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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Canton Laboratories Pvt Ltd
Corporate address of manufacturer	Plot No.110-B, GIDC Makarpura, Vadodara – 390 010. Gujarat, India
Inspected site	
Name &Address of inspected manufacturing site if different from that given above	Canton Laboratories Pvt Ltd Survey No.: 350, Near Gambhira Bridge Village: Mujpur; Taluka: Padra; Dist: Vadodara-39 I 440. Gujarat, India Latitude: 22.2516585 Longitude: 73.0038767 D-U-N-S: 650844579
Synthetic Unit /Block/ Workshop	➢ Building I – lines 2, 3 and 5involving production stages I (dissolution) up to stage V (drying and sifting). ➢ Building I – blending and packaging areas1 and 2 involving production stages VI(blending) and VII (packing). ➢ Building I – raw materials warehouse, finished good warehouse and packing and labelling materials warehouse. ➢ Building II – lines 6involving production stages I (dissolution) up to stage V (drying and sifting). ➢ Building II – blending and packaging area 5 involving production stages VI (blending) and VII (packing).
Inspection details	
Dates of inspection	4 – 6 March 2024
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	The premises at Mujpur village (unit II) were established in mid-2015 and these comprise of process area, controlled area, warehouse area (store), utilities area, Quality Assurance, Quality Control, and microbiology laboratory area. The total area of the land is 19332 m^2. The built-up area is 9104 m^2 and is licensed to manufacture pharmaceutical products (APIs and excipients) along with food additives. There are two manufacturing blocks, each with 5 segregated production lines. Each production line consists of a dissolution tank, sparkler filter, reactor, centrifuge, and FBD Drier. There are separate areas for blending and packing after the production line within the controlled area.

	A wide range of products are manufactured at the site including, among others: – Acetates of Ammonium, Calcium, Magnesium, Potassium, Sodium, and Zinc, – Carbonates/Bicarbonates of Ammonium, Calcium, Magnesium, Potassium, Sodium, and Zinc, – Chlorides of Ammonium, Calcium, Magnesium, Potassium, Sodium, and Zinc, – Citrates of Potassium and Sodium, – Edetates of Potassium and Sodium, – Hydroxides of Calcium, Magnesium, Potassium, and Sodium, – Phosphates of Ammonium, Calcium, Potassium, and Sodium, – Sulphates of Ammonium, Aluminium, Calcium, Ferrous, Magnesium, Manganese, Potassium, Sodium, and Zinc.
General information about the company and site	Canton Laboratories Pvt Ltd was founded in 1981. It is engaged in the manufacturing and marketing of pharmaceutical products, mineral fortifiers, food additives and speciality chemicals. It has two manufacturing units: Unit-l is located in Makarpura, Vadodara and Unit-2 is located at Mujpur village, Padra, Vadodara. The company is managed by the Board of Directors. The day-to-day activity of the plant is looked at by the plant head and respective department HOD along with top management.
History	The site has been regularly subject to regulatory inspection by the Food and Drugs Control Administration (FDCA), Gujarat as part of the regular GMP certification. In addition, the site had been granted (based on inspection) several certifications including Halal Certification and Kosher Certification. The site had been inspected by WHO two times in July 2016 and in November 2019. The main changes since the last WHO inspection, as declared by the company and apart from CAPA submitted in response to that inspection, include (noting that some of these changes are related to the areas not covered by this inspection): – New balance installation in the manufacturing and packaging area. – New sparkler filter installation. – New controller installation in autoclave for printing provision. – Printer installation for the weighing balance. – New micro pulverizer introduction at building I. – Replacement of conductivity meter and sensor. Replacement of flow transmitter and flow sensor. Installation of a new temperature controller and sensor (Flow vent filter). – A new sifter was installed in 2021 – Cleaning validation activity at a facility based on the ADE/PDE study – New instrument fluorimeter – new rubber line centrifuge of 36" installation in manufacturing 7 of building II

	– AHU and AHU VA HEPA 0.3 micron filter installation in manufacturing lines 6, 7, 8, 9 and 10 of building II – New instrument fluorimeter.
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. In addition, lines and areas not listed under the scope of this inspection were not covered and as such were out of the scope of this report.
WHO APIs covered by the inspection	WHOAPI-146 Zinc Sulphate Monohydrate
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 packing record
CC	Change control
CIP	Cleaning in place
COA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
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
RA	Risk assessment
RCA	Root cause analysis
RO	Reverse osmosis
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. Quality management

Principle / Quality Manual / Quality Policy

The company produced mainly chemicals and products that were not traditionally under the scope of pharmaceutical manufacturing. Several products were produced and sold as additives to foods. Over the years, the company implemented the components of GMP. Similarly, production and control operations were specified in writing, and the implementation of the basic principles of GMP was established. Products and processes were monitored. Regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to specified procedures such as Product Quality Review (PQR).

Management Review

The SOP for quality management review meeting was briefly reviewed. Meetings were held every six months. The last meeting was reviewed and the typed minutes were presented to inspectors. A list of participants was available. A meeting report was signed, including the CEO (Technical).

Product Quality Review

The current version of the SOP on annual product review was in place. There were 22 points defined to be part of the PQR, including all relevant QA topics. The last year's PQR, namely 2023, was discussed and found to be in compliance with the relevant SOP.

The Quality parameters were established and listed in the PQR including:

- Key starting material (KSM) status
- In-process quality parameters
- Critical intermediates
- Qualification / Calibration / PM status
- Batches failed / OOS / OOT
- Incident/deviations
- Changes
- Stability data summary and trend analysis
- Returns
- Complaints
- Recalls
- Corrective actions
- Validation
- Revalidation

According to the SOP on process validation, periodic review of validated systems should be done.

Calculation of Cpk was done for finished product attributes. If Cpk ≥ 1.33 had not been obtained, a root cause investigation would have been necessary. A validated Excel sheet was used for Cpk calculations. Details of the calculation were checked during the inspection.

A complete list of batches supplied based on WHO-APIMF146 was available (period from 2019 until January 2024).

BMR issuance record was available, listing all batches produced in the year 2023.

Specification for Zinc sulphate monohydrate was available, including all related impurities.

Batch numbering described in the format of "YY P XXXX RS" was found in conformity with the description in the WHO-APIMF146. "P" stands for Pharmaceutical, and RS for regulatory submission.

Quality Risk Management

The SOP on risk management was briefly reviewed. According to the SOP, risk management was applicable to the entire quality system, processes and practices across GMP functions. Details of the process (e.g. FMEA, calculation of RPN, risk assessment numbering system) were described.

A risk assessment log was available. A risk review period was implemented. A risk assessment and control plan for Zinc Sulphate Monohydrate as an API was available.

In addition, the Risk Management Report File "RA and control plan for raw material receiving-storage, sampling, approval, issuance, usage, production, blending, packing, labelling and dispatch" was reviewed.

Deviations

The SOP on Deviation, and logbooks for 2023 were briefly reviewed. Deviations were classified as planned, unplanned, critical, major, and minor.

An example deviation report for missing autoclave requalification was reviewed.

Internal audit (self-inspection)
Quality audits were designed once in 6 months to seek out any shortcomings in the quality systems, suggest corrective actions and permit regular review of the status of implementation in an impartial manner so as to encourage and improve the quality of work in all areas of manufacturing to meet the standards laid down by regulatory agencies as well as in-house disciplines.

Details on the selection and qualification of internal auditors as well as the planning, execution, documentation, CAPA and closure of the audit were part of the SOP. Details of the internal audit programme were not checked during this inspection due to time constraints.

CAPA Management
The SOP on CAPA management was in place. CAPA logbook and evaluation of the effectiveness of CAPAs were implemented. CAPAs after the last WHO inspection were reviewed.

2. Personnel

A total of 65 personnel were employed by the company for different technical and administrative work within the site. The 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 SOP for roles and responsibilities.

The Job descriptions for key personnel including CEO Technical, Head Manufacturing and Packaging, Head CQA and QA Head were reviewed.

3. Buildings and facilities

Production premises were located, designed, constructed, and maintained to suit the operations to be carried out. Production buildings visited during this inspection were clean and in an acceptable order.

There were two manufacturing blocks, each with 5 segregated production lines. Each production line consisted of a dissolution tank, sparkler filter, reactor, centrifuge, and FBD. There were separate areas for blending and packing after the drying process.

Utility areas for the generation of process water and compressed air were situated outside of the manufacturing blocks. The HVAC systems for production areas were installed on the first floor of each manufacturing block.

Environmental control
Blending/packaging rooms were monitored for humidity. A limit of < 55% RH was set. Logbooks for all rooms were available and logbooks for 4 blending and packing rooms situated in building 1 were viewed including the procedure for temperature and humidity monitoring. In addition, differential pressures were monitored. Logbooks were available and the results were documented accordingly.

Temperature monitoring was established for the area within the finished product warehouse which was used for storage of the WHO prequalified Zinc Sulphate Monohydrate API (separate room).Temperature mapping protocol and report of separate storage room for API in finished goods store in building no. 1 NMT 30 °C were available. The size of the room was calculated to be 20.22 m^3. Mapping was done using 10 data loggers and documented for 72 hours and the performance level of the cooling system was found satisfactory.

Environmental monitoring (EM)

EM (viable particles) for all production rooms was performed monthly. Action and alert limits were specified. A summary of data for the year 2023 was available. All data were found below the alarm limit. Relevant SOP was reviewed. Settle plates with Soyabean Casein Digest Agar Medium were used. Exposure time was defined as 4 hours. Incubation was done for 3 days at 20 – 25 °C (reading for fungi was done afterwards) and 2 days at 30 – 35 °C (final reading counting of total aerobic microbial count [TAMC] was done). Positive and negative controls were part of the SOP. Positive controls were defined to be prepared with reference cultures and some growth should be observed. Validation of settle plates was documented for the exposure time of 4 hours.

Utilities (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning)

HVAC system

The HVAC system serving building 1 was requalified in January 2024. There were 13 AHUs. According to the document, no deviations were observed. Acceptance criteria were defined for temperature (< 27 °C), humidity (< 55 % RH), differential pressure between two adjacent rooms (≥ 6 Pa), air changes per hour (≥ 20), and viable particle count (< 100 CFU/4 hours).

The HVAC system for building 2 was upgraded in 2023. Final filtration by HEPA filters was established. All relevant data, including particle counts and microbial assessment by contact plates, were documented during the PQ following the installation of the final HEPA filters in 2023.

To prevent cross-contamination, positive pressure was ensured in the corridor areas of production in relation to the production rooms. The areas for blending and packing operations were also monitored in terms of humidity (< 55%).Separate filtered air blowers were installed for each fluid bed drier (FBD) unit. These units were installed on the second floor of the production blocks.

Water generation unit

The site had its own borewell for water supply. This well water was treated to generate process water (two-stage RO system combined with mixed bed deionisation system). After transfer to the distribution tank (1500 litres), the process water was circulated in loops through UV light to all user points in production buildings 1 and 2.

A specification for "process water" was available. Conductivity was specified as ≤ 10 µS/cm. Other parameters were specified according to BP/USP. The absence of *E. coli, Salmonella, P. aeruginosa, S. aureus, Candida albicans, Aspergillus brasiliensis, Enteriobacteriaceae* was specified. Details of the water system and the sampling points installed were evaluated during this inspection. Logbooks for relevant parameters (conductivity, water flow, UV unit) were available. The process water loop was sanitised at a predefined frequency (once a week) by circulating hot process water (≥ 75 °C) for one hour.

Water analysis

The procedure for water sampling was reviewed. Samples were collected and analysed daily from the sampling points at the storage tank and return loop. Other sampling points were sampled once per month on a rotational basis. Action and alert limits were specified.

Process water quality periodic verification report was done annually. The quality of process water was confirmed. There were no deviations or other problems mentioned. Detailed evaluation was documented including a summary of trending done on a monthly basis and a detailed review of the system including changes, review of logbooks and confirmation of appropriate system status.

Compressed air

A compressed air generation unit was established. The system consisted of two compressors. Refrigeration dryers (DOLPHIN) were installed to reduce the water content.

4. Process equipment

Design and construction

In general, the equipment used in the production and control of Zinc Sulphate Monohydrate at the site were of good design; well maintained and cleaned; and calibration (if needed) was regularly performed. Equipment qualification and requalification were governed by SOP on the qualification of instruments and equipment. Requalification was also mandated by the SOP to be performed on a regular basis. Sample equipment qualification reports were spot-checked.

Equipment maintenance and cleaning

The equipment was well maintained. The preventive maintenance was regularly executed. Several equipment specific cleaning procedures were in place which provided procedural guidance on cleaning the equipment in alignment with the validated cleaning process. Examples of equipment cleaning procedures were spot-checked.

Within the above-mentioned SOPs, two different cleaning types exist namely (1) the batch to batch (of the same product) cleaning and (2) the product to product (change over) cleaning. The latter cleaning was also mandated as per the procedures after a maximum of 10 batches of a single product. The rationale for the 10 batches was justified based on a retrospective study of campaign batches for product changeover cleaning.

Calibration

The SOP for calibration and recalibration was in place. The SOP provided for the establishment of an instrument master list which indicates equipment location, name, ID, make, range, and frequency. The 2024 calibration schedule was reviewed. In addition, the 2023 calibration schedule was reviewed.

Computerized systems

Few computer systems were used at the site. These included PharmaSuite Software (ERP), software for ICP-MS, software for auto-titrator and software for atomic absorption spectroscopy. The OQ and PQ protocol and report of PharmaSuite software were reviewed.

5. Documentation and records

The SOP on SOP was in place. The SOP guided the development (in terms of need), template, format, distribution, revision history, preparation, numbering, implementation, control and regular review of the SOP related to all departments within the site. The list of SOPs was also checked and it was found to cover different activities and departments within the site including QA, QC, operations and others.

Master production instructions

The master formula record was reviewed.

Batch production and control records

The issuance of batch manufacturing records was controlled by the SOP for batch manufacturing records. The BMR was issued by QA with a unique issuance number including the assigned batch number which was indicated on the issued BMR.

The batch manufacturing record template was in place. The template was revised in 2021through a change control system. The main change from the previous to the current BMR is that the old template had separate redundant sections for each lot which was confusing. The current template, on the other hand, had one consolidated form with continuous pagination.

The batch manufacturing records along with analytical reports and the release of three different batches were reviewed.

At the end of the blending, the full batch was unloaded from the blender through the sifter and packed into double LDPE bags and one external HDPE bag each of 50 kg. The “bulk” products were then stored at the finished goods warehouse. Upon receipt of orders from the customers, the required number of HDPE bags were transferred from the warehouse back to the packaging area (through a dedicated material flow and after dedusting)where the HDPE bag is removed while the double-wrapped (in LDPE) product was placed into a drum. The aforementioned process was governed by the SOP for the repacking activity of the finished product.

Batch release

The SOP for the release of the finished product was in place. The SOP provided comprehensive guidance on the batch release process including the designation of personnel assigned for batch release namely QA Head or designee. The batch release was executed through a release slip. The term “designee” within the SOP was further controlled through another document entitled “authorized QA person for batch release”. The document listed six people who could perform batch release. The SOP was also complemented with another procedure entitled SOP for batch manufacturing record which included a checklist for batch release by QA personnel (i.e., checklist for batch release was completed by QA personnel which was further reviewed, among other documents, by the person in charge of batch release).

An Enterprise resource planning(ERP) system named PharmaSuite was used to manage all materials including raw materials and finished goods. As part of the QA release process, the QA Head or designees had the authority to access this software and change the status of the product from “quarantined” to “released”. That computer system has been in use since 2018 and was validated.

Batch numbering system

The SOP for assignment of batch number was in place. The batch number was made up of three blocks in the format of YYPXXXX while:

- YY is two digits marking the year of manufacture,
- P indicates pharmaceutical/food grade material (which also means the product is coming from unit II in Mujpur village)
- XXXX is a four digit sequential number starts from 0001 and which is not product specific.

The batch number was also suffixed with "RS" if the batch was supplied to DMF/APIMF markets. Products supplied as part of WHO prequalification were among this category and as such batch number was in the format of YYPXXXXRS.

6. Materials management

Warehouses

A separate storage area (room) for the WHO prequalified Zinc Sulphate Monohydrate API with a temperature below 30°C was established in the warehouse for finished products.

Raw material stores had de-dusting, quarantine area (under test area), sampling and dispensing area with reverse laminar airflow (RLAF). Rejected material storage areas were segregated in the warehouse. Separate acid storage was also established. SOP on receipt and approval of raw materials and packing materials was reviewed.

Supplier evaluation

List of approved suppliers

The list of approved suppliers was available. Manufacturers were part of the listing. For Zinc Sulphate heptahydrate, two manufacturers were listed: Satyam Metal Industries and Satyam Laboratories, both situated in Anand. However, the material for WHO API was produced and supplied by Satyam Laboratories. That is why the second supplier was not included in the submission dossier of WHOAPIMF-146.

The last audit of Satyam Laboratories was completed and the audit report was available.

Raw material specification and analysis

Specification for Activated Charcoal was reviewed was available.

KSM Zinc Sulphate heptahydrate was available in the raw material store.

Packaging of API

The final step in the batch production and control records was the creation of the batch packaging record for the filling of 50 kg HDPE bags with inside double LDPE liners. Final packaging as per the customer's need was done afterwards and controlled by "Intimation Slip" and Packaging area line clearance record. The SOP on repacking activity of the finished product defined the system for the repacking activities. According to the description, activities like details of repacking, product analysis report and packed product release were only documented through the software PHARMASUITE.

7. Production and in-process controls

The production process of Zinc Sulphate Monohydrate can be summarized in 7 stages:

- Stage I: Dissolution of Zinc Sulphate Heptahydrate
- Stage II: Filtration
- Stage III: Evaporation and cooling
- Stage IV: Centrifugation
- Stage V: Drying and sieving
- Stage VI: Blending and sieving
- Stage VII: Packing

The manufacturing process did not involve any "chemical reaction" or usage of solvents.

Inspectors toured production areas several times including an orientation tour on the first day of the inspection where block I was thoroughly visited and actual operations (stage I and stage III) were observed along with the raw materials warehouse and finished goods warehouse. On the second day of the inspection, the inspectors visited block II and witnessed actual production at line 6 (stage V, stage VI and stage VII).

The SOP for packaging and labelling was reviewed.

Blending batches of intermediates or APIs

The SOP for handling tailing quantities of approved batches was in place. The SOP guided the blending of tailing batches (small quantity leftovers from originally approved batches). The process involved the blending of the tailing batches along with further processing. A specific batch blending/mixing and packing record was used for this purpose. In practice, this process was never performed for Zinc Sulphate Monohydrate as the product was in high demand. An example batch blending/mixing and packing record was reviewed.

8. Packaging and identification labelling of APIs and intermediates

Details of packaging and labelling of intermediates and finished products were described under points 3 and 6 in this report (buildings and facilities and materials management).

9. Storage and distribution

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

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

10. Laboratory controls

Simple chemical test methods, mostly titrimetric compendial and non-compendial methods, were used for routine testing of starting materials, intermediates and finished products. The specification for Zinc sulphate monohydrate did not include microbiological testing. Microbiological monitoring relates to water and controlled areas were in place.

Laboratory facilities were toured several times by the inspectors including an orientation tour on the first day and an in-depth visit on the last day of the inspection. The visits covered the physicochemical laboratory, the microbiological laboratory, the retention samples store, the stability chambers, and the instrumentation laboratory. The latter was not used for any testing service of Zinc Sulphate Monohydrate. A few observations were noted during the aforementioned visits to the quality control laboratory.

Qualification of analytical instruments
The testing of Zinc Sulphate Monohydrate did not involve any instrumental testing at Canton Laboratories, other than those few testing activities needed for the in-house standard which were outsourced to contracted laboratories.

Analytical method validation
Zinc Sulphate Monohydrate was tested at Canton using titrimetric methods. The test methods were verified in 2016. Analytical method verification (not validation as the test methods used were pharmacopeial ones) protocol along with report were reviewed. On top of the mentioned analytical method verification, analysts were qualified before being assigned for particular testing activity as per SOP on analyst qualification.

OOS Handling
The SOP for OOS was in place and few OOS were spot-checked.

All reviewed OOS were concluded at stage I laboratory investigation where obvious assignable causes were detected by the analyst supervisor (e.g., wrong set of temperature of the oven, wrong reagent, spillage while processing Karl-Fisher [KF] test). In all cases, CAPA were minimal and focused on retraining.

Stability studies
Three stability chambers were available in a dedicated room within the QC laboratory. Procedure for stability study management was in place. Three stability conditions were maintained at the three chambers namely (1) 40 ºC ± 2ºC / 75± 5 RH for accelerated stability studies; (2) 30 ºC ± 2ºC / 75± 5 RH for real-time stability studies (zone IVb); and (3) 25 ºC ± 2ºC / 60± 5 RH for real-time stability studies(zone II). The chambers were regularly qualified by an outsourced qualification and calibration service provider.

Reference and working standards
The SOP for handling and preparation of working standards was in place. The SOP provided for the procurement and handling of reference standards; validity of reference standards; numbering of working standards; qualification of working standards; validity; storage; and destruction of working standards.

The logbook of reference and working standards were reviewed and samples of the same were spot-checked.

Retention samples.
The retention samples were properly stored at the store located within the QC laboratory at temperature-controlled conditions. The samples were retained up to 1 year after the expiry. A logbook was maintained for retention samples. The retention sample store was secured with access limited to QA staff.

Microbiology laboratory

The microbiology laboratory was modified after the last WHO inspection. The area was separated from the general QC area. A separate entrance has been created, including a changing room. The microbiology laboratory was equipped to carry out environmental monitoring, microbial count and pathogen testing. Two autoclaves were installed to ensure sterilisation and safe disposal of the growth media.

A laminar airflow unit was installed in the microbial limit test room. Access to the area was via suitable airlocks and change rooms. The monitoring of temperature and pressure differences were established. Materials and samples were transferred through one pass box with interlocked doors.

The traceability of growth media production and use was ensured by media consumption and validity record (including batch number and expiry date). A quantitative growth promotion test was documented.

Details of the environmental monitoring are described under point 3 in this report (buildings and facilities).

Monitoring of water quality was reviewed. R2A media was used. 1 ml of water sampled was given to the petri plate and 20 ml of media was added. Temperature was specified at ≤ 45 °C (pour plate method according to USP).

11. Validation

The SOP on Validation Master Plan was in place and provided guidance, among others, on validation policies including types, and frequencies.

Qualification

The document on qualification of instruments and equipment was in place. In general, equipment qualification was well established and maintained at the site. Please refer to section ***4. Process Equipment*** for further details on equipment at the facility including documentation reviewed for equipment qualification.

Process Validation

Manufacturing process validation of Zinc Sulphate Monohydrate was originally performed in 2016 at line 2. The process was revalidated in 2019 at line 6 as it was newly operational at that time. According to VMP, process validation had to be re-executed every 5 years at the latest. Protocol and report of process validation up to drying along with blending validation report were reviewed and the process seemed to be robust and well in control.

Cleaning Validation

Based on the last WHO inspection report, the company reconsidered the cleaning validation of the equipment and accessories used in production which in turn took into account PDE data of all APIs manufactured at the site. The CV protocol along with the CV report were reviewed. The PDE data of all APIs was supplied to Canton Laboratories by an external service provider. The qualification of the toxicologist was provided and reviewed. The acceptance criteria in terms of MACO based on PDE calculations were compared with MACO based on 10 ppm criteria and the lower limit was decided to be taken with the exception of three equipment namely vibro sifter (this piece of equipment was used for the production of Zinc Sulphate), multi mill and pulverizer (these two pieces of equipment were not used

for the production of Zinc Sulphate). Elemental test methods were used for the detection of traces of cleaned products (worst case based on PDE, therapeutic daily dose [TDD] and batch size)including Chloride, Zinc, Calcium, Iron, Nitrate, Carbonate, Sulphate, and others using qualitative titrimetric testing methods. The scope of this CV covered lines 2, 3, and 5 in building I and line 6 in building II.

Hold time studies

The holding time protocol along with the report of Zinc Sulphate Monohydrate wet material after stage IV (centrifugation) were reviewed. The study provided for storage of this in-process material for 72 hours. In practice, the production was usually continued from stage IV (centrifugation) to stage V (drying) due to process aspects (i.e., avoiding delay in the processing of subsequent lots and crops).

12. Change control

The SOP for Change Control together with the change control logs for 2023 and 2024 were reviewed. A classification of changes (major or minor) was made. Evaluation of changes after implementation was part of the system and performed after 3 months (minor changes) or up to 12 months (major changes). Impact assessment was part of the description in the SOP, including process validation, stability, documentation, and analytical method validation. The change control number was given in the document information where relevant (e.g. for specifications).

13. Rejection and re-use of materials

Reprocessing and reworking

The SOP for reprocessing and reworking was in place. The SOP allowed for the reprocessing of batches while limiting the distribution of reprocessed batches to “lower grade non-pharma markets”. The batch number of the reprocessed and reworked batches showed the same batch number as the original batch and was suffixed with the letter “W”. The procedure for reprocessing and reworking provided for the consideration of the relevant batches within the accelerated term stability studies.

Recovery of materials and solvents

No solvent was used in the manufacture of Zinc Sulphate Monohydrate. Only process water was used throughout the production process.

14. Complaints and recalls

The SOP for customer complaints handling was in place. The SOP provided for logging of complaints received from the customer and initiation of investigation and actions as necessary by the Compliance Head or his designee who in turn forward the same to site Head QA. The SOP gave reasonable guidance on receipt, logging, numbering, recording, investigation (including initial classification), CAPA (including the possibility for recall) and closure of the complaint. The timeline for a complaint was linked to its initial classification. 7 working days were mandated for the investigation of critical complaints, 21 working days for major complaints and 28 working days for minor complaints. A list of complaints for the year 2023 was reviewed and few example complaints were spot-checked.

The SOP for product recall was in place. No recall was needed since the establishment of the site in 2015. Mock recalls were conducted annually. The last mock recall was conducted for one batch for domestic distribution and one batch for overseas distribution.

15. Contract manufacturers (including laboratories)
This section was not covered during the inspection due to time constraints.

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, ***Canton Laboratories Pvt Ltd, India***, located at ***Survey No.: 350, Near Gambhira Bridge, Village: Mujpur; Taluka: Padra; Dist: Vadodara-391440. Gujarat, 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.

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

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

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. Fiftieth 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

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