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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Schazoo Zaka (Pvt) Ltd.**
Corporate address of manufacturer	20-km Lahore-Jaranwala Road, Kalalwala, Sheikhupura Pakistan
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Schazoo Zaka (Pvt) Ltd 20-km Lahore-Jaranwala Road, Kalalwala, Sheikhupura Pakistan
Unit / block / workshop number	Solid Antibiotic Section
Inspection details	
Dates of inspection	7-11 October 2024
Type of inspection	Re-inspection
Introduction	
Brief description of the manufacturing activities	The site is authorized to manufacture tablets, hard gelatin capsules, dry powder suspensions, and dry powder sachets. The site is divided into three manufacturing areas. More specifically, there is a Solid Antibiotic Section, a Solid General Section, and a separate and segregated facility for Nutraceuticals. No hormones, steroids, beta lactams or narcotic products are manufactured on-site
General information about the company and site	Schazoo Laboratories were established in 1951. The Schazoo Laboratories were earlier situated on the Grand Trunk Road in Lahore. In 2008, the manufacturing activities were transferred to a newly constructed site at Kalalwala, approximately 25Km northwest of Lahore. The company changed its name to Schazoo Zaka Pvt. Ltd. This is a family-owned business and the senior management positions are assigned to family members.
History	This was the second WHO Prequalification inspection. The first inspection was carried out in September 2022. The site is periodically inspected by the local authorities (DRAP).

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The following documents and procedures were reviewed: • Organization Chart. • Job descriptions for key personnel. • Personnel training and hygiene. • Product Quality Review. • Quality Risk Management. • Responsibilities of the quality units and production. • Complaints and Recalls. • Deviation control and change control. • CAPA. • OOS and investigation. • Material release. • Self-inspection and vendor qualification. • Validation and qualification. • Technology Transfer – Method Transfer. • Equipment calibration. • Data integrity. • Sampling and testing of materials. • Batch processing records. • Materials management system. • HVAC system • PW system. • Stability studies Areas visited: • Starting materials, packaging materials, and FPP warehouses • Manufacturing operations • QC laboratories
Restrictions	The inspection was restricted to products under WHO PQ
Out of scope	All other products and workshops were outside of the inspection scope and were not visited.
WHO products covered by the inspection	Ethambutol hydrochloride/Isoniazid/Pyrazinamide/Rifampicin Tablet, Film-coated 275mg/75mg/400mg/150mg
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record

BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CNC	Controlled but not classified
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FeFo	First expiry first out
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment

RCA	Root cause analysis
RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

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

1. Pharmaceutical quality system

The PQS of the company was described in the Quality Manual which integrated ISO 9001:2015 principles and GMP guidelines. The QM followed the structure of ISO 9001 standard. It is recommended that high-level text is added in the QM to describe certain GMP principles that are not adequately addressed by the ISO standard, for example investigations, qualification/validation, and recalls. The QM distribution list was made available. The quality policy and the Laboratory Quality Policy were also presented. The company was certified for ISO/IEC 17025, ISO 14001, and ISO 9001. The first two standards were not integrated in the QMS and separate quality manuals and policies were available. The commitment and accountability of the senior management for the implementation of the PQS were adequately described in the QM. There were separate and independent departments for QA, QC, and Production. Similarly, the QC and Production functions were separate and independent. There was a procedure in place for performing batch release.

Product Quality Review (PQR)

A procedure for conducting PQRs was in place. PQRs were conducted annually including batches manufactured from January to December. PQRs for products manufactured in the Solid Antibiotic Section had to be completed between January and May of the following year and products manufactured in the Solid General Section had to be completed between June and October. Additionally, PQRs could be performed on a rolling basis, according to the procedure. PQRs were performed even if no batches were manufactured during the review period. The 2024 plan for Solid Antibiotics was presented.
The Rifampicin/Isoniazid/Ethambutol/Pyrazinamide 150/75/275/400mg f.c. tab (Rifa 4+) PQR was reviewed. Five batches were manufactured during the review period. Two deviations and three changes were registered. No complaints, recalls, or returns were registered.

Deviations

A procedure for handling deviations was presented. According to the procedure, the person identifying any departure from approved instructions, or established standards during manufacturing, testing or distribution had to register a deviation. The head in charge of the concerned department ensured that the QA department was immediately informed. The deviation was recorded in a restricted access Excel sheet, maintained on a server. An initial risk assessment was carried out by a cross-functional team. Similarly, root cause investigations were carried out by a cross-functional team. After identifying the root cause, CAPAs were implemented. Examples of deviation handling were reviewed.

Change control

Change management was described in a written procedure. The procedure was applicable to all GMP related operations and it provided instructions on registering and handling change requests. The change control committee was responsible for assessing the change request and proposing approval or rejection of the change request. The decision was taken by the QA department. An initial risk assessment would be performed and an implementation plan would be determined. After implementation, the QA department was responsible for verifying the implementation. Examples of change management cases were reviewed.

All the non-compliances relating to the QMS observed during the were adequately addressed by the manufacturer.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were generally well defined in SOPs and implemented. Manufacturing processes were adequately described and documented in BMRs and BPRs. Records were made during the manufacturing process. Qualifications and validations were performed according to the prepared protocols. Records of equipment calibration, maintenance, and cleaning were in place. The required resources were available, including premises, equipment, and utilities, as well as qualified and trained personnel

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

3. Sanitation and hygiene

Premises and equipment were generally maintained at an acceptable level of cleanliness, and they were appropriately labelled. There were cleaning procedures in place for facilities and equipment. In general facilities including warehouse and production areas, were found to be tidy. Pictorials of gowning/de-gowning instructions were posted in personnel entry rooms. Rooms and areas for equipment and utensil cleaning were established. The procedures and records for utensil cleaning at the sampling rooms and the dispensary were reviewed in detail.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

4. Qualification and validation

The sequence of activities to ensure that facilities, equipment, systems, and utilities were maintained in a validated state were described in procedures and protocols. In general, validation/qualification reports were generated following a specific format and provided detailed information and results on the tests, challenges and calibrations carried out.

Rifa4+ Packaging Process

The Process Design protocol and report for the packaging process of Rifa 4+ tablets were reviewed. The aim of the protocol was to set and optimize the Quality Target Product Parameters. More specifically, the packaging process included: a semi-automatic air-blowing machine for empty HDPE jars, manual feeding of tablets into the hopper of the tablet counting and pouch filling-sealing machine, an automatically rotating tablet counter tray (2x100 pockets), formation of the LDPE pouch, filling of tablets in the pouch, sealing and cutting of the pouch, transfer of the pouch by belt, manual weighing and

filling of the pouch in the jar and addition of 2 desiccants and the patient leaflet, manual capping and induction sealing, transfer of the jar by belt to the labelling station (secondary packaging area) and inkjet printing of batch number, manufacturing/expiry dates and 2D barcode. Improvements in the automation and reproducibility of the packaging process are sought. The company is committed to validating the packaging process for at least the first three commercial batches.

Qualification of the Tablet counting, pouch filling, and sealing machine

The qualification included protocols for the following stages: User Requirement Specifications (URS) and Design Qualification (DQ), Factory Acceptance Tests (FAT), Site Acceptance Tests (SAT), as well as Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Each of these stages was documented in separate protocols and SOPs.

The SOP for Operational Qualification, and the SOP for Performance Qualification were reviewed. The DQ and URS forms for the tablet packaging line (Jar filling) for packing of 4FDC tablets in pouches and jars and the corresponding reports dated 06.07.2023 were reviewed. The FAT protocol, was available, dated 12.9.2023. The SAT Protocol dated 12.9.2023 was also available, indicating the expectations, actual conditions obtained and the remarks.

The IQ Protocol, dated 12.09.2023, was carried out by the engineer from the equipment manufacturer, located in Lahore. It described the installation work for an automatic pouch vertical form-fill-seal machine with 3-side sealing jaws, a PLC system, and two thermal sealing heaters (vertical and horizontal). Parts in direct contact with the product were made of SS304L. The PLC required a password for parameter setting and equipment access protection. Equipment components that were qualified included: the feeding hopper, tablet counting hopper, tablet rotating brush, LDPE film blocking wheel/rollers, vertical sealing heater, horizontal sealing heaters with cutters, pouch conveyer belt (from the cutter to the SS table), PLC (password protected).

In the OQ Protocol, control points and alarm functionality were verified against acceptance criteria, and results were stated. The protocol was approved on 12.9.2023, and the OQ was carried out on 22.9.2023.

The PQ report of the tablet counting, pouch filling, and sealing machine was reviewed. The performance qualification status was also documented on the relevant log in the server under the folder/equipment qualification/status Excel, which was used as a PQ monitoring tool for all equipment. The report dated 27.09.2023 indicated that the following parameters were studied: proper cutting, the weight of each filled pouch, leakage test of filled pouch, and machine speed.

Cleaning Validation

A procedure for conducting cleaning validation was established. The SOP was limited to the 4 antibiotic APIs used in the Solid Antibiotic Section. The worst-case scenario was determined (Rifa4+, 4 API product). The toxicological reports and the ADE calculations for Isoniazid, Pyrazinamide, Ethambutol, and Rifampicin were presented. The CVs of the toxicologists were readily available. The swab method was adequately described in the SOP. Recovery studies had to be performed and a recovery factor was determined and used in the calculations. Similarly, the rinse sampling method was adequately described and the last equipment rinse cycle was used for sample collection. The cleaning validation protocol and report for the Rotary Machine were reviewed in detail. The sampling locations for each production

equipment were determined. Rinse and swab samples were collected. The following acceptance criteria were determined:

- No residue should be visible on equipment after cleaning.
- Not more than 0.1% of the normal therapeutic dose of one product (selected active) in the maximum daily dose of the following product batch.
- Not more than 10ppm (or 0.001%) of one product will appear in the next product.

The most stringent limit was applied.

All the non-compliances related to validation/qualification activities observed during the inspection were adequately addressed by the manufacturer.

5. Complaints

The customer complaints procedure was reviewed. Complaints were received in writing only (via the company's website or email). Examples of complaint handling were reviewed.

Analysis of complaints was carried out every six months. The records for January to June 2023, and July to December 2023 were available.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

6. Product recalls

The SOP for Product Recall indicated that recalls were categorized in 3 classes (Class 1, Class 2, or Class 3). It also described the depth of recalls in terms of recall level (level 1- the consumer, level 2 -the distributors, and level 3-certain distributors). The logbook of recall/withdrawal for the period from 12.11.2016 to 24.11.2021 indicated a total of 6 recalls and 2 mock recalls. Also, from 18.03.2022 to 02.08.2024, one recall and 2 mock recalls were registered. The SOP required that if there was no recall in a period of two years, then a mock recall had to be initiated. No recall for 2024 was registered until the time of inspection. Examples of recalls and the relevant documentation were reviewed.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

7. Contract production, analysis and other activities

None of the production steps for Rifa4+ (the product under Prequalification) were outsourced. According to the SMF, the company was contracting out residual solvent testing by GC of Rifampicin, Isoniazid, and Ethambutol, APIs included in the Rifa4+ formulation.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

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

There was a procedure in place for vendor evaluation. Three samples were requested for analysis and a quality questionnaire was used before approving a new supplier. An on-site audit of the API suppliers was not always carried out. Revaluation of suppliers took place every three years or when a quality issue was identified. Examples of audit reports and of supplier quality questionnaires were presented and discussed.

Due to time constraints, self-inspection was not reviewed in detail.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

9. Personnel

The Organization Chart was presented. The job descriptions (JD) of the following key personnel in quality assurance, quality control, and production departments were selected and reviewed:

- The JD of the QC Manager (JD/2/08 Issue 15) indicated that he was directly reporting to the Technical Director and to the Chief Executive Officer (CEO). The JD was signed by the Technical Director and the CEO on 01.04.2024. Acknowledgment of receipt of the JD by the incumbent was confirmed by his signature on 03.04.2024 recorded on the Circulation Record.
- The JD of the Production Manager was also reviewed.
- The JD of the Quality Assurance Manager was presented. The QA was responsible among others, for the review of the complete batch documents including production and QC documents and complete history of material inventory control system of each batch before giving final approval in the Material Inventory Control for sale. The circulation record indicated that the JD was signed on 01.04.2024.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

10. Training

The training schedule for officers for the period October to December 2024 was reviewed. It included 18 courses/modules including data governance, health-based exposure limits in cleaning validation, and others. The training schedule for the previous quarter July – September 2024 was discussed. It included 5 pending trainings from the previous quarter and 24 training courses for the new quarter. All training courses were conducted within the scheduled time frame. Training for the QC Manager was selected for detailed review.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

11. Personal hygiene

The procedure on Personnel Hygiene and Working Environment and the Personnel Hygiene Form were reviewed. The form indicated the names of personnel and hygiene status checked for cloth/uniform, hands/ nails, haircut, shave, checked and filled by each section supervisor and the QA every two weeks.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

12. Premises

The production building housed two separate and independent units, namely, the Solid Antibiotic Section and the General Solid Section. Layouts of the facilities were made available. Access to these sections was provided through a common CNC corridor. Change rooms for personnel and visitors were in place before entry to the common CNC corridor. Separate and independent change rooms for accessing each production section were available. The inspection focused on the Solid Antibiotic Section, which was supplied with filtered air by a dedicated HVAC system consisting of five AHUs. The premises were designed to minimize the risks of cross-contamination and mix-up. Pressure differentials were

maintained and were spot-checked to verify implementation of CAPA deriving from the previous inspection.

The warehouse served both production sections and it included a general area for storage of raw and packaging materials (30ºC/70%RH), an area for temperature sensitive materials (25ºC/65%RH) and a cold room (2-8ºC). The temperature mapping report for RM/PM Warehouse conducted on 10.07.2019 was reviewed. It was detailed and contained all raw data. A dedicated area for finished products and a dispatch bay were also established. There were separate sampling and dispensing rooms for each production section. Materials dispensed at the warehouse were transferred through pass-boxes and a separate corridor to the core production areas. In general, production areas were adequately maintained. AHUs were installed on the technical floor. The same floor housed the PW system.

Heating ventilation and air conditioning system

Temperature and humidity were required to be maintained at not more than 28˚C and not more than 60%, respectively. A special condition of temperature specified as NMT 25˚C and relative humidity NMT 50% were required to be maintained for specific products.

Production process zones (e.g. granulation, blending, compression, coating, sachet (pouch) form-fill-seal, were classified as Grade D. Pressure gradient between the process zone and the corridor was maintained between 5-15 Pascal. Optimal pressure ranges were shaded green on the analogue pressure gauges that were used to measure pressure differentials between rooms and airlocks in the classified areas.

A dedicated area was used for washing and drying the G4 filters with potable water in one room, while bag filters were cleaned using oil-free compressed filtered air in a separate room.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

13. Equipment

In general, equipment was installed and adequately maintained to suit the requirements for the dosage forms manufactured. Production equipment was of appropriate standard and appeared to be well maintained. The workflow in the facility was appropriately designed, and the equipment was installed in a logical order to facilitate production, reduce the risk of contamination and mix-up. All production equipment reviewed were identified as to their content or cleanliness status by appropriate labels. Cleaning, maintenance, and calibration records as well as operation instructions were spot-checked.

Purified water generation and distribution system

The purified water (PW) generation and distribution system was verified against the schematic drawing. The system was fed with potable water which then went through, a 5µm in-line filter, a carbon, and a sand filter, a 5µm filter, a reverse osmosis unit (RO1 and RO2), a 5µm filter, an electro-deionization unit, and finally stored in a stainless-steel PW storage tank. The distribution loop consisted of a 0.5µm ceramic filter, PW 16 user/sampling points, and an in-line UV-light disinfection unit at the return point of the PW before the PW storage tank. There was an in-line conductivity meter of the PW feed line from the EDI unit to the PW storage tank, but the device did not appear to function properly because the unit of displayed measure was in ppm instead of µs/cm. Conductivity and total organic carbon of the PW in the distribution loop were both monitored off-line. The usage hours of the UV light lamp were monitored and the lamp was required to be replaced after 10,000 hours.

An ozone generator was installed and used for the sanitation of the purified water distribution loop. A PW sanitization- utilization log sheet of the ozone generator indicated that sanitization of the PW distribution loop was carried out monthly.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

14. Materials

There was a dedicated area for the receipt of raw and packaging materials at the warehouse. A checklist was used to register the controls performed during receipt and the process was defined in a written procedure. Upon completion of the receipt process, materials were registered in the Material Inventory Control System (MIC) and a Good Receipt Note (GRN) was generated. Quarantine labels were printed out through MIC and affixed on the containers. The QA department was responsible for performing sampling in dedicated sampling areas. The sampling room for Antibiotic APIs was dedicated. The sampling room for the General section was used both for APIs (except antibiotics) and excipients. There was also a sampling room for packaging materials. Sampling labels were also generated by MIC and affixed on the containers after sampling. The process of printing labels was not adequately controlled. Inventory was managed through MIC and the principles of FeFo were built in the system. It was noted that for some APIs and excipients retest dates were established. According to the company, at the beginning of each month, a list was generated through MIC indicating the materials that needed to be retested. The rule was embedded in the materials' system, with retest dates in the next three months entered in the retest list.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

15. Documentation

A procedure for document and data control was established. The procedure defined the documentation hierarchy and the coding system, as well as the documentation structure. All quality documents had to be reviewed every 3 years unless otherwise necessary. It was noted the revision frequency had been revised but there were still several procedures that had not been reviewed and maintained the previously established 5-year review frequency. In addition to the above-mentioned procedure, there were two document and data control SOPs applicable to production and Quality Control, respectively, which included some duplication and instructions on the codification of Production and QC documents. Retention times for quality documents were defined in different SOPs. Procedures were retained for one year after becoming superseded. Batch processing, testing and release records were maintained for a period of one year after the expiry of the batch. The procedure for writing SOPs and the procedure for the control of Records were also available.

A procedure for issuing Manufacturing Control Documents, Packaging Control Documents and assigning batch numbers was presented. The batch numbering system included 6 alphanumerical characters. The first two letters were representative of the brand name of the product, and the third one reflected the dosage form. The three letters were followed by 3- serial number starting from 001.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

16. Good practices in production

The production areas were visited on different days to observe packaging and tablet coating activities. Areas inspected included the dispensaries, the powder compaction area, the punches and dies storage room, compression machines suites, the tablet coating room, the IPC laboratory, the primary packaging in bottles, and secondary packaging. Spot-checks on equipment cleaning and maintenance records were made. In general, line clearance was documented in BMRs. Metal detectors were used on the tablet compression machine. Temperature, relative humidity, and pressure differentials were monitored. Rooms and equipment were appropriately labelled.

The coating process for Rifa4+ tablets, batch: RPT746, batch size 250,000 tablets was observed. Two operators in the coating room were gowned in red color one-piece (overall) with bootie-like footwear and headgear that covered the entire head and neck, face masks and gloves.

All the non-compliances observed during the inspection were adequately addressed by the manufacturer.

17. Good practices in quality control

Sample Testing

The laboratory analytical worksheet for Benzodep 5mg tabs batch: BN T083, manufacturing date 30.09.2024, that was sampled on 01.10.2024 and for which testing was ongoing at the time of the inspection, was reviewed. The worksheets were issued by QA and stamped on each page. Print-outs from measuring equipment were signed and attached to the worksheet.

Class F_2, dead-weights, calibrated on 27.08.2024, were used for verification of the analytical balances before use. Records of balance verification were available.

The logbook for the pH meters indicated that calibration of the pH meters was conducted in the morning. Standard pH buffer solutions used (pH 4.00, pH 7.00 and pH 10.00) were metrologically traceable. Records kept for the digital pH meter included utilization log, and equipment maintenance checklist. Similar logs were maintained for other laboratory equipment.

Chemical reference substances (CRS) available included Ethambutol HCl Ph. Eur. batch number 4.0 assay 100.00%, received on 20.04.2024; Isoniazid batch number 2.0, assay 100.00%, received on 11.04.2023; Pyrazinamide Ph. Eur., batch number 2.1, assay 100.0%, received on 01.06.2024, and Rifampicin Ph. Int., Batch number 3.0 assay 97.20%. The CRS were in the original glass vials, and re-sealed using ordinary thin polyethylene wrapping. The vials were kept in a desiccator containing blue silica gel and placed in the refrigerator (2-8ºC). Temperature monitoring was performed by a digital data logger placed inside the refrigerator.

The preparation sheet for Potassium Bromate volumetric solution was reviewed. It had been prepared with respect to USP Vol. 6. The information on the reagent bottle was verified with that in the preparation sheet and found to tally.

The laboratory used water generated by the UltraPure® water purification system, terminally filtered through a 0.22µm filter. The water was stored in a large plastic container that indicated the date of preparation and signature of the person who prepared it. However, at the laboratory benches, the purified water was in plastic wash bottles with labelling only indicating "Purified Water" and was therefore not traceable to the bulk purified water that was prepared and put in the big plastic container.

The SOP for password policy, user rights, data backup, and storage for computer systems was reviewed. The HPLCs, UV visible spectrophotometer, and FT-IR were connected to the laboratory server (Windows Server 2012R2). Data generated on these three computerized systems was backed-up on the Laboratory server.

Data integrity governance incorporating the ALCOA+ principles and chromatographic practices were verified in the Shimadzu HPLC QC/HPLC 20AT. The HPLC used LabSolutions 6.83 software and was networked on the Laboratory server. Logging on to the Windows and LabSolutions software required individual usernames and passwords. The date and time functions were locked and could therefore not be changed by the analyst. The LabSolutions system indicated four types of users:

1. Operator (analyst) with 4 rights,
2. Test Manager (QC Manager) with 12 rights.
3. Quality Assurance (QA Manager) with 1 right (to browse entire log /audit trail log).
4. System Administrator (the Database Administrator from IT department)

None of the four users above had the right to delete data acquired in the HPLC. Data backup was automatically done. Audit trails functionality in the HPLC was permanently enabled. Test method parameters (referred to as projects) were pre-set and locked in the HPLC. HPLC analysis sequence table indicated the following order used: blank injection (1); standard injections (5); samples injections (6 injections, one solution prepared for each sample); bracketing standard injection (1).

Auto peak integration was used. Manual peak injection was used in exceptional circumstances and required justification and special authorization from the QC manager and the QA manager. The Justification Form for manual peak integration raised for N, N-Dimethyl Formamide standard 2 in Rifampicin QC number API-24-104 tested on 2708.2024 on HPLC QC/HPLC 20AT was reviewed. Manual peak integration was conducted with the approval of the QC manager and verified by the QA manager, as required in the SOP for HPLC Analysis, Documentation and Chromatographic Peak Integration. The original chromatograms using autointegration failed to select the peaks and the manual integration was able to select the peak at retention time 13.250. The original chromatograms acquired using autointegration and the chromatograms acquired using manual integration were both attached to the test report.

Stability Studies

The inspection team was requested to investigate the dissolution results for the stability studies performed for Rifa4+ batches: RPT714 and RPT175 at T:18months and T:24months.

According to the stability protocol, Rifa4+ batches: RPT713 and RPT714 in HDPE jars were placed in long-term stability studies (30±2ºC/75±5%RH). The following specifications/instructions were included in the protocol for dissolution:

i. Rifampicin NLT 75% (Q) of the labeled amount after 30 mins. Dissolution results of each of the 6 units must not be less than Q+5% (Stage S1). Dissolution sample will be tested after 30 mins, if results are NLT 75% of the labelled amount, then sample collected at 45 mins would not be tested.
   The average dissolution result of 12 units (S1+S2) must be equal to or greater than Q and no unit is less than Q-15% (Stage S2)
   Where Q is the amount of dissolved active ingredient specified in the individual monograph expressed as the percentage of the labelled amount.
ii. Isoniazid, Pyrazinamide, Ethambutol NLT 75% (Q) of the labelled amount after 45 minutes

According to the protocol a sample of 12 tablets is dedicated for this test for each time point.

A new stability protocol, for Rifa4+ batch:715 was approved. The same specifications/instructions for dissolution as in the above protocol applied. The codification of the protocol is confusing because it has the same code number, with different revision number and date but it applies only to batch:715, implying the previous protocol is obsolete. However, the long-term stability studies for batches: RPT713 and RPT714 continued.

Following a WHO communication, a new stability protocol for all three batches (RPT713, 14, 15) was approved, introducing microbial testing at the end of the stability studies (24 months) and tightening the specifications for dissolutions. More specifically:

i. Rifampicin NLT 80% (Q) of the labeled amount after 30 mins. Dissolution results of each of the 6 units must not be less than Q+5% (Stage S1). Dissolution sample will be tested after 30 mins, if results are NLT 80% of the labelled amount, then sample collected at 45 mins would not be tested.
   The average dissolution result of 12 units (S1+S2) must be equal to or greater than Q and no unit is less than Q-15% (Stage S2)
   Where Q is the amount of dissolved active ingredient specified in the individual monograph expressed as the percentage of the labelled amount.
ii. Isoniazid, Pyrazinamide, Ethambutol NLT 80% (Q) of the labelled amount after 45 minutes

According to the protocol a sample of 12 tablets was dedicated for this test for each time point.

Additional communication from WHO resulted in a revised stability protocol for all three batches (RPT713, 14, 15) tightening further the dissolution specifications. The new protocol was applicable to the remaining time points (T18 months and T24 months) of the stability studies. More specifically:

i. Rifampicin, Isoniazid, Pyrazinamide, Ethambutol NLT 80% (Q) of the labeled amount after 20 mins. Dissolution results of each of the 6 units must not be less than Q+5% (Stage S1). Dissolution sample will be tested after 20 mins, if results are NLT 80% of the labelled amount, then sample collected at 30 mins would not be tested.
   The average dissolution result of 12 units (S1+S2) must be equal to or greater than Q, and no unit must be less than Q-15% (Stage S2) where Q is the amount of dissolved active ingredient specified in the individual monograph expressed as the percentage of the labelled amount.

According to the protocol, a sample of 12 tablets was dedicated to this test for each time point.

The results and raw data related to the long-term stability study report for Rifa+4 batch: RPT714 were reviewed in detail. Stability testing for batch RPT714 at T18 months was carried out in March 2022. The dissolution result was 84% (87%, 85%, 83%, 83%, 84%, 84%) but some of the individual results were lower than Q+5%. Thus, the sample collected at 30 minutes was used, giving an average of 94% (95%, 94%, 94%, 95%, 93%, 92%).

Stability testing for Rifa+4 batch: RPT714 at T24 months was carried out in September 2022. However, the specifications described in the protocol were not followed. More specifically, the stability report and raw data indicated that each of the 6 units did not meet the Q+5% limits and therefore the 30min sample had to be tested. Despite the 30 min sample was tested, the company also calculated S1+S2 results and reported the latter in the stability report. The analytical workbook for the 24month dissolution testing of Rifa4+ RPT714 was presented.
The stability report and raw data for Rifa4+ batch: RPT715 at T18 months and T24 months was also reviewed.

Retention Samples
Reference (retention) samples were placed on metallic racks in their secondary packaging in an airconditioned room. Temperature data logger was used to capture temperature and relative humidity. The data was downloaded on a PC every 15 days and manually recorded twice a day. Trends of temperature and relative were graphically evaluated. For September, max. and min. temperature were 27.3ºC, and 24ºC respectively; and relative humidity max. and min. 70% and 49%, respectively.
All the non-compliances observed during the were adequately addressed by the manufacturer.

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, **Schazoo Zaka (Pvt) Ltd**, located at **20-km Lahore-Jaranwala Road, Kalalwala, Sheikhupura, Pakistan** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

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

Please note that acceptance of compliance with WHO GMP does not necessarily mean that Ethambutol hydrochloride/Isoniazid/Pyrazinamide/Rifampicin Tablet, Film-coated 275mg/75mg/400mg/150mg has been prequalified by WHO. Information on the prequalification of the product is found on the relevant WHOPAR.

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

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

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
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6. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4.
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https://www.who.int/publications/m/item/trs957-annex3

8. 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.
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9. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
Short name: WHO TRS No. 1019, Annex 2
https://www.who.int/publications/m/item/trs1019-annex2

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