the Chief Executive Officer. The Head of Quality Control reported to the Head of Quality Assurance, who in turn reported to the Chief Quality Officer, and ultimately to the Chief Executive Officer.

All key positions in production, quality assurance, and quality control had been filled with personnel holding valid contracts. Job descriptions for these positions were reviewed during the inspection and found to be appropriate.

Product Quality Review

Regular quality reviews of APIs were conducted to verify the consistency of the process. Such reviews were conducted and documented annually on a rolling period according to the annual planner.

SOP for "Annual product quality review of drug substances and saleable intermediates" was discussed. Cpk and control charts were used for statistical process capability evaluation.

The following PQRs were discussed:

- APQR/API/Pyrazinamide USP, covering the review period from January 2024 to December 2024.
- APQR/API Darunavir Ethanolate, review period January 2024 – December 2024.

The APQRs were seen to be well-organized and detailed. Both manufacturing processes seemed to be well established and all CpKs were well within established limits.

The results of these reviews were evaluated, and an assessment was made of whether corrective action or revalidation should be undertaken.

Quality risk management

SOP for "Quality risk management" was discussed. The SOP outlined the following steps for QRM:

- Hazard identification
- Risk analysis ranking 1 - 5
    - Severity
    - Detectability
    - Likelihood of occurrence
- Risk evaluation
- Risk control

Categorization:

- High 41 – 125
- Medium 21 – 40
- Low 1 - 20

According to the SOP, periodic risk reviews were to be conducted as follows:

- Standalone prospective QRM: Every 3 years plus 6 months, or earlier if a need for revision was identified.
- Manufacturing process/product-related QRM: Every 5 years plus 6 months as part of the periodic evaluation, or earlier if a revision was deemed necessary.
- QRM must also be reviewed or revised in the event of any changes to the process or product.

Risk assessment protocol and report registers for 2022, 2023 and 2024 were checked.

A planner for periodic evaluation of quality risk assessment was presented to inspectors.

The SOP titled "Assessment for the presence of nitrosamine impurities in drug substances/saleable intermediates" was discussed. The SOP covered the risk assessment of small molecule nitrosamine impurities and nitrosamine drug substance-related impurities (NDSRIs) for the following:

- All chemically synthesized drug substances/saleable intermediates
- Semisynthetic and fermentation-based drug substances

The SOP specified a control strategy for US supply products and for EU/Canada products. US control strategy testing and manufacturing controls were recently revised according to the US FDA guideline "Control of Nitrosamine Impurities in Human Drugs Guidance for Industry" September 2024, revision 2.

The following documents were discussed:

- Technical justification report (theoretical) for "Nitrosamine impurities assessment for Dolutegravir Sodium (process A) PDP-1":
    - Assessment of starting materials, including solvents used in the process
    - Route of synthesis, including intermediates and finished API
- Risk assessment for N-Nitrosamine impurities in drug substance Dolutegravir sodium (process A) PDP-1 Manufacturing facility

Conclusion: Based on assessment it can be stated that it is unlikely to form NDMA, NDEA, or other N-Nitrosamine impurities in the manufacturing process of Dolutegravir sodium (process A) employed by Lupin due to the use of DMF-DMA and TEA and these impurities levels were observed well within the limit.

Control strategy: NDMA (N-Nitrosodimethylamine) and NDEA (N-Nitrosodiethylamine) were tested in six exhibit batches as part of confirmatory testing and were found to be below the disregard limit. As of the date of inspection, no additional batches had been manufactured.

Management Review (MR)
The procedure titled Management Review of Quality Metrics was established to define the process for conducting management reviews and evaluating the performance of Lupin's quality and cGMP systems. It was applicable to all facilities involved in manufacturing, packaging, testing, holding, and related activities, and served as a mechanism to identify potential significant discrepancies. Furthermore, annual management reviews were conducted to assess site performance and determine the necessity for corrective actions or revalidation of any process. The outcomes of these reviews were evaluated, and any agreed corrective actions were required to be implemented in a timely and effective manner.

The Site Quality Council Meeting (SQCM) was conducted monthly at the site level. A corresponding monthly quality review report was prepared, summarizing the status of key quality indicators, including laboratory testing, market complaints, recalls, field alert reports, batch failures, and QMS parameters. Additionally, a separate monthly report on quality timeliness metrics was generated, capturing key performance indicators (KPIs) used to measure progress against defined quality objectives. Furthermore, a table was established to outline the topics to be reviewed during each level of management review, categorized into three groups with defined frequencies: site-level SQCM, QCM, and the Global Quality Council Steering Committee (QCSC). The review frequencies were specified in the applicable SOP.

The most recent SQCM invitation was issued on 10 March 2025. The meeting minutes, along with the list of attendees, were available and reviewed. The minutes were prepared in accordance with the applicable SOP and included a table of actions as well as a review of the minutes from the previous meeting. Relevant KPIs were also made available for review by the council.

Deviations
Deviation from established procedures was documented and explained. Critical deviations were investigated, and the investigations and their conclusions were documented. Deviations and CAPA were managed by the quality assurance management system (QAMS).

The SOP for "Handling of deviations" was discussed. According to the SOP, deviations related to manufacturing or packaging were to be evaluated as part of the batch production review prior to batch release and must be documented in the respective batch records. Deviations were trended quarterly by:
- Overall trend
- Repetitive deviations
- Timelines for closure
- CAPA effectiveness and any additional actions identified or initiated

Deviations were categorized as:
- Critical
- Major
- Minor

Critical deviations should be closed within 15 working days from the date of initiation in QAMS. Other deviations should be closed within 30 working days from the date of initiation in QAMS. If deviation could not be closed within the defined timeline a maximum of two extensions would be allowed, justifications should be supported by a risk assessment. 1st extension: NMT 30 working days from the initial defined period, approved by site Quality Head, 2nd extension of NMT 30 working days from the 1st extension period, approved by CQA lead.

Randomly selected deviations documented in the deviation logbook for 2024, as well as the deviation trend covering the period from October 2024 to December 2024, were checked.

Handling of CAPA
SOP for "Handling of CAPA" was discussed. The SOP was applicable to:
- Complaints
- Product failure (OOS)
- Recalls/returns
- Deviations
- Audit
- Rejection
- Management review
- OOT
- Regulatory inspection findings
- Trends from process performance and product quality monitoring
- OOC (out of calibration)
- Laboratory incidents
- APQR
- Improvements in design of QS

According to the SOP, the target closure date for CAPA was defined as 90 working days from the date of initiation. A maximum of three extensions was permitted:
- 1st extension: Not more than 30 working days beyond the initial closure period.
- 2nd extension: Not more than 60 working days beyond the closure of the 1st extension period.
- 3rd extension: Timeline to be extended based on the justified time required to close the issue, subject to approval by the Quality Head.

A procedure for CAPA effectiveness evaluation was in place, and a CAPA register was maintained.

Root cause investigation (RCI)
SOP for root cause investigation was discussed. The SOP was applicable to all investigations carried out at the facility. The following tools were used for RCI:
- Check sheet
- Pareto
- Histograms
- Scatter diagram, flow chart
- Fault tree analysis
- 5-Why
- Brainstorming

Batch release
The SOP titled "Release of API & sealable intermediates" was discussed. The responsibilities were defined as follows:

- Production: review and submission of completed BPR
- QC: review of analytical records and submission of raw data for QA
- QA: review of BPR and analytical records

A checklist was used for batch release. Checks and releases of the batch in SAP were done by QA-authorized persons.

Batch production record (BPR) and batch cleaning record (BCR)
SOP for "Preparation, review, approval, and issuance of BPR and batch cleaning records" was discussed. BPR and batch cleaning records were prepared by production reviewed and approved by QA. BPR and batch cleaning records were printed from SAP, and the batch number was also generated by the SAP. A checklist was used for the BPR review of intermediates, saleable intermediates, and APIs. BPR was reviewed by the section in charge, the production, and IPQA personnel. Different BCR checklist was reviewed by the section in charge, the production, and IPQA personnel.

Analytical test records (ATR)
SOP for "Review of analytical data and test results" was discussed. A checklist was used for the review of ATRs. The checklist contained the following sections and was reviewed by the QA reviewer:

- Test data sheet
- Analytical documents
- Electronic data and audit trail review

Upon finalization of the Analytical Test Report, the reviewer was responsible for entering the test results into the SAP system to generate the CoA. The CoA was signed by the individual who entered the test results into SAP and was subsequently approved by the QA Manager or designee.

Self-inspection
The manufacturer adhered to the SOP for self-audits to ensure compliance with current Good Manufacturing Practices (cGMP). This procedure covered various departments, including manufacturing, quality control, quality assurance, training, and warehouse management, and was structured to assess adherence to GMP standards across key operational areas. The inspection schedule was established to conduct audits of each department twice a year. Auditor qualifications were governed by the SOP for Auditor Certification.

A checklist was used to guide the self-inspection, ensuring a thorough evaluation of compliance. Key areas assessed during the self-inspection included facility and equipment standards, documentation and record-keeping practices, personnel competency and training, quality control and assurance procedures, and material handling and storage. Critical or major findings identified were escalated to the management review meeting for prompt discussion and resolution, ensuring timely corrective actions.

Several key documents were reviewed as part of the self-inspection process:

- The self-audit calendar for the year 2025, which outlined the planned inspection areas, including QA, Microbiology, IT, Production, Administration, Technical Training, Quality Control, Engineering, Human Resources, Process Development Laboratory, and Warehouse.
- The self-audit report for production, along with corrective and preventive actions. The timelines for addressing the identified issues were observed to be in line with established procedures.

2. Personnel

There was an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in their respective job descriptions.

Job descriptions for Senior Managers in Quality Control were available and reviewed. The job descriptions were identical, outlining their responsibilities for overseeing Quality Control activities. They reported to the Head of Quality, who in turn reported to the senior management.

The manufacturer had established a comprehensive and well-documented training program, as outlined in the respective SOP. This procedure covered the identification, planning, execution, and documentation of training for personnel involved in pharmaceutical manufacturing, research, and support activities. The training program included initial training for new employees, as well as ongoing education for all staff members. Key components of the training included induction (e.g., organizational culture), cGMP (e.g., cGMP regulations and guidelines), and job-specific training (e.g., SOPs and protocols for critical tasks). Refresher training was conducted based on a training needs assessment, which informed the creation of the site's annual training needs calendar. Training effectiveness was monitored, with evaluations such as written exams, practical demonstrations, and performance reviews incorporated to ensure the program's impact.

An electronic system was utilized to track employee training history, including course completion, dates, and content covered. Overall, the training program demonstrated the site's commitment to ongoing personnel competency, with a strong emphasis on compliance with GMP guidelines.

Other reviewed documents included:

- GMP Training plan for the year 2025
- Functional training plan for the year 2025

Personnel hygiene

The manufacturer had established an SOP for personal hygiene to ensure that all personnel adhered to proper sanitation and hygiene practices while working within the facility. The primary objective of this SOP was to maintain a high standard of cleanliness and hygiene to prevent contamination during the production and handling of active pharmaceutical ingredients (APIs).

The prescribed hygiene practices outlined in the SOP included the mandatory use of protective and appropriate clothing, strict hand hygiene practices, and regular training on personal hygiene. The SOP also prohibited the wearing of jewelry or makeup while working in critical areas, including production, quality control, and the warehouse. In these areas, smoking, eating, or drinking was strictly forbidden to avoid contamination risks. Additionally, the document emphasized the importance of preventing direct contact between unprotected hands or personnel and raw materials, intermediate products, and other critical items.

Furthermore, the SOP outlined the requirements for health monitoring, ensuring that all personnel were free from infections and illnesses. Regular medical check-ups were also mandated to maintain a healthy workforce and minimize the risk of contamination.

The manufacturer had established an SOP for the medical examination of employees to outline the procedures for pre-employment and periodic medical examinations. The SOP required periodic medical examinations to be conducted once every six months. In the event of an illness, employees were required to obtain clearance from the facility's medical officer before rejoining work.

The periodic medical tests included clinical examinations, such as eye vision testing and skin assessments, as well as blood examinations, such as liver function tests. Additional tests included urine tests, tuberculosis screening, X-rays, and electrocardiograms (ECG), among others. These examinations were intended to ensure the health and fitness of employees to perform their duties without compromising their well-being or the safety and quality standards of the facility.

Entry and Exit Procedure in Powder Processing Area:
The inspectors reviewed the entry and exit procedures for the powder processing area as outlined in the applicable SOP. The SOP was applicable to both the powder processing areas in the production facility and the finished goods sampling and dispensing area in the warehouse. It was noted that strict access controls were implemented, ensuring that only authorized personnel were allowed into the powder processing areas. Personnel were required to follow a set of gowning procedures before entering these areas, which included wearing a nose mask, and head cap, removal of jewellery, and shoe covers, and performing hand sanitization. These measures were in place to prevent potential product contamination and maintain GMP compliance.

Consultants
Not covered during the inspection.

3. Buildings and facilities
Design and construction
Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities were designed to minimize potential contamination. Buildings and facilities had adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination. The flow of materials and personnel through the building or facilities was designed to prevent mix-ups or contamination.

The site layout comprised several distinct areas supporting API manufacturing operations. It included multiple production blocks such as MPP1, MPP2, MPP2A, and MPP3, along with areas designated for future production (MPP4). Supporting facilities included a utility block, hydrogenator, code drum tank farm, solvent tank farm, and a day tank farm. A large warehouse was centrally located, along with an in-process tank farm to support material handling. The premises also housed a quality control and administration block, an occupational health centre (OHC), and a QC laboratory. Additional infrastructure included a weighbridge, security cabins, an engineering area, and a contractor shed. The layout demonstrated clear segregation between production, utilities, warehousing, and administrative functions, with provision for future expansion.

In addition to the scope of the inspection, the MPP4 production facility, designed as a single-stream API plant with dedicated intermediate and powder processing areas, was visited during the inspection. It was noted that the facility was in the qualification phase, with only the reactor system for the synthesis of a single intermediate operational at the time of the visit. This intermediate was not within the scope of the current inspection. The inspection included a comprehensive walkthrough of all key process areas, including centrifugation, vertical tray dryer (VTD), agitated nutsche filter dryer (ANFD), and the associated air handling units (AHUs). The responsible staff were interviewed about the procedures for cleaning, filter integrity testing, and filter replacement on site. The water generation and distribution systems were visited and assessed, including verification of applicable water quality parameters, temperature and pressure differential controls, and the respective monitoring systems. Logbooks were randomly reviewed for completeness and traceability. The cleaning status of the facility was not deemed GMP compliant at this stage, as parts of the facility, in particular the cleaning rooms remained under qualification and were not yet maintained in a validated state.

Laboratory areas and operations were separated from production areas.

Microbiological Laboratory (MBL)
MBL, called as "Central Microbiological Laboratory" was located separately from other areas. The laboratory had:

- Media storage room. Media were stored according to the specified conditions in locked metal cabinets,
- Documentation room,
- Washing and de-contamination room. Appropriate autoclaves were available: one for the destruction of media, one for sterilization of Mili-Q water, and one as stand-by,
- MLT testing room. Entrance via change rooms, tests were carried out in RLAF,
- Culture room. Entrance via change rooms, work with live strains was carried out in biosafety cabinet,
- Media preparation room, and
- Media incubation room.

Process Water (PW) system
Potable water was received by pipelines from the area developer. The process was as follows: chlorination → two storage tanks → multi-grade filter → softener → 5 µm cartridge filter → ultrafiltration → chlorination → potable water storage tank. Water from the portable storage tank was distributed to various water purification systems. One such system was located in the MPP1 plant, which included two loops—one supplying water to the MPP1 plant and the other to the MPP2 plant. The MPP2A and MPP4A plants had their own dedicated process water generation systems.

The process water generation systems in all plants followed the same design: potable water storage tank → RO1 and RO2 (with pressure differentials monitored) → EDI → process water storage tank → distribution loop → UV → return to the storage tank. Online monitoring was implemented at the return loop for TOC, conductivity, and velocity. Integrity checks of hydrophobic filters were conducted annually. The water systems were equipped with audible alarm systems and were sanitized every seven days using hot water at 80 °C for 60 minutes. In addition, chemical sanitization was performed every three months using a chemical. The water systems were observed to be clean and well-maintained.

Process water specification was defined in the respective SOP.

Tests	**Specifications**
Description	A clear colourless, odourless liquid
pH	5.0 to 7.0
Conductivity at 25 °C	NMT 10.0 µS.cm1
Microbiological analysis TAMC	NMT 100 cfu/ml
Nitrite content#	NMT 1 ppm
Nitrate content#	NMT 1 ppm
TOC	NMT 500 ppb
# Nitrite content and Nitrate content shall be testes at supply & return points of process water once in a month	

HVAC system
Two types of AHUs were used to supply air to the cleanrooms: 100% fresh air systems and re-circulation systems with 10% fresh air intake. All AHUs installed across the plants followed the same design.

Primary and secondary filter cleaning was carried out monthly in filter cleaning rooms. Filters were cleaned with potable water and compressed air. HEPA filter integrity checks were performed annually by a third party. If no damage, HEPA filters were replaced every 5 years.

A Performance Verification Report for the Heating, Ventilation, and Air Conditioning (HVAC) System was conducted and reported for the MPP2A/PP Area, dated 23/05/2020. The following tests were conducted: airflow pattern test, HEPA filter leak test, air velocity and air changes per hour, recovery test, particle monitoring in air (non-viable particles), microbial monitoring, differential pressure (DP) monitoring, temperature (temp) and relative humidity (RH) mapping. All results were found to be within acceptable ranges.

Based on the performance verification study, the following recommendations were made:

- The Air Handling Unit (AHU) should be started 30 minutes before the onset of operations.
- Temperature and RH mapping should be performed in accordance with any applicable product requirements.
- Regular monitoring should be conducted in areas as per identified hotspot locations.

A guideline was available and implemented for the shutdown and subsequent start-up of the production facility. In addition, excursions in temperature, relative humidity, and differential pressure were monitored in accordance with the procedure defined in the SOP for Environmental Monitoring in Product Processing and Storage Areas.

As evidence, documentation related to the temporary cessation and re-initiation of manufacturing activities at the MPP2A facility, covering the period from 23 to 27 March 2025, was provided for review.

Production personnel were required to record the differential pressure in the powder processing area once per shift in the respective plant annexure. In cases where the differential pressure did not comply with the established limits, operating personnel were instructed to notify the maintenance department for rectification. Furthermore, as per the SOP for Preventive Maintenance of Control Systems, verification of critical alarms was performed during preventive maintenance activities in accordance with the applicable annex. Critical alarms were defined as those that could impact process parameters.

The site did not have an alarm system in place to provide notification when the differential pressure in the HVAC facility deviated from the acceptable range. Monitoring was limited to manual readings from Magnehelic gauges, recorded at the beginning and end of each shift, resulting in an interval of approximately eight hours. However, the effectiveness and performance of the system were verified through the recovery test report for airborne (non-viable) particle count.

Environmental monitoring (EM)

There was an SOP to outline the environmental monitoring for production areas, specifically targeting microbial monitoring in the powder processing area and the finished goods sampling and dispensing areas of the warehouse. This procedure included a schedule set annually for the production areas, detailing the name of the processing area, scheduled dates, actual dates, and any relevant remarks (e.g., whether monitoring had been performed).

The schedule for 2024 (January to December) was reviewed, alongside the plan for January to March 2025. Monitoring was found to have occurred monthly, and the plan was found to be developed by the microbiology department and approved by Quality Assurance.

The established alert and action limits for Total Aerobic Microbial Count were 15 CFU/hour/90mm plate (alert limit) and 20 CFU/hour/90mm plate (action limit), with a maximum of 100 CFU as per ISO Class 8, Class D standards. Monitoring was performed using the settle plate technique, with sample locations selected based on factors such as the work area, product exposure, door positions, return risers, and material movement. Exposure time in cleanroom areas was not less than 1 hour. A yearly schedule was prepared every December,

with checks for intermediate areas as well. Additionally, the shutdown SOP for production areas and the restart procedure included microbiological monitoring.

Relevant documents reviewed included the environmental monitoring schedule for production and finished goods areas, test data sheets for environmental monitoring in clean areas, intimation for shutdown/startup of the powder processing area, and environmental monitoring trend data from October to December 2024, all of which were found to be within the established limits and/or adhere to the requirements.

Nitrogen gas system

Nitrogen gas was produced on-site; however, this system was not visited during the inspection. Nitrogen was used for blanketing and during micronisation. 0.2 µm filters were installed at user points and were replaced annually. Samples were analyzed by the contract laboratory. The following tests were performed:

- Oxygen concentration
- Nitrogen concentration
- Dew point
- Carbon monoxide concentration
- Carbon dioxide concentration
- Non-viable particulate matter
- Oil mist
- Hydrocarbons concentration

During the inspection of the pharmaceutical manufacturer's nitrogen gas system, it was observed that the SOP for the operation of the Nitrogen Gas Generation Plant was available. The frequency of testing for the generated nitrogen gas was quarterly at the generation plant, while all other user endpoints were tested on an annual basis.

The reviewed test certificates for the source point and utility area included tests for several parameters such as oxygen concentration, nitrogen concentration, dew point, carbon monoxide concentration, carbon dioxide concentration, non-viable particulate matter, oil mist, hydrocarbons concentration, and Total Aerobic Microbial Count (TAMC). A total of 16 sampling points were reviewed, and the test data sheets for various quarters were also examined. The parameters were found to be within the specified limits.

Compressed air system

Compressed air was used only for the generation of nitrogen gas. This was not checked during the inspection.

4. Process Equipment

Design and construction

The equipment used to manufacture intermediates and APIs was of appropriate design, adequate size, and suitably located for its intended use, cleaning, sanitization, and maintenance. Equipment was constructed so that surfaces in contact with raw materials, intermediates, or APIs did not alter the quality of intermediates and APIs. Production equipment was used within its qualified operating range. Equipment had calibration labels, showing calibration date and due date as well as “status tags” and preventive maintenance labels. Control, weighing, measuring, monitoring, and testing equipment critical for assuring the quality of intermediates or APIs were calibrated according to written procedures and an established schedule.

Three types of reactors were used:

- SS 316
- Glass-line
- Hastelloy

Equipment maintenance and cleaning

There was an SOP that outlined the procedure for equipment cleaning in the production facility. The SOP covered multiple cleaning procedures, including Type-A cleaning (i.e. batch-to-batch cleaning and cleaning after 48 hours) and Type-B cleaning (i.e. product changeover cleaning and periodic cleaning). It also included passivation for new equipment and cleaning protocols for newly installed, transferred, or modified equipment, as well as cleaning after preventive maintenance, breakdowns, or general maintenance. The procedure was applicable to all equipment cleaning in the production facility.

Cleaning of equipment prior to preventive maintenance was carried out using the required solvent, followed by process/potable water. All cleaning details were recorded as per the SOP. A clean status label was attached to cleaned equipment, and the hold time for cleaned equipment was identified as 48 hours. Deviations in cleaning processes were addressed in accordance with the SOP for handling deviations. Cleaning operations, including equipment operation, cleaning, and maintenance, were documented in the equipment operation, cleaning, and maintenance logbook.

Inspection of cleaned equipment involved visual inspection, rinse/swab sample analysis, and testing for genotoxic impurities, where applicable. Cleaning in process lines was performed by production staff, and periodic verification of equipment cleaning was carried out by performing rinse/swab sampling. For non-dedicated equipment, sampling was performed every six months or whenever a new campaign for a respective product was planned. For dedicated equipment, testing occurred annually. If a specific product was not produced regularly in the respective manufacturing area, testing was carried out whenever the product was produced.

Equipment Qualification

An SOP outlining the qualification process for equipment and systems used in the manufacturing of drug substances and intermediates was reviewed. It included the identification of user requirements as well as the execution of installation and operational qualifications.

The SOP specified that requalification was required following any significant changes, modifications, or equipment breakdowns that could have impacted its validated status. In the absence of such events, periodic requalification for critical equipment was mandated every five years.

During the inspection, the Installation and Operational Qualification protocol and report for the reactor in MPP4 were thoroughly reviewed. The inspection confirmed that the qualification process had been appropriately executed in compliance with user requirements and established procedures. All related documentation was traceable, and the equipment handover had been formally approved by the production department.

Calibration of Equipment

The calibration procedure for the reactor/agitated vessel, as outlined in the respective SOP was reviewed during the inspection. The procedure described the calibration process for the reactor and the maintenance of related records. Recalibration was required following any modification or relocation of the reactor/agitated vessel.

Calibration records and checklists for the reactor located in MPP4 were examined and found to be in order.

During the inspection of the production facility, calibration charts and labels were observed to be displayed near various pieces of equipment across different areas. These were found to be current and up-to-date.

Preventative Maintenance
During the inspection, it was noted that the equipment was well-maintained. All production equipment displayed preventative maintenance labels, and status labels (indicating cleaning and operational status), and various logbooks were maintained for their usage and cleaning operations.

An SOP on the equipment maintenance program outlined the procedure. Preventative maintenance was carried out according to the PM schedule available in the SAP system. The maintenance of each equipment was guided by individual SOPs, with the frequency and checkpoints determined based on factors such as equipment criticality, frequency of use, handling, operation, manufacturer recommendations, and the criticality of the process.

Preventive and breakdown maintenance history cards were generated from SAP and reviewed annually, with comments from the reviewer. Based on the review of these records, the planned preventive maintenance program was adjusted as needed, including changes to the frequency of maintenance or the addition or deletion of checkpoints.

Additionally, the maintenance work permit and notifications for preventative maintenance were selectively reviewed. The checklist for the centrifuge's preventative maintenance, signed off by both maintenance and production staff, was also examined. It was noted that these activities followed the Preventative Maintenance schedule year 2025, for facility MPP4A, dated 27/01/2025, signed off by engineering and QA department heads and as per SOP: Preventative maintenance of Reactor/Agitated Vessel.

A weekly review sheet for the preventative maintenance/calibration planner was traced for plant MPP1, with four pieces of equipment checked against the yearly schedule. The corresponding logbook was also reviewed. The training history for one of the operators was traced through the eLearning system and confirmed that the operator received area-specific training, GMP-related training, etc.

5. Documentation and records
Documents related to the manufacture of intermediates or APIs were prepared, reviewed, approved, and distributed according to respective SOPs. Documents were maintained in paper or electronic form (such as e-logbooks for equipment usage).

The issuance, revision, superseding, and withdrawal of documents were controlled in accordance with the SOP for Document Control Procedure, with revision histories maintained. The procedure covered the issuance, control, distribution, retrieval, reconciliation, and destruction of documents and logbooks.

Document management at the site was supported by computerized systems (for SOPs, STPs, and training) and DMS (for uploading approved documents for printing and execution)—as well as a manual system involving logbooks.

Templates used for various site activities were uploaded into a database system, a corporate document management application. When printed, the templates included the date of printing and the identity of the person who initiated the print, shown as a footnote. Consequently, the issuance of templates was considered to be controlled.

GMP documents were stored under the responsibility of the Quality Assurance (QA) department, with appropriate access restrictions in place.

Documents were retained for defined periods—for example, Master Batch Manufacturing Records for drug products and SOPs were retained indefinitely, while Batch Manufacturing and Packaging Records were retained for one year following batch expiry.

Additional relevant SOPs review included the SOP on the Destruction of Documents and the SOP on Handling Master Documents in the respective database. Retention periods were outlined in the SOP for Storage Period for Documents/Records, which included a table specifying the retention timelines for each type of document.

At the site level, electronic signatures were not in use; however, at the corporate level, procedures for the implementation and use of electronic signatures had been established.

The main components of data governance, intended to ensure the accuracy, consistency, and completeness of data throughout its lifecycle when generated to support product quality, safety, and efficacy, were defined in the SOP for Data Governance.

Master (approved) labels were maintained and used for comparison with issued labels to ensure accuracy and traceability.

Master production instructions for each intermediate and API were prepared, and the respective records were dated, signed by one person, and independently checked, dated, and signed by a representative of the Quality Unit to ensure batch-to-batch uniformity. The following master production instructions were reviewed to verify the inclusion of:

- The name of the intermediate or API being manufactured and an identifying document reference code.
- Raw materials and intermediates were designated by names or codes sufficiently specific to identify any special quality characteristics.
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity was not fixed, the calculation for each batch size or rate of production was included. Variations to quantities were included where they were justified.
- The production location and major production equipment to be used.
- Detailed production instructions, including:
    - Sequences to be followed,
    - Ranges of process parameters to be used, and
    - Time limits for completion of individual processing steps and/or the total process, where appropriate, and expected yield ranges at appropriate phases of processing or time.
- Where appropriate, special notations and precautions to be followed, or cross-references to these.
- The instructions for storage of the intermediate or API to assure its suitability for use, including labelling and packaging materials and special storage conditions with time limits, where appropriate**.**

It was noted that each document, including Master Batch Records (MBRs), specifications, and SOPs, was assigned a unique identifier (e.g., document number, revision number) for easy tracking and retrieval. A formal review and approval process was followed to ensure all documents met the required quality standards. Access to master documents, such as MBRs and specifications, was restricted to authorized personnel, as outlined in the IT SOP on user management for the e-DMS system.

The document control system maintained an audit trail of all changes, including the date of the change, the reason for the change, and the personnel who authorized the change, all controlled by the electronic system. Version control was implemented for MBRs to track any changes or updates, with obsolete versions removed or marked as obsolete to prevent errors.

Batch production records
Batch production records were prepared for each intermediate and API and contained complete information related to the production and control of each batch. Prior to issuance, each record was checked to ensure that it corresponded to the correct version and was a legible, accurate reproduction of the relevant master production instruction. Templates were issued through the SAP system, which generated a batch-specific barcode along with the date and time. This barcode served as a unique identifier. The final batch number was allocated.

The batch production records for Pyrazinamide, released on 18 March 2025, were randomly selected for review and verification during the inspection.

Original data were maintained, and all test records were generally complete, contemporaneous, and included the required signatures and dates. A second person (Shift In-Charge) confirmed the accuracy and completeness of the records, serving as an integrity check. The complete set of records was subsequently reviewed and verified by the Quality Assurance unit.

During the inspection, it was noted that the identification numbers of some equipment used during the analysis, such as the pH meter, sonicator, and water bath, were not documented in the analytical sheets. Additionally, the exact times of equipment usage were not consistently recorded. In response, the site identified the equipment and amended their procedures to ensure the documentation of identification numbers and the use of an electronic logbook to accurately record the exact ID number and the times of usage.

Documentation of the completion of each significant step in the batch production records included all required information, as outlined in the SOP for Preparation, Review, Approval, and Issuance of Batch Production Records and Batch Cleaning Records.

Batch production and laboratory control records of critical process steps were reviewed and approved by the Quality Unit before any API batch was released or distributed. All deviation, investigation, and OOS reports were reviewed as part of the batch record review before the batch was released, where applicable.

6. Materials management
A system was established for the evaluation and approval of suppliers of critical materials. Materials were procured in accordance with agreed specifications from approved suppliers.

Sampling and testing of incoming production material, intermediates, and finished APIs
The receipt of solvent delivered in tankers was assessed during the inspection. The activity was governed by an SOP, which was applicable to the receipt of raw materials/solvents in tankers at the warehouse.

Upon arrival, notification of the tanker was received by warehouse personnel either via telephone communication from the security gate or through accompanying shipment documents. The designated warehouse personnel were responsible for verifying the Certificate of Analysis, cleaning certificate, and the corresponding Purchase Order or Stock Transfer Order (STO) in SAP.

Following confirmation, the tanker was directed to a dedicated parking area, and upon registration of the solvent in SAP, sampling was performed by personnel from Quality Control. Sampling was conducted using a glass sampling device approximately 4 feet in length. To ensure representative sampling, valves located at both the top and bottom of the tanker were utilized.

Upon completion of analytical testing and approval of the sample, the solvent was released and transferred to the tank farm area designated as NON-CCOE.

At least one test to verify the identity of each batch of material was performed, in accordance with applicable regulatory and quality requirements.

Tanker contents were transferred through dedicated pipelines. In cases where mixing of different lots was required, this was managed and documented in SAP, and a new batch number was assigned to the resulting mixed batch. The mixed batch was subject to full analytical testing by a designated QC team prior to release. The applicable SOP for mixed solvents was titled Testing of Mixed Solvents, effective from 14/12/2023.

Earthing pits were installed to safely discharge static electricity during the unloading operation.

The tank farm area was visited, and the labeling of storage tanks was verified to be compliant with applicable GMP requirements. The area was equipped with appropriate warning signage and fire safety measures, including the presence of fire extinguishers, to manage potential incidents.

The flammable liquid storage area was physically segregated. Solvents were stored in drums, each labeled with product information and a barcode generated by the SAP system to indicate the material status. In cases where drums were used for sampling, this was marked on the drum in accordance with internal procedures, as defined in the respective SOP.

The manufacturer maintained designated sampling areas for carbon materials, liquid materials, and solids, which were equipped with fume hoods, calibrated weighing balances, and Restricted Localized Air Flow (RLAF) systems. During the inspection, no sampling activities were conducted for packaging materials. The sampling areas for products were separated, with distinct entry points for both personnel and materials to ensure controlled access. Qualified QC staff performed the sampling activities in accordance with the established procedures, i.e., SOP on sampling.

Although no sampling was performed at the time of the inspection, the required documentation and environmental controls were found to be in place. A logbook titled "Raw/Packing Material Sampling Booth Usage and Cleaning Records" was maintained to document key operational parameters.

The logbook included detailed entries such as RLAF system on/off times, pressure differentials, sampling times, material and batch numbers of the sampled materials, cleaning records, and verification checks. It served as a comprehensive record of the sampling process, supporting GMP compliance and environmental monitoring.

Sampling plans and procedures were adequately defined and implemented to prevent contamination of the sampled materials, intermediates, or APIs while ensuring the integrity of samples following collection.

Samples were requested through a requisition form, and samples were collected from each container. A composite batch sample was prepared and divided into three portions: control sample, visual inspection, and extraneous particles. Control samples were retained for the expiry date plus one year. Information regarding batch details and the number of sampled containers was documented in the SAP system.

No further tests were conducted after the initial testing of mixed solvents in the farm tanks. During the inspection, the company initiated a change control request to revise the applicable SOP. Specifically, point 5.1.3 was proposed to be updated to state: “Upon completion of 10 mixed lots of solvents in each over-ground solvent storage tank, testing shall be performed once every six months ± 15 days.”

To support the proposed change in sampling frequency, a prospective quality risk assessment was conducted on 02/04/2025. The risk assessment was performed to evaluate the potential risks associated with the revised testing frequency of mixed solvents.

Storage
Materials were handled and stored in a manner that prevented degradation, contamination, and cross-contamination. Materials stored in fiber drums, bags, or boxes were kept off the floor and, when appropriate, suitably spaced to permit cleaning and inspection. Materials were stored under conditions and for periods that had no adverse effect on their quality and were normally controlled to ensure that the oldest stock was used first. A separate storage area was provided for carbon powder.

7. Production and In-process controls
Products under PQ were manufactured in the following plants:
- MPP1 (non-dedicated facility), Strems A, B and C:
  - Bedaquiline fumarate
  - Pretomanid
  - Darunavir Ethanolate
- MPP2 (non-dedicated facility):
  - Linezolid
  - Dolutegravir Sodium
  - Tenofovir Alafenamide
- MPP2A (dedicated facility)
  - Pyrazinamide

All the aforementioned production plants—including the synthetic sections and cleanrooms—were visited during the inspection. MPP1, MPP2, and MPP4A consisted of distinct synthetic and cleanroom areas, each operating as a separate unit. Notably, MPP1 included three production streams—A, B, and C—each connected to dedicated cleanrooms. MPP2A, which is dedicated to the production of Pyrazinamide, did not include a synthetic area. The entire manufacturing process was carried out within cleanroom environments.

The inspectors were informed that the company intends to submit variation applications by the end of 2025 to increase batch sizes for the use of MPP4A in the manufacture of the following products:
- Pretomanid
- Tenofovir Alafenamide
- Dolutegravir Sodium

Accordingly, MPP4A was also included in the inspection.

Production operation
Raw materials for the manufacturing of intermediates and APIs were weighed or measured under appropriate conditions that did not affect their suitability for use. Weighing and measuring devices were of suitable accuracy for the intended use.

Critical weighing, measuring, or subdividing operations were controlled. Prior to use, production personnel verified that the materials corresponded to those specified in the batch record for the intended intermediate or API. Actual yields were compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges were established.

Vendor management
The manufacturer followed a structured Vendor Qualification procedure as outlined in SOP: Vendor Qualification, which governed the qualification and requalification of vendors supplying materials and services for drug products and substance manufacturing. The vendor evaluation process involved reviewing key documents such as the Product Registration Form (PRF), Certificate of Analysis, Nitrosamine declaration, TSE/BSE documentation, and the Site Quality overview. However, the evaluation did not include a review of the regulatory compliance history for new vendors. Vendor requalification was based on assessments of specifications, Quality Risk Management, annual evaluation reports, and user test reports, with a detailed risk

assessment conducted when necessary. Vendor approval was valid for three years, except for secondary and tertiary materials like solvents, where approval was considered perpetual. The annual vendor evaluation included a review of performance data from the previous year, focusing on quality, regulatory compliance, complaints, rejections, and delivery consistency. The SOP also defined processes for disabling or re-approving vendors, including actions for repeated failures, audit outcomes, or overdue Quality Agreements, with extreme cases leading to permanent disqualification, such as when a vendor ceased manufacturing a material.

Vendor audits were conducted in accordance with the respective standard procedures. The audits were performed to assess GMP compliance and evaluate vendor performance. Audits were planned based on product/material criticality, with critical vendors prioritized. Different types of audits, including onsite, desktop, and virtual, were conducted as per risk-based assessments, and deficiencies were classified, with critical deficiencies leading to disqualification.

During the inspection, the audit report for a selected vendor, conducted on 20 October 2023, was reviewed.

The 2024 annual vendor evaluation was reviewed. The evaluation encompassed batch acceptance/rejection data, testing methodologies, complaints, and CAPA implementation by the vendors. Additionally, the written quality agreement between the manufacturer and the vendor, signed on 11 February 2020, was reviewed. The agreement outlined quality specifications, GMP compliance expectations, and documentation responsibilities.

However, certain gaps were identified. These included the absence of defined delivery schedules and Nitrosamine Assessment Declarations within the quality agreement, as well as a lack of sufficient evaluation of the vendor's capability to consistently deliver materials within the required timelines.

Overall, the vendor management and auditing processes were largely aligned with GMP requirements, though areas for improvement were identified, particularly in the quality agreements and vendor performance evaluations. Addressing these gaps will be essential for further enhancing vendor management practices and ensuring ongoing compliance with regulatory standards.

Lists of Approved Manufacturers of KSM for WHO PQ products, packaging materials were available and found adequate.

Blending batches of intermediates or APIs

According to the company’s explanation till the date of inspection, blending of batches had not been carried out.

SOP titled “Operation of Blender/RVD”, was reviewed during the inspection. As per the SOP, out-of-specification batches must not be blended with other batches. Each batch incorporated into a blend must have been manufactured using an established process and individually tested to confirm compliance with appropriate specifications prior to blending.

The expiry or retest date assigned to the blended batch was determined based on the manufacturing date of the oldest batch or tailings included in the blend. Furthermore, blending operations were required to be validated, and the resulting batches must be included in stability studies to ensure continued product quality.

8. Packaging and identification labelling of APIs and intermediates

Packaging operations were not carried out during the inspection and, therefore not inspected. Labels applied to the APIs containers were printed by production personnel and checked by QA. Labels were attached to the BPRs.

9. Storage and distribution

Warehousing procedures

Facilities were available for the storage of materials under appropriate conditions. Records of these conditions were maintained. SAP system was used for materials management.

Distribution procedures

APIs and intermediates were released for distribution to third parties only after approval by the Quality Unit. A system was in place to allow the distribution of each batch of intermediates and/or APIs to be readily determined to facilitate recall if necessary.

10.Laboratory controls

The independent Quality Unit was provided with adequate laboratory facilities. Written procedures were established and implemented for the sampling, testing, approval, or rejection of materials, as well as for the storage and retention of laboratory data. Laboratory records were maintained in accordance with applicable requirements.

Scientifically justified specifications, sampling plans & schedules, and test methods were in place to ensure compliance with defined quality and purity standards. These specifications included appropriate controls for impurities.

Reagents and standard solutions were prepared and labelled in accordance with the procedure defined in SOP titled Reagents, Chemicals and Volumetric Solutions, with "use by" dates applied where applicable.

The use and cleaning of chromatography columns were managed in accordance with the SOP titled Good Chromatographic Practices and Documentation, effective from 12 November 2024.

Primary reference standards were obtained from recognized sources such as USP, EP, and IP, and were documented, stored, and used in accordance with the respective supplier recommendations. Pharmacopeial reference standards were utilized during the preparation of in-house working standards. Both reference standards (RS) and working standards (WS) were managed through the software application, with receipt, usage, and other relevant information recorded in the system.

Working standards were dispensed in single-use vials to avoid repeated handling, and the dispensing took place in a dedicated LAF bench. The usage of Pyrazinamide USP RS and WS for a selected batch was reviewed in the application, during the inspection.

Authentic Certificates of Analysis were issued for each batch of intermediate or API upon request.

Appropriate safety measures, including safety showers, eye-wash stations, first aid kits, goggles, and warning signs, were available throughout the laboratory. A spillage kit was presented during the inspection; however, the site was advised to provide suitable brooms and equipment for the safe handling of broken glass.

Sample receiving and distribution
Samples were received through a designated pass-through window along with the corresponding test request and subsequently transferred to a temperature-controlled sample storage room. Each sample was stored in a dedicated sample cubicle, labeled with the sample name and batch number.

Temperature and humidity conditions in the room were monitored using a digital data logging system and the associated application. The system was reviewed during the inspection.

Analytical tests were assigned to analysts based on documented competency, as recorded in a dedicated logbook. Sample distribution and corresponding entries were maintained in the Competency List logbook.

Testing of starting materials, intermediates, and APIs
For each batch of intermediate and API, appropriate laboratory tests were performed to confirm compliance with established specifications. The drug substance release specification for Pyrazinamide USP and the corresponding analytical record for a selected batch, with sample number was reviewed for verification during the inspection.

Appropriate microbiological tests were conducted on each batch of intermediate and API where microbial quality was specified.

OOS management
Laboratory controls were performed and documented in real time. Any deviations were recorded and appropriately justified. Out-of-specification results were investigated in accordance with the SOP for Handling of Out-of-specification Test Results. The procedure included defined provisions for resampling or retesting, which were carried out as per documented requirements. The SOP, including the decision tree for OOS investigations and procedures for handling non-conclusive cases, was reviewed and discussed during the inspection. Randomly selected OOS investigations were reviewed during the inspection.

Retention samples
Reserve samples were retained for potential future evaluation of the quality of API batches, and not for ongoing or future stability testing.

Appropriately identified reserve samples of each API batch were retained for one year after the expiry date assigned by the manufacturer.

Samples were stored in the same packaging system as the API or in packaging that was equivalent to, or more protective than, the marketed packaging. Sufficient quantities were retained to allow for at least two full specification analyses.

Stability study
Walk-in chambers with the following conditions were used:
- T 25 °C ± 2°C, RH 60% ± 5% (2 chambers- one standby)
- T 30 °C ± 2°C, RH 65% ± 5% (2 chambers- one standby)
- T 40 °C ± 2°C, RH 75% ± 5% (2 chambers- one standby)

Temperature and Relative Humidity were monitored using a digital monitoring system. Data was recorded every hour and verified once per day. Chambers were equipped with audible alarm system and text message alarms. During the inspection, the stability monthly schedule for the period 01/02/2025 to 30/04/2025 was reviewed against the commercial batch for Pyrazinamide USP, and the sampling and testing plan was noted to have been respected. Alarm records for the month of March for chamber T 30 °C ± 2°C, RH 65% ± 5% (ID:

VZE-064) were reviewed and no excursions were noted. Stability studies for API and intermediates were managed as per SOP for management of stability studies.

Microbiology laboratory

The Microbiology Laboratory (MBL) was visited during the inspection. The laboratory was observed to be well-organized and well-maintained.

MBL utilized only ready-to-use culture media. Upon receipt, each lot of media underwent a Growth Promotion Test (GPT), preceded by pH verification. In-house labels included the date of receipt and the date of GPT. Vendor certificates of analysis were available for each lot.

The laboratory used commercially prepared, single-use Reference culture containing live microbial strains. These strains were stored in a deep freezer maintained at –18 °C to –32 °C. Temperatures in the deep freezer and incubators were continuously monitored, with printouts generated and reviewed every 24 hours. Both the deep freezer and incubators were equipped with audible alarm systems located within MBL.

However, as the laboratory operated in two shifts, temperature excursions occurring outside operational hours could only be identified with a delay. In response, during the inspection, the company implemented a corrective measure by connecting the local alarm system to a remote alarm panel located at MPP3, where security personnel were present 24 hours a day.

Additionally, the laboratory was equipped with a system for the identification of microbial strains other than local isolates. The system featured an in-built reference strain library.

11.Validation

Systems and processes were periodically evaluated to verify that they were still operating in a valid manner. When no significant changes had been made to the system or process, and a quality review confirmed consistent production of material meeting its specifications, revalidation was not required. Validation and qualification of critical systems, including computerized systems, processes, and analytical methods, were considered essential to ensure the reliability and integrity of data generated and managed through these systems.

Validation master Plan (VMP) was discussed. According to the applicable SOP, VMP should be reviewed once every two years. VMP described the qualification and validation policy. VMP was applicable to:

- Equipment qualification
- Facility qualification
- HVAC qualification
- Water system qualification
- Nitrogen system qualification
- Process validation
- Cleaning validation
- Analytical method validation
- Computerized system validation

Process validation
The respective SOP specified:

- Stage 1 – process design
- Stage 2 – process qualification
- Stage 3 – continued process verification – verification of "validated" status of the manufacturing process:
    - Trend analysis of quality parameters
    - APQR

Re-validation or re-qualification was required whenever changes are introduced to the facility, manufacturing process, specifications, processing equipment, or input materials that may impact the validated status. Such changes must be assessed, and if deemed significant, must trigger re-qualification.

In the absence of changes to the manufacturing facility, process, batch size, route of synthesis, or equipment, periodic evaluation of the validated process was to be conducted—specifically, every five years with an additional allowance of six months—to determine the need for re-validation or re-qualification. This applied, for example, in cases where there was a change in the KSM.

The re-validation/re-qualification schedule for the year 2025 was presented to the inspectors during the inspection.

Process performance qualification report of product Dolutegravir sodium (process A) was spot-checked.

Process water qualification
At MPP4, the process water generation, storage, and distribution system were visited. They were designed and qualified in accordance with GMP principles and relevant qualification protocols. The design process included preparation of a User Requirement Specification (URS), vendor selection and evaluation, and execution of qualification activities.

The water system comprised a pre-treatment stage, cartridge filtration, and a two-pass reverse osmosis (RO) system (RO1 with 6 membranes, RO2 with 4 membranes), followed by EDI. Post-EDI, water was transferred to a distribution tank equipped with a hydrophobic vent filter and spray ball for cleaning. The system included sanitary pumps and an ultraviolet (UV) disinfection unit with online monitoring. UV intensity was monitored, with a maximum allowable usage of 9000 units. Water was continuously circulated to the production area and returned to the tank.

The system was equipped with online monitoring for conductivity, and velocity. Total organic carbon (TOC) monitoring equipment was under installation. A total of 23 sampling points (each with ports smaller than 3 mm) were available across the loop. The distribution piping was designed with a 1:100 slope to ensure drainage. Welded joints (10%) were radiographically examined, and passivation was conducted using nitric acid (70% stock, 1% solution), with pH monitored until values between 5–7 were reached (final pH: 6.5). Qualification was carried out in three phases. During OQ, velocity was challenged; and conductivity was evaluated during PQ. Both were documented. Phase I sampling was conducted for 14 days at all points, with a report prepared and signed off. Specifications were confirmed prior to Phase II, which followed the same 14-day sampling plan. TOC samples were analyzed by a third-party laboratory. Phase III, extending up to one year, involved routine sampling on a rotational basis. Following completion of the qualification, alert limits were established.

The process water met specifications equivalent to purified water. For system MPP4A, a Phase III sampling schedule ensured representative sampling from all 23 designated points. Records for sample point PWDSP-4A23 at the return line were requested and reviewed during the inspection.

Qualification of analytical instruments
The usage of equipment for QCL activities was generally documented in an electronic logbook system, including calibration and maintenance activities. This applied to all equipment except those operated through chromatography software applications. The usage of those equipment was maintained by the software itself.

Equipment was randomly selected during the inspection to verify the availability and compliance of their qualification and performance verification documentation.
- Balance
- Balance
- FTIR, including the associated KBr cells and polystyrene reference material used for calibration
- HPLC, Boiling Water Bath

Cleaning validation:
The SOP titled "Cleaning Validation for Drug Substances and Intermediates" was established to define the requirements for ensuring that the cleaning process was capable of reducing chemical residues of previous products (drug substances and intermediates), genotoxic impurities such as nitrosamine impurities and NDSRIs (where applicable), cleaning agent residues, and microbiological contamination (where relevant) on both direct and indirect product contact surfaces to acceptable levels. This SOP encompassed the design and development of the cleaning process, cleaning validation, cleaning verification, and maintenance of the validated state, as well as the associated documentation requirements. The procedure applied to the lifecycle management of cleaning validation, including Cleaning Process Design, Cleaning Process Qualification, and Continued Process Verification.

For the calculation of swab and rinse sample limits and the determination of the worst-case scenario, every product was considered as the representative product. The following documentation for Darunavir was randomly selected and reviewed:
- Document for the Determination of Acceptable Daily Exposure (ADE) for Darunavir
- Instruction for the Determination of Acceptance Criteria for Swab and Rinse Samples
- Documentation on the Establishment of Maximum Allowable Carry Over (MACO) for MPPQ Stream B – PP Area and Micronisation Area-2
- Swab Limit Calculation
- List of equipment with product contact surface areas for MPPQ Stream B – PP Area and Micronisation Area-2
- Cleaning Validation Protocol for Darunavir Ethanolate (Stage: Darunavir Ethanolate)
- Analytical Method Validation Protocol for the cleaning method of Darunavir Ethanolate,
- Analytical Method Validation Report for the cleaning method of Darunavir Ethanolate by HPLC

The cleaning validation protocol for MPP1 was selected for review, as this building is utilized for the manufacture of multiple products, including Darunavir Ethanolate, Bedaquiline Fumarate, and Pretomanid, among others.

Cleaning procedures were validated with a focus on process steps where the risk of contamination or product carry-over could significantly impact the quality of the active pharmaceutical ingredient (API). The cleaning validation approach reflected actual equipment usage. As multiple APIs and intermediates were manufactured using shared equipment, an analytical method was specifically developed, validated, and applied based on the product processed immediately prior to the cleaning activity.

The cleaning validation protocol clearly described the equipment to be cleaned, cleaning procedures, materials used, acceptable residue limits, critical process parameters to be monitored, analytical methods, sample types, and sampling techniques.

Sampling strategies included swab sampling for accessible surfaces, and rinse sampling where swabbing was not feasible, particularly for hard-to-reach or complex internal areas.

Validated analytical methods with adequate sensitivity were employed to ensure the detection of residue levels within acceptable limits. The limit of detection (LOD) and other relevant detection thresholds were duly considered during the validation of the analytical methods used for cleaning verification.

Residue limits were practical, achievable, verifiable, and based on the most deleterious residue, considering pharmacological, toxicological, or physiological activity.

Cleaning procedures were monitored at defined intervals—specifically, after every two product manufacturing campaigns—following the initial validation, to ensure the continued effectiveness of the cleaning process. Equipment cleanliness was verified through analytical testing, and, where feasible, visual inspection was performed to detect any gross contamination, particularly in concentrated areas that might not be adequately identified through routine sampling or analytical methods.

Documentation related to the cleaning verification of equipment intended for the production of Bedaquiline (February 2025), following the manufacture of Raltegravir Potassium Crystalline (December 2024), was requested and reviewed. The worst-case product for cleaning validation was identified as Elagolix Sodium (Bedaquiline), with a Maximum Allowable Carryover (MACO) of 82,500, as per the risk assessment dated 19 June 2024.

The cleaning validation report for Raltegravir Potassium Crystalline, dated 18 September 2024, was available. Additionally, the cleaning verification report for Raltegravir Potassium USP (Process A) in MPP1 A Stream PP Area was reviewed. The cleaning activity was part of a commercial campaign.

The following documentation was reviewed to support the verification:
- Swab sampling details, including results and compliance with specifications
- Analytical results from samples collected from the centrifuges used in production

Hold time
During the inspection, hold time studies for all WHO Prequalified (PQ) products were reviewed. Protocols for each product were available and presented for inspection. The hold time sample testing summaries, including the respective annex, were thoroughly examined for all products.

Each study was conducted over a 12-month period under validated temperature conditions consistent with those used during manufacturing. Sampling was performed at multiple time points—0, 1, 2, 3, 6, 9, and 12 months. A comprehensive range of parameters was tested, including description, identification, water determination, loss on drying, purity, and related substances.

For all seven products reviewed, no significant changes were observed throughout the study period, and all tested parameters remained within the specified limits. It was confirmed that validated analytical methods were used for all testing activities.

Additionally, the following documents were reviewed during the inspection:

- SOP on Hold Time Study of Drug Substance and Intermediates, which outlines the roles of the Production, QC, and QA teams in performing and approving the hold time study protocol and report.
- Certificate of Analysis for Darunavir Ethanolate.
- Hold Time Study Report.
- Test Data Sheet for Darunavir Ethanolate at 12 months.
- The hold time study protocol for Darunavir Ethanolate was conducted under validated environmental conditions of 2 to 8°C, and the selected batches were reviewed under the study. The Hold Time Sample Testing Summary for Darunavir Ethanolate was also examined, and no OOS (Out of Specification) results, OOT (Out of Trend), or other deviations were reported. All parameters were within the specified limits.

Validation of Analytical methods
This topic was covered during the evaluation of other validation categories.

Computerized system validation
GMP-related computerized systems were required to be validated in accordance with the procedure for Validation of Computerized Software Systems to ensure their suitability for intended tasks. Adequate controls were implemented. The site maintained an inventory index and a periodic review schedule for GxP-relevant computerized systems. Each system was listed with its associated equipment or instrument number, software name, and version, and classified according to GAMP categories. Additional documented details included intended functionality, hostname, and configuration parameters such as operating system and RAM. Integration status with other systems was recorded, including the names of any connected systems. The applicability of electronic records and electronic signatures (ER/ES) was specified for each system. Validation activities were monitored through records of initial and most recent validation dates. A defined periodic review frequency was established, with both past and upcoming scheduled review dates documented. Actual review dates were recorded upon completion.

A study titled “Protocol cum Report for Assessment of GxP Computerized Systems with Respect to Operating System” was conducted to identify GxP-relevant computerized systems operating on versions earlier than Windows 10. A corresponding risk assessment was available and reviewed during the inspection. The assessed risk was considered low and acceptable.

An application was used for managing master data and user access requests, including User ID creation, deactivation, reactivation, modification, account unlocking, and password resets. It was applicable to all GxP computerized systems, encompassing both site-specific and enterprise applications implemented across all Lupin Limited sites, including Head Office, R&D sites, and Lupin Manufacturing. The process was governed by the SOP for User Access Management. This SOP provided adequate provisions to prevent unauthorized access or data modification and to ensure data completeness. All data changes were required to be traceable, with audit trail entries capturing the previous value, the identity of the user making the change, and the date of the change.

In addition, the SOP for Standalone Computer Software System Administration was applicable to all standalone systems where data or audit trail information was stored on local hard drives. This SOP established the procedures and controls for the administration of such systems. Where manual data entry was used, additional verification for accuracy was expected.

Computerized systems were equipped with adequate controls to prevent unauthorized access or unauthorized changes to data. Measures were also implemented to ensure data integrity by preventing omissions in data entries.

In cases where system breakdowns or failures could result in the permanent loss of records, a backup system was implemented in accordance with the SOP for Backup, Restoration, and Archival of Computerized System. Backups were performed based on defined schedules for both networked and standalone non-networked computerized systems. The backup process was illustrated through a flowchart depicting the data transfer from user systems to the server and subsequently to tapes. Backup tapes were stored in a secured cabinet onsite, with duplicate copies maintained offsite for disaster recovery purposes.

For networked systems, backups were generally performed daily. For non-networked standalone systems, weekly or monthly backups were implemented based on risk assessment and criteria defined in the applicable SOP. A specific risk assessment related to a selected system was available and reviewed during the inspection.

There were processes in place to verify that electronic records remained readily retrievable, so-called restoration in accordance with the applicable SOP. The evidence of the last restoration was reviewed and discussed.

A Disaster Management and Business Continuity Plan for Computer Software Systems was available and reviewed during the inspection.

Furthermore, a separate Business Continuity Plan (Revision No. 00), effective from 1/03/2024, was available to provide a broad framework for maintaining business operations in the event of a contingency. The scope of the plan covered production planning and execution, quality management and quality control laboratories, distribution, and IT systems. Provisions were included for scenarios such as data failure, epidemics, and pandemics, among others. For each scenario, consequences, contingency measures, and recovery strategies were defined.

12.Change control (CC)

A formal change control system was established to evaluate all changes that could affect the production and control of intermediates or APIs.

The applicable SOP covered the identification, documentation, appropriate review, and approval of changes related to:

- Manufacturing facilities
- Procurement
- Warehousing
- Distribution
- Equipment
- Utilities
- Manufacturing processes
- Materials/products
- Systems and instruments
- Document management systems:
  - Specifications
  - Test methods
  - Operating procedures

CC were managed by QAMS. Changes were defined as:

- Minor
- Major

According to the applicable SOP, Change Controls (CC) were required to be closed within 90 working days from the date of initiation for complete closure, and within 70 working days for completion of all proposed action plans. Based on justified reasons, a maximum of three extensions may be granted beyond the initially defined closure timeline. For major changes, a risk assessment had to be conducted to evaluate potential impacts. Additionally, effectiveness monitoring was mandated for all changes to ensure the intended outcomes were achieved.

Randomly selected Change control requests were checked.

13.Rejection and re-use of materials

Rejection

Intermediates and APIs that did not meet established specifications in the respective SOP were identified and quarantined. These intermediates or APIs could be reprocessed or reworked as appropriate. The final disposition of rejected materials was documented.

Reprocessing and reworking

SOP for "Reprocess and rework of drug substances/intermediates" was checked. Reprocessing or reworking was undertaken to improve the quality of a batch for specific parameters by undertaking the same established manufacturing process. According to the SOP, reprocessing was allowed up to two times. The reprocessed or reworked batch was analysed for all test parameters. The target date of closure of the reprocessed or reworked batches should be 150 working days for the complete cycle and 120 working days for the action plan closure from the date of initiation in the QAMS. A maximum of three extension times were allowed. 1st: NMT 30 working days from the initial defined period, approved by Head QA/designee; 2nd: NMT 60 working days from the 1st extension period, approved by site Quality Head; and 3rd: the timeline should be justified and approved by CQA Lead. Manufacturing and expiry/retest dates were to be assigned based on the date of reprocessing or rework. In case reprocessing or rework was carried out for the first time, the substance was subject to stability studies. Process validation studies should be performed, whenever required. In the case of reworking, a concurrent validation approach was followed.

Reprocessed batches register 2023 – 2024 were checked. According to the company, no products were reworked.

Recovery of materials and solvents

SOP for "Handling of recovered solvent and distilled solvent" was available. The company indicated to the PQT assessment team that no recovered solvents were used for APIs under PQR.

Returns

Returned intermediates or APIs were mandated to be identified as such and quarantined and stored in locked returned goods areas. A returned goods receipt checklist was used. Records of returned intermediates or APIs were maintained. The following aspects, among others, were checked by QA:

- Quantity
- Labelling
- Seal of containers
- Conditions of containers
- Deviations identified in storage/shipping
- Sampling required

14.Complaints and recalls

All quality-related complaints, whether received orally or in writing, were recorded and investigated according to SOP titled "Handling of market complaints for drug substances and intermediated". Complaints were managed by QAMS. According to the SOP complaints were categorized as:

- Critical, category I. Shall be closed within 15 working days form the day of initiation
- Major, category II
- Minor, category III

Major or minor complaints should be closed within 30 working days from the day of initiation. No more than three extensions were allowed. 1st extension: NMT 30 working days from the initial defined default period approved by Head QA/designee; 2nd extension: NMT 60 working days from the initial defined default period, approved by Site Quality Head; and 3rd extension: The timeline for issue closure was extended based on a justified request, with approval granted by the CQA Lead. Complaints trending was documented and reported during management review meetings.

According to the impact assessment procedure, investigations must be extended to other batches of the same product, as well as to other products manufactured during the timeframe of the complaint in question. In cases where a product defect, such as an out-of-specification result, was identified, any affected batches that had not yet been distributed must be immediately quarantined. Appropriate actions should be initiated for product recall. Furthermore, all customers to whom the impacted batches were distributed must be promptly informed.

Investigation of the a selected complaint was checked.

SOP for "Recall of API/Saleable intermediates was discussed. The SOP was established to define the circumstances under which a recall of an intermediate or API should be considered. The recall procedure specified responsibilities for evaluating information, the process for initiating a recall, individuals and authorities to be informed, and the handling of recalled materials. In serious or potentially life-threatening situations, local, national, and/or international authorities were informed, and their advice was sought. The mock recall was carried out for at least one batch of any product dispatched for sale or export. The last mock recall was carried out in February 2025. Till the date of inspection, no recalls were carried out. There were two types of recalls specified:

- Voluntary
- Statutory

15.Contract manufacturers (including laboratories)

A list of contractors was available.

Contract laboratories

The facility had established an SOP for the qualification of contract testing laboratories. This procedure outlined the process for the selection, approval, maintenance, and lifecycle management of contract testing laboratories. The evaluation of new external laboratories included a request from the Research & Development (R&D) department, followed by the completion of a questionnaire, a thorough audit of the laboratory, and the signing of a quality agreement valid for three years. Test samples were sent to laboratories that held valid quality agreements, accompanied by requisition slips, and all relevant records were maintained. The list of approved contract testing laboratories was reviewed during the inspection.

The facility had a contract for outsourced testing. This laboratory had been physically inspected on 20/05/2022, and the next audit was scheduled. The laboratory maintained a valid quality agreement effective from 02/04/2024. The quality agreement and associated documents were reviewed and found to be compliant.

The list of products/materials to be tested included Dolutegravir Sodium, a WHO Prequalified product, for testing of N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) content.

Contract Manufacturing

A contract had been established between the manufacturer, Lupin, and the contracted manufacturer to produce Bedaquiline intermediate (Bedaquiline NBLAA salt). The contract outlined the responsibilities of both the manufacturer and the contracted manufacturer, and these responsibilities were found to be adequately defined. An audit of the contract manufacturing facility was conducted in August 2022, and the findings indicated that both the production and quality management systems were in full compliance, as reported in the audit report.

Miscellaneous	
Samples taken	*N/A*
Assessment of the site master file	The Site Master File (SMF) with an effective date of 12/02/2025 was submitted and reviewed.
Annexes attached	A list of change controls was submitted before the inspection.

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, **Lupin Manufacturing Solutions Ltd., (Multi Production Plant-1, Multi Production Plant-2, Multi Production Plant-2A & Hydrogenation Block, Multi Product Plant–4A)** located at **Plot No. 130, Road No. 11, J. N. Pharma City Parawada (M), Anakapalli, Andhra Pradesh 531019; India** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

The deficiency observed during the inspection that was listed in the full report was addressed by the manufacturer, to a satisfactory level, before the publication of the WHOPIR.

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

Part 4	**List of GMP guidelines referenced in the inspection report**

1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO GMP for APIs or WHO TRS No. 957, Annex 2***
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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

3. 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/

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. 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/

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

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. ***Short name: WHO TRS No. 981, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3.
Short name: WHO TRS No. 992, Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

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

22. WHO general guidance on variations to multisource pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report. Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO Multisource guidance or WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. 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
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Short name: WHO TRS No. 1025, Annex 3
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25. 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
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26. 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.
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