20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Virchow Laboratories Ltd
Corporate address of manufacturer	Plot No 4, SV Cooperative Industrial Estate, IDA, Jeedimetla Hyderabad, 500 055 Telangana State, India
Inspected site	
Name & Address of inspected manufacturing site if different from that given above	Plot No 4 to 10, SV Cooperative Industrial Estate, IDA, Jeedimetla Hyderabad, 500 055 Telangana State, India Latitude: 17.519076 N Longitude: 78.456666 E DUNS: 6503315664
Synthetic Unit /Block/ Workshop	Block 1, Block 2, Pharma Block
Manufacturing license number	57/HD/AP/96/B/R valid through 31 December 2026 issued by Drugs Control Administration, Government of Telangana
Inspection details	
Dates of inspection	28 February – 1 March 2024
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	The plant is dedicated for the manufacture of Sulfamethoxazole (SMX) and its intermediates. All the reactors and other equipment are also dedicated for usage for that particular stage of manufacturing. Currently, the site is the world's largest producer of SMX, where approximately 80% of production is exported all over the world. SMX is produced from basic (early) stage with synthesis of all critical intermediates in-house (intermediates supplied by other vendors are excluded from SMX supplied to WHO and other DMF filed markets). Production activities are conducted at three production blocks (Production Block-I, Production Block-II and Pharma Block). Quality Control testing and in-process controls are conducted in-house at three facilities (IPC-I at Production Block-I, IPC-II at Production Block-II and the main QC laboratories at QA/QC block).
General information about the company and site	This unit of Virchow Laboratories Ltd was incorporated under the Indian Companies Act in the year 1981 and started production of Sulfamethoxazole (SMX) in 1983. The manufacturing site is located in Industrial Development Area (IDA), Jeedimetla, a suburb of Hyderabad, 20 km away from the centre of the city, State Telangana, Country India. A substantial Number of bulk drugs, fine chemical manufacturing, plastic, and engineering units are located

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

	in the same area. The manufacturing site is of the size 17 acres (69,000 m^2) and the build-up area for plant and offices is around 14,495 m^2, laboratory 523 m^2 and for storage facilities is 2535 m^2. The production unit at Jeedimetla is fully dedicated to the production of Sulfamethoxazole and its intermediates. Virchow produces around 3500 MT of Sulfamethoxazole per annum. The Sulfamethoxazole manufacturing process at Virchow is highly mechanized and utilizes efficient modem equipment like microprocessor controlled bottom discharge centrifuges, spin flash driers, vapour absorption cooling systems and stainless-steel reactors and condensers of various types and capacities.
History	The site used to be subject to regular inspections by several regulatory authorities including: – US FDA in … → March 2003 → November 2008 → October 2012 and → December 2015 – COFEPRIS, Mexico in August 2015 – PMDA, Japan in March 2018 – EDQM and AIFA, Italy in November 2019 – CDSCO/DCGI (latest in December 2021) In addition, the site is certified by local certification body for ISO 9001:2015 since September 1999 with latest audit in June 2023; and certified for ISO 14001:2015 since June 1998 with latest audit in June 2023.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Pharmaceutical Quality System Documentation Facilities and Equipment (warehouses, workshops) Utilities Production Packaging and labelling Product Release Quality Control laboratories
Restrictions	N/A
Out of scope	APIs not submitted to WHO Prequalification were excluded from the scope of this inspection
WHO APIs (including WHO API or APIMF numbers) covered by the inspection	Sulfamethoxazole in connection with …. – HA735 (Sulfamethoxazole/Trimethoprim Tablet 400mg/80mg), – HA736 (Sulfamethoxazole/Trimethoprim Tablet 800mg/160mg), – HA748 (Sulfamethoxazole/Trimethoprim Tablet 800mg/160mg), – HA762 (Isoniazid / Pyridoxine hydrochloride / Sulfamethoxazole / Trimethoprim Tablet, Film-coated 300mg/25mg/800mg/160mg)

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

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
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
DMF	Drug Master File
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
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
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
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

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
SMF	Site master file
SMX	Sulfamethoxazole
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. Quality management

Quality Manual / Quality policy

The Quality policy was defined in the Quality Manual. The Policy was established by the managing directors. References to ISO 9001, GMP and ICH Q7 were given.

Management Review

The Annual quality council meeting and the management review documentation were defined in the Quality Manual as part of the performance evaluation. The relevant SOP detailed the Quality council meetings, including the responsibilities of the Managing Director and other relevant staff of the company. Topics of the management review and documentation were defined in the procedure.

Quality unit

A quality unit independent of production was in place. Quality Assurance (QA) and Quality Control (QC) were part of the quality unit. Persons authorised to release intermediates and APIs were specified and were part of the quality unit.

Documentation system

Documents were only valid after QA approval. There were several documents describing the details of the documentation system. Examples included:

- The SOP for SOP writing. Definitions of "master copy", "controlled copy", "uncontrolled copy", distribution of "controlled copies", retrieval of previous revisions of SOPs, revision history and review period were part of the procedure.
- The SOP for the preparation of master production formula, master batch record and batch manufacturing record. The master batch record was prepared based on the master production formula and contained a reference to it. An approved copy of the master batch record was submitted to an authorised printer and serially numbered pre-printed multiple copies of the BMR were obtained and used for batch documentation.

The current version of the master production formula for Sulfamethoxazole USP/BP/JP/Ph.Eur/IP was effective since 2020. The numbering of the master production formula was defined in the SOP.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Product Quality Review

This process involved reviewing the quality of SMX and its intermediates and confirming that all batches produced during the review period (January to December of the previous calendar year) were in accordance with approved procedures and that results were within acceptable limits.

As part of the Annual Product Quality Report (APQR), batch yields, quality data, stability test reports, out of specification results, out of trends, reprocessing, impurity profile, critical processes, and quality parameters, change controls, customer complaints, returns and recalls, audits (internal and external), deviations, CAPAs, validations, and qualifications performed during the period were reviewed. Critical raw material data was also part of the review.

The PQR was prepared in accordance with the respective SOP. The latest version of this SOP was made available. Critical in-process controls, yield parameters, analytical results to be checked and details of the reporting format were defined in the document.

Monitoring of environmental parameters and water quality were not part of the procedure/report. However, problems in these areas were also handled according to the OOS procedure and this topic was part of the APQR.

The Report for the period from January to December 2023 was made available. All quality related issues were reviewed in the document.

OOS Procedure

A detailed SOP including a complete OOS decision tree was available. A couple of OOS reports were reviewed and discussed during the inspection.

Deviations

The SOP related to deviation control was made available. OOS investigations (laboratory deviations) were not covered by the deviation control SOP and this was defined in the “purpose” section of the SOP.

Deviations were classified as critical or non-critical deviations. Details of the deviations documented for the year 2023 and 2024 were checked during the inspection.

An additional procedure for handling and reporting QC incidents was implemented.

An annual review of incidents was carried out for 2023. CAPAs were taken wherever necessary.

Quality Risk Management

Quality risk management was performed using FMECA (Failure Mode, Effects and Criticality Analysis). Quality risk management protocol for SMX manufacturing process was available and reviewed. The quality risk assessment process carried out included risk assessment, control, communication, and review of risks to the quality of SMX. The QRM was performed in accordance with the respective SOP.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Root Cause Investigations
In general, investigations were performed in case of deviations, incidents, OOS, complaints, and other observed departures from GMP at the site.

In addition, the example investigations reviewed in conjunction with complaints, deviations, incidents and OOS were found to be reasonable and of acceptable quality and depth.

CAPA
The current version of the SOP on the corrective and preventive actions was well-established. Batch deviations were defined as being within the scope of the SOP.

In addition, audit findings were also addressed through the CAPA system. The review of some cases showed that most of the CAPA's in the year 2023 resulted from external audits.

Internal audit (self-inspection)
Quality audits were performed every 6 months to identify any shortcomings in the quality system, to suggest corrective actions and to permit regular review of the status of CAPA implementation in an impartial manner so as to encourage and improve quality of work in all areas of manufacturing to meet the standards laid down by regulatory agencies as well as in-house disciplines. Details were not checked during this inspection due to time constraints.

2. Personnel
A total of 263 personnel were employed by the company for different technical and administrative work within the site. An organization chart was in place for the overall company's organization including provisions for dedication between production (operation) activities and quality assurance/quality control activities. The organization chart was established as part of the SOP for job description and organogram.

Job descriptions for key personnel were in place. Sample Job descriptions were spot-checked including job description of the QA Manager and job description of the senior QA Chemist.

The SOP for personnel hygiene was reviewed. The SOP provided for good hygiene practices by all personnel at the site including wearing of appropriate clothing and personal protective equipment (PPE). The SOP provided also for periodic medical examination of the personnel engaged in production activities. Medical reports of two staff operating at packing area (and those who were observed during the witness of the packing operation at pharma block) were reviewed.

The SOP for cleaning of gowns, shoes and gloves used in the pharma packing block was reviewed and found to be implemented. Another SOP entitled provided for issue of uniforms and shoes to each employee on annual basis.

An SOP for training of employees was in place. As per the procedure, safety, GMP and other specific training activities were provided to new as well as existing staff. Training on JD was also noted within the scope of the mentioned SOP. The procedure provided for training evaluation by paper examination, observation of staff's work or conduct of mock drills. Training needs were conducted on need basis. Training schedule and templates were also provided within the mentioned SOP. Training schedules of

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

the year 2023 for QC and production departments were reviewed and example training records were spot checked.

3. Buildings and facilities

Production blocks, warehouses for raw materials and finished products as well as areas with utility installations, storage areas for solvents (tank farm) and QC laboratories were evaluated during this inspection. Buildings and facilities used in the SMX manufacture were dedicated to the production process of this API.

Manufacturing areas were generally constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of API manufacture. The various synthesis steps for the production of SMX were carried out in Production Block-I and Production Block-II. The transfer to the Pharma Block took place for the final purification and filling.

Utilities

HVAC system

The air handling system in the Pharma Block production area, blender and micronizing area was provided with 0.3µ terminal HEPA filters and microbiology area was provided with 0.3µ plenum HEPA filters which provided a clean and dust free air throughout the entire operation meeting class D clean room standard classification.

All the areas in the Pharma Block were provided with ventilation systems to maintain the required room condition with respect to the pressure differential, Air Change per Hour (ACPH), particulate matter count and potential risk of microbial contamination. There were dedicated positive air handling units (AHUs) for all core areas. AHUs were provided with 10 µ prefilter, 5 µ fine filter and 0.3 µ HEPA filters with efficiency 99.97 %. The HEPA filters were mostly installed in the ceiling. Extraction openings in the lower part of the room were intended to ensure sufficient mixing of the air in the production environment.

Positive pressure was set up within the classified areas for the prevention of contamination and cross-contamination. Manufacturing and quarantine area were connected via a pass-through hatch box (of passive type i.e., not air supplied) to enable the transfer of the packaged finished product out of the packaging area as well as the transfer of empty drums and other packaging and labelling materials into the packaging area. The hatch had two doors that were interlocked. This meant that a maximum of two containers could be inserted at the same time.

During the site visit, logbooks for differential pressure were checked. The documented values were within the specified range.

The Procedure for environmental controls described the environmental controlled areas, including the classification of the production area. The Pharma Block was divided into three areas: production area, blender & micronization room and finished product quarantine area.

Primary packaging was done in the blender & micronization room. Afterwards, the product was transferred to the product quarantine area (by transfer via the pass-through hatch box). Particle counts in the production area were performed every 6 months at rest. The specification was defined according to Grade D. For the quarantine area, the specification was reduced to a limit of 5 µm particles only, defined according to Grade D. Results for the last annual PQ for AHUs, PAHS-1, and PAHS-2 for the production rooms (particle measurement of the Pharma Block performed every 6 months, HEPA filter integrity and

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

air change per hour tested every year) were available and results were found meeting the predetermined particle specifications.

The Microbial monitoring report for 2023 was available. No results above the limit were observed during the monthly testing. SOP about handling the air sampling system was available.

The installation areas for the air handling units were viewed during the inspection. Logbooks and facilities for assessing the differential pressures on the filters were established.

Steam and process gases

Steam was used through the jacket of the equipment, compressed air and nitrogen were used for transferring the reaction mass from one equipment to another. The compressed air and the nitrogen were verified yearly for quality. Logbooks were available. Documents for nitrogen and compressed air supply were checked.

Nitrogen

The PQ protocol for the annual Nitrogen requalification was available. Technical parameters (e.g., lube oil pressure) and oxygen content (< 1,0 %) were confirmed. A layout of the Nitrogen generation plant (NT-819) was available. Nitrogen was concentrated by PSA-technique (pressure swing adsorption). Two PSA-Towers were installed together with air compressor and 5µm gas filters before and after the PSA-Unit. Usage of Nitrogen was limited to reaction mass transfer in Stage-I. The Test certificate for the Oxygen sensor installed in the oxygen analyser was available.

Compressed air

The PQ protocol for the annual compressed air requalification was available. This was limited to technical parameters only. The quality evaluation was done annually by an external company, based on ISO 8573 requirements. The sampling was done after desiccant air dryer installed for the pharma block. In this case, desiccant air dryer or refrigerated air dryer could be used, depending on the compressor used for air supply (2 compressors were installed in front of the desiccant air dryer; 1 compressor in front of the refrigerated air dryer also used for air supply to the Nitrogen plant).

In addition, the SOP about operation of the air compressor was available.

The blueprint of the "clean dry air generation and distribution" system was available. Compressed air was generated, dried, and filtered. Usage of compressed air was limited to production block-II (Stage-III) and for bag filter instrumentation (pulsating equipment). Compressed air generation units were equipped with heatless desiccant air dryers.

Compressed gases supplied in cylinders

The procedure for receipt, unloading and loading of gas cylinders was available. Passed/rejected labels based on verification of COA were pasted on the cylinders.

Water

Purified water and potable water were used in different stages of SMX manufacturing processes at Virchow Laboratories. Potable water was used only in the synthesis of initial and intermediate stages. The Potable water was passed through pre-UF system (to reduce silt density index [SDI]), Reverse Osmosis Plant, Demineralizing Plant, 5.0 µm filter, UV chamber and 0.2 µm filter to get purified water collected into purified water storage tank. The purified water from storage tank was supplied to all usage points under circulation after passing through UV chamber. This purified water was used in the final

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

stages of SMX processing and washing of the wet cake before drying. Sampling points were specified to get a complete picture of the water quality. Sanitisation procedure was done once a year or in case of a microbial result > 175 cfu/ml before 5.0 µm filtration. Documentation about the last sanitisation including analytical report for the absence of Sodium hypochlorite and appropriate turbidity were available. The Daily logbook included documentation for conductivity (< 1 µS/cm) and pH (5.5 until 7.0) in addition to other parameters.

The SOP for water sampling detailed the methodology for the collection of water samples. Rinsing of the sampling container after opening the valve of the sampling point was described in detail. Before sampling, sampling containers for microbial analysis were autoclaved. Sample storage after sampling was described. Microbial analysis was to be performed as soon as possible. If not done within 2 hours, samples had to be stored at 2 to 8 °C for a maximum of 24 hours. Labelling of the samples and format of the sampling logbook were described. Testing frequency was defined to be weekly for PW from storage tank and sampling points. The remaining sampling points in the production area were sampled in alternative weeks (one sample every three months for every sampling point).

Raw material specification for PW from usage point was available. TAMC was specified with NMT 100 cfu/ml. Additionally, Absence of E.coli, Pseudomonas aeruginosa, Staph. Aureus and Salmonella abony were included.

Trend graphs of all sampling points were verified. It was found that all the results were within the specification and the normal trends.

Microbial analysis of TAMC was done by membrane filtration of diluted sample (10 in 100 dilution).

Water system validation report 2023 was available. System was found qualified for its intended use.

Control of storage conditions at FP warehouses

Four warehouse areas for finished product were available. Temperature limit of 30 °C was introduced in 2019. For this reason, introduction of the HVAC system of the storage areas and temperature mapping was done for all warehouses. Protocol and report for warehouse-I were checked during this inspection. Mapping was done using data loggers placed in load conditions at bottom, middle and top layer at different places according to a schematic diagram (a total of 25 data loggers were used). The hotspot was determined . After the mapping study, temperature and humidity were checked by the use of thermohygrometers in 24-hour cycle. There were no problems to comply with the 30 °C specification. Installation of measuring equipment, calibration and logbooks were checked during the inspection in all FP warehouses. Daily checks of minimum and maximum temperature were introduced.

4. Process equipment

In general, equipment used in production and control of SMX at the site were found of good design; well maintained and cleaned; and calibration (if needed) is regularly performed. Equipment qualification and requalification was governed by SOP on equipment qualification master plan. The SOP mandated full qualification of production equipment including URS, DQ, IQ, OQ and PQ. Requalification is also mandated by the SOP to be performed on annual basis. Sample equipment qualification reports were spot checked as follows:

- The PQ (annual) of spin dryer located at the pharma block.
- The PQ (annual) of centrifuge located at the pharma block.
- The PQ (annual) of activated carbon reactor located at the production block II.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Specifically, with respect to the spin dryer, where HEPA filters were installed supplying filtered air for drying the product, in addition, of the annual qualification of the dryer, testing of moisture content of the product, particle size, pressure drop across the HEPA filter, and air temperature at the outlet/downstream of the HEPA filter were included. Regular monitoring of the pressure drop across the HEPA filter was monitored for each production batch and documented within the batch production record; and annual preventive maintenance was performed where again pressure drop across the HEPA filter was monitored with two limits.

Design and construction

In general, equipment used in the manufacture of intermediates and APIs were of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization, and maintenance. Major equipment was well identified, including valves, pipes, and monitors.

Equipment maintenance and cleaning

The SOP for preventive maintenance of the equipment was reviewed and found in place. The procedure provided for annual preventive maintenance schedule. It also referred to a number of SOPs on preventive maintenance of specific equipment (e.g., micronizers, blenders, sifters). The 2023 Preventive maintenance schedule was reviewed and a number of maintenance activities were spot checked. In addition, the SOP for vacuum cleaner operation and cleaning (used for cleaning of surface at the packing area) was checked and verified.

All production equipment were cleaned on regular basis, but not after each single batch, considering the fact that the facility is single-purpose (only one product [SMX]) and the equipment were dedicated for a particular stage of production. Cleaning of the equipment was not performed according to one single procedure. Rather, each equipment or group of similar equipment which could be alternated and used for unit operation was cleaned according to a cleaning procedure. The frequency of equipment cleaning for production stages III and IV as well as critical equipment for stages I and II, ranged from 15 to 30 days based on the dirty equipment holding time study (DEHT).

Calibration

SOP for calibration of equipment was in place. The procedure provided for in-house (internal) as well as external calibrations; frequency of regular calibration, calibration plan and acceptance criteria for calibration activities including traceability to national or international standards. Calibration schedule of the year 2023 was reviewed and a number of calibration activities were spot-checked. On top of calibration, regular verification was needed for some equipment (e.g., weighing balances, PH meters). Guidance on such verification was provided for within the SOPs related to the operation of the relevant equipment.

Computerized systems

The SOP for computer system validation was in place. This SOP provided for classification of computerized systems into equipment/instrument software (e.g., chromatographic instruments, automated manufacturing systems); application software (e.g., laboratory information management system [LIMS] and documentation management system); and infrastructure software (e.g., operating systems). The procedure also provides for proportional effort on CSV based on the associated criticality and risk of the equipment following Good Automated Manufacturing Practices (GAMP-5).

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Few computer systems were used at the site. No computerized systems were used in the production. On the other hand, at the QC laboratory, a number of computerized systems (e.g., LabSolution CS version 6.90 for management and backup of HPLC, GC, IR, and UV) were used. The IQ, OQ and periodic qualification of the LabSolution CS were reviewed. In addition, IQ and OQ of ASDASS version 1.2 (the software used to run and control the stability chamber) were reviewed.

The SOP for data integrity policy was reviewed and found to refer to ALCOA+ principles. The SOP also referred to audit trail. The latter was further explained and guided, among other data integrity aspects, in the SOP for operation and maintenance of computer and server systems attached to analytical instruments. Review and approval of audit trail by the Assistant Manager QC was spot-checked.

5. Documentation and records

The documentation system at Virchow laboratories Ltd., can be described as a horizontal system, rather than the traditional hierarchical/pyramidal system. The system for documentation was paper based and was composed of SOPs along with logbooks and records; specifications and methods of analysis (MOA) along with worksheets and analytical records; validation related documents along with validation protocols and reports; master formula including master production formula, master batch record and [completed] batch manufacturing records; and calibration schedules and records.

The SOP for writing SOPs was in place. The list of SOPs was also checked, where it was found to cover different activities and departments within the site, including QA, QC, operations, and others.

Master production instructions

The Master production formula was reviewed. The Master Production Formula stated that no rework was performed in any stage of the production of SMX. The master formula was typical to the empty master batch record. Both documents had the same effective date. It was noted that a standalone master production formula is available for the blending and packing of SMX (leftovers of the batches). The latter document was confined to the blending and packing process. Reprocessed and blended batches were well traced and marked within the batch numbering system (with the addition of the letter R for reprocessing to the batch number and the letter BLD to the internal batch number [not the commercial one]). It should be noted that the internal batch number was included in the certificate of analysis, which was shared with the customers.

Batch production and control records

Four batch manufacturing and analytical records were reviewed:

- Final API batch number 01040124
- Final API batch number 20381023
- Final API batch number 00750124
- Final API batch number 19631023

Batch release

The SOP for batch release was in place. The SOP provided comprehensive guidance on batch release process including designation of personnel assigned for batch release namely the QA Manager, the Assistant QA Manager and the Senior QA chemist (only in the absence of QA Manager). The SOP also detailed the checklist for batch release including the assigned market for release (i.e., DMF filed market or non-DMF filed market). WHO was indicated in the SOP among DMF filed markets where in-house intermediate Isoxamine is solely used in production (i.e., vendor-supplied Isoxamine was not possibly

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

used for these DMF filed markets). In conjunction with the batch release SOP, job descriptions of the QA Manager and the QA Senior Chemist were reviewed and found to describe the responsibility of batch release. An Example of batch release was spot-checked as part of the review of the four above-mentioned executed batch records.

Batch numbering system

An SOP for batch numbering was available. The SOP gave the methodology for batch identification at different stages of sulfamethoxazole manufacture. The internal batch number had the format Apr/SMX/145. The third segment was the serial number of the sulfamethoxazole manufactured in that month. This batch number was used during phase III (technical sulfamethoxazole) and phase IV (sulfamethoxazole pharma). On the other hand, an eight-digits code was used for the batch number of the finished product (made up of the consecutive serial number, month, and year of manufacture, e.g., 00010124 for the first batch in 2024).

In addition, batch numbering was defined for raw materials, including isoxamide from Stage I and key starting material isoxamine from Stage II.

Different batch numbering was defined for batches produced with outsourced isoxamine and for batches blended from batch residues/leftovers (both products were only supplied to domestic customers and to the non-DMF-filed market).

6. Materials management

Approval of suppliers

The List of approved vendors for raw materials of Sulfamethoxazole was available. The Name and address of manufacturers and suppliers in relation to the individual raw materials were listed. The conformity of the list with the materials stored in the warehouses and storage tanks was randomly checked and no discrepancies were found during this inspection.

Vendor [Supplier] Approval:

The vendors of critical raw materials / packing materials were evaluated and qualified as per the respective SOP. For each product being manufactured, critical raw Materials / packing materials were identified. For critical raw material / packing material vendor audit had to be conducted along with vendor assessment questionnaire once in three years. Periodical vendor evaluation was done as per the respective procedure. No materials sourced from animal origin and genetically modified organisms were used in manufacturing of SMX. It was explained by the company that key starting, and primary packaging materials have been classified as critical materials. Details were not checked during this inspection due to time constraints.

Raw material specification and analysis

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available.

Labelling of intermediates and finished product

Appropriate labelling was found during the site visit.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

The tentative/provisional labels applied during the filling process were replaced by the final labels. Batch information was printed in the labelling area. The required labels were supplied on QC approved rolls (500 labels each) and fed into the printer. The consumption of labels was documented in detail and checked by the responsible personnel.

In addition to the batch number, expiry date, drum number and contents, the gross weight was printed on the labels. Information was also provided by means of a QR code. The drum number and the number of the seal used could be traced in the batch report.

Liquids

Most of the solvents and liquid raw materials were stored in dedicated storage tanks. For Pyridine, separate warehouse was established and used. Incoming deliveries were sampled by QC. After QC approval, the tankers were weighed and the transfer of the materials to the storage tanks was supervised. Additional cumulative samples were taken from the storage tanks. QC confirmation for individual and cumulative samples were available at the warehouse (green colour copy) together with checklists.

Warehouse procedures

The SOP for receipt, unloading and handling of solid raw materials, checklist for in-warding solid raw materials (including confirmation of CoA receiving), SOP for liquid raw materials, goods receiving register were available. After the dedusting procedure (usage of dedusting booth) and additional controls, materials were labelled with material identification labels. Details were specified in the relevant SOP.

Dedicated rooms for sampling (done by QC) and dispensing of materials were established. During the inspection it was noted that these rooms were over-pressurised in relation to the adjacent storage areas. Pressure data (1 – 2 mmwc) and the respective logbook were available. Sensitivity checks and calibration of the scales used were documented. The SOP for dispensing of solid raw materials by FIFO system was available. The delivery of raw materials to production usually took place entirely in the delivery container. Weighing and packaging of small quantities (issue of loose solids) was only required for 3 substances (EDTA, Citric Acid, Hydrose).

7. Production and in-process controls

Production activities were conducted at three production blocks (Production Block-I, Production Block-II and Pharma Block). Production operations could be summarized as follows:

- Stage I for the production of Isoxamide Intermediate
- Stage II for the production of Isoxamine Intermediate
- Stage III for the production of SMX Technical
- Stage IV for the production of SMX (finished API)

Production operations were carried out in three shifts (8 hours each).

As part of the inspection, inspectors visited the three aforementioned production blocks. Inspectors visited the packing area at the pharma block and witnessed the packing operation. The BMR of the observed batch was reviewed.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Blending batches of intermediates or APIs

The SOP for Blending and Packing of Sulfamethoxazole was in place. Blending of batches was limited to the tailings (leftovers) of original batches. Blending of intermediates was not possible as per the respective master production documents. There was a standalone master batch production record for the blending of leftovers.

8. Packaging and identification labelling of APIs and intermediates

Details of packaging and labelling of intermediates and finished API products are described under sections 3 (buildings and facilities) and 6 (materials management) in this part II of the report. Please refer to the mentioned sections for further details on packaging and labelling of APIs and intermediates.

9. Storage and distribution

Appropriate storage conditions for all materials were assured. Details are described under sections 3 (buildings and facilities) and 6 (materials management) in this part II of the report.

Details of distribution were not evaluated during this inspection because of time constraints.

10. Laboratory controls

Three quality control laboratories were established on-site: one for in-process control (IPC) at production block I; another one for IPC at production block II and one central QC laboratory for testing of raw materials, packaging materials, and finished products. Inspectors visited the main QC laboratory on the second day of the inspection with focus on wet laboratory section, HPLC section, GC section, retention samples storage, archiving room, and stability chambers.

Qualification of analytical instruments

Equipment at the QC laboratory was found to be in a maintained status of qualification. Several qualifications (or annual requalification reports) were reviewed including:

- Annual qualification of the HPLC
- Annual qualification of the GC
- Annual qualification of the autoclave
- Annual qualification of the stability chamber

Analytical Method Validation (AMV)

The protocol along with the report of the AMV of the assay determination of SMX were reviewed. The AMV was executed where selectivity, precision, linearity, accuracy, range doggedness and robustness were established for the assay of SMX.

The SOP for sterility and growth promotion test (GPT) of incoming media was reviewed.

OOS Handling

The SOP for handling OOS was in place. The SOP provided detailed guidance on managing and handling OOS at the QC laboratory. An example OOS was spot-checked.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Stability studies

The SOP for the stability study programme was in place. The procedure provided for a comprehensive stability programme including accelerated stability at 40 ± 1 °C at 75 ± 5% RH and long-term stability at 25 ± 2 °C at 60 ± 5% RH as well as 30 ± 2 °C at 75 ± 5% RH. The SOP also mandated that two samples of at least one commercial batch of the finished API was included every year in the long-term stability programme. It is worth noting that the shelf life of SMX API was 5 years and the storage condition was below 30°C (no requirement for humidity control).

Reference and working standards

The company used several reference standards (purchased from suppliers) as well as working standards (established in-house). All these standards were stored in a refrigerator between 2°C and 8°C. The refrigerator was located at the main QC laboratory where a log for stored quantities was maintained. The SOP for handling, maintenance, and storage of reference standards was in place. In addition, several other SOPs were in place for the preparation and storage of working standards, including the SOP for working standard of SMX. The latter SOP provided for the preparation of the SMX working standard on annual basis (once in a year in the month of January) or when pharmacopoeial specification changes or when the current lot of the pharmacopoeial reference standard changes.

Retention samples.

The SOP for preservation of control samples was in place. The SOP provided for retention of 50 g of each produced batch of SMX for six years (expiry + 1 year). The temperature-controlled room where retention samples are stored was visited by the inspectors. The room was monitored for temperature using a logger and data was recorded once per day in a bounded logbook.

11. Validation

The SOP for master validation was in place and governs the policies and practices for different validation and qualification activities. The Validation plans (schedules) for 2023 and 2024 were reviewed.

Process Validation

The Process validation was covered under section III of the SOP for master validation. Revalidation was also guided within the mentioned SOP and was stated to be required on annual basis on the first 10 consecutive batches of each manufacturing stage from stage I to stage IV by the month of April. It was noted that, on top of the mentioned revalidation requirement, trend analysis as part of the PQR was also considered by the manufacturer and contributed to continued process verification.

Another SOP dedicated to PV was available. Although, the procedure was entitled with respect to PV, it was found indeed limited to procedural guidance on process revalidation.

The process revalidation of the four stages of SMX conducted in 2023 showed a stage of complete control and that the established process was maintained in a validation status over the years.

Cleaning Validation

The SOP for master validation stated that “production and services are dedicated to one product only”. Furthermore, each process equipment was dedicated only for that particular unit operation. Therefore, there was no chance of cross contamination at any stage of the production and it was not necessary to thoroughly clean between each batch”.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

Specifically for cleaning validation, the SOP on cleaning validation was in place. The procedure provided guidance on CV activities with referral to approaches, risk assessment, DEHT and CEHT, acceptance criteria, sampling, and others. The Analytical method validation for the determination of residual SMX content in the last water rinse of equipment by UV-VIS spectrophotometer was also reviewed as part of the discussion related to CV.

Hold time studies

Production of SMX involved two intermediates which can be held for some time before subsequent processing. These intermediates were Isoxamide and Isoxamine. Hold time studies for both intermediates were presented and dated back to 2012. The holdup stability data for Isoxamide and Isoxamine conducted between in 2012 were reviewed and found to support hold time of 60 days of each of these intermediates. These hold times were well reflected within the master production formula and master batch records.

12. Change control

The SOP on change control was introduced to provide guidance for controlling the initiation, authorisation, and implementation of all the prospective changes. Changes were classified as minor or major changes and handled accordingly. The List of changes for 2023 was available and examples were evaluated.

13. Rejection and re-use of materials

Intermediates and APIs were well managed at the site. For further details on materials management please refer to above mentioned section 6 (materials management).

Reprocessing and reworking

As mentioned above, reworking was not allowed as per the master production formula. Reprocessing, on the other side, was possible for all manufacturing steps, including reprocessing of Isoxamide, reprocessing of Isoxamine, and reprocessing of SMX.

Recovery of materials and solvents

Recovery of solvent was governed by the SOP for solvent recovery. The SOP provided for recovery of four solvents used in the manufacture of SMX namely Methanol, Methylene Chloride, Toluene and Pyridine. No solvent was used in stage IV of the manufacturing process. Only purified water was used in stage IV. Testing and quality of the recovered solvents were well regulated by the mentioned SOP.

14. Complaints and recalls

The SOP for handling of customer complaints and customer returned materials was in place. The SOP provided for logging of complaints received from the customer and initiation of investigations and actions, as necessary. The SOP indicated the QA Manager was the designated person for logging, investigating and acting upon receipt of complaints. Handling of a Complaint had to be concluded within 30 working days unless the deadline was extended. In the latter case, an interim complaint report had to be drafted. In all cases, feedback had to be provided to the complainant. The List of complaints of the year 2023 was reviewed and some example complaints were spot-checked.

15. Contract manufacturers (including laboratories)

No manufacturing or testing activities were outsourced by the company.

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

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, ***Virchow Laboratories Ltd***, located at ***Plot No 4 to 10, SV Cooperative Industrial Estate, IDA, Jeedimetla, Hyderabad, 500 055 Telangana State, India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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

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

Part 4	List of GMP guidelines 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.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   Short name: WHO TRS No. 957, Annex 2
   https://www.who.int/publications/m/item/annex-2-trs-957

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
   Short name: WHO TRS 1010, Annex 9
   https://www.who.int/publications/m/item/trs1010-annex9

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   https://www.who.int/publications/m/item/annex-3-trs-1033

5. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   https://www.who.int/publications/m/item/annex-4-trs-929

6. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
   Short name: WHO TRS No. 957, Annex 1
   https://www.who.int/publications/m/item/trs957-annex1

7. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   Short name: WHO TRS No. 957, Annex 3
   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.
   Short name: WHO TRS No. 1010, Annex 8
   https://www.who.int/publications/m/item/Annex-8-trs-1010

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
    https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. 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 2
    https://www.who.int/publications/m/item/trs1044-annex2

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

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***
https://www.who.int/publications/m/item/trs943-annex3

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
https://www.who.int/publications/m/item/trs961-annex2

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
https://www.who.int/publications/m/item/trs981-annex2

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
https://www.who.int/publications/m/item/annex-3-trs-981

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
https://www.who.int/publications/m/item/tr961-annex14

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

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
https://www.who.int/publications/m/item/trs992-annex4

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

19. 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**
https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

20. 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
https://www.who.int/publications/m/item/trs992-annex5

21. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6.
Short name: WHO TRS No. 992, Annex 6
https://www.who.int/publications/m/item/trs-992-annex-6

22. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-1033

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
https://www.who.int/publications/m/item/trs966-annex10

24. 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***
https://www.who.int/publications/m/item/trs1010-annex10

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2.
Short name: WHO TRS No. 1033, Annex 2
https://www.who.int/publications/m/item/annex-2-trs-1033

This inspection report is the property of the WHO
Contact: prequalinspection@who.int

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.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications/m/item/trs-1025-annex-6

27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

27. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications/m/item/trs1025-annex4

28. Good trade and distribution practices for pharmaceutical starting materials. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 6.
Short name: WHO TRS No. 996, Annex 6
https://www.who.int/publications/m/item/annex-6-trs-996

This inspection report is the property of the WHO
Contact: prequalinspection@who.int