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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
of the Quality Control laboratory

Part 1	**General information**
Laboratory Details	
Name of the Laboratory	Shenzhen Institute for Drug Control (SZIDC)
Address of inspected Laboratory	Site I Shenzhen Institute for Drug Control (Shenzhen Testing Center of Medical Devices), No.28, Gaoxin Central 2nd Avenue, Nanshan District, Shenzhen, Guangdong, China, Postcode: 518057
GPS Coordinates	113.943497, 22.552266
Dates of inspection	21-24 May 2024
Type of inspection	Routine inspection with PQ scope expansion
Introduction	

Brief description of testing activities

Type of analysis	**Finished products**	**Active pharmaceutical ingredients**
Physical/ Chemical analysis	pH, Density, Refractometry, Water content, Limit tests, Disintegration time, Dissolution, Uniformity of dosage units (by mass or content), Friability	pH, Refractometry, Optical rotation, Loss on drying, Water content, Heavy metals, Acid value, Iodine value, Limit tests, Nitrogen determination
Identification	HPLC (UV-VIS, Refractive index detection, Fluorescence), GC with headspace (FID), TLC, IR, basic tests	HPLC (UV-VIS, Refractive index detection, Fluorescence), GC with headspace (FID), TLC, IR, basic tests
Assay, impurities and related substances	HPLC (UV-VIS, Fluorescence and Refractive index detection), GC with headspace (FID), TLC, UV-VIS spectrophotometry, AAS, IR, Volumetric titrations	HPLC (UV-VIS, Fluorescence and Refractive index detection), GC with headspace (FID), TLC, UV-VIS spectrophotometry, AAS, IR, Volumetric titrations

	Microbiological tests	Sterility, Microbial limits	Sterility, Microbial limits
	Bacterial endotoxins test (BET)	Bacterial endotoxins (Gel-clot method: limit test)	Bacterial endotoxins (Gel-clot method: limit test)
General information	The Shenzhen Institute for Drug Control (SZIDC) was established and approved by the People's Government of Shenzhen Municipality in July 1982 and put into operation in 1986. In January 2003, it became part of the Shenzhen Testing Centre of Medical Devices (STCMD). SZIDC (STCMD) is a legal governmental institution established for implementing quality supervision and inspection of drugs, cosmetics, medical devices, and other related products in accordance with national legislation. Its business is subjected to the guidance of the National Institutes for Food and Drug Control (NIFDC), the Guangdong Institute for Drug Control (GDIDC), and the Shenzhen Administration for Market Regulation (SAMR). SZIDC (STCMD) consists of two laboratory sites: • Site I located at No.28, Gaoxin Central 2nd Avenue, Nanshan District, with a construction area of 62,000m^2, involved with *inter alia* the testing of drugs, cosmetics, Chinese traditional medicines, • Site II located at Tongfa Road, Nanshan District, with a construction area of 625m^2 and involved with only testing of Medical Devices. Testing services are mainly provided to National bodies, Guangdong Provincial and Shenzhen Municipal Drug Administration with limited testing services to enterprises and institutions. The main responsibilities of SZIDC included: – testing and technical arbitration of drugs, medical devices, cosmetics, pharmaceutical excipients, and pharmaceutical packaging materials. – technical support and related research on establishment and revision of quality standards, quality control and quality evaluation of drugs, medical devices, cosmetics, and pharmaceutical packaging materials. – research on new technologies, methods and standards for the testing of drugs, medical devices and cosmetics. – technical guidance and training services for quality control of drugs, medical devices and cosmetics.		
History	SZIDC was prequalified by WHO in 2018 and included in the list of WHO prequalified Quality Control Laboratories (QCL). Recently SZIDC applied for expanding the prequalification to include microbiological tests and bacterial endotoxin tests in API and Finished products.		

	The SZIDC premises included chemical, physical, electronic, instrumental, light resistant, microbiological, and cytological laboratories, common and SPF animal laboratories and Chinese Medicine specimen rooms. SZIDC had the following accreditations: – Authentication by the Administration of Quality and Technology Supervision for China Mandatory Approval (CMA) since 1990, with certificate number 202319001159. – Accredited by the China National Accreditation Service (CNAS) for Conformity Assessment since 2004, with the certificate number CNAS L1446. – Qualified by WHO for Quality Control Laboratories Prequalification since 2018.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Organization and management Quality Management System Personnel Training and Safety Documentation and Records Premises and Equipment Validation – Qualification –Calibration of equipment, including computerized systems Laboratory Practices Reference standards – Reagents, including water production
Restrictions	None
Out of Scope	Refer to the list of activities. Site II involved with the testing of Medical Devices was out of scope.
Abbreviations	**Meaning**
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
COI	Conflict of interest
CAPA	Corrective action & Preventive action
DQ	Design qualification
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometry or spectrophotometer
GC	Gas chromatography or Gas chromatography equipment
GMP	Good manufacturing practices
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
IQ	Installation qualification
IR	Infrared spectrophotometry
KF	Karl Fischer titration
LIMS	Laboratory information management system

MB	Microbiology
MR	Management review
N	Normality
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
OQ	Operation qualification
Ph.Eur.	European Pharmacopoeia
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PT	Proficiency testing
PTS	Proficiency testing scheme
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QM	Quality manual
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure
TCM	Traditional Chinese Medicine
TLC	Thin layer chromatography
TOC	Total organic carbon
URS	User requirements specifications
USP	United Stated Pharmacopoeia
UV	Ultraviolet-visible spectrophotometry or spectrophotometer
VMP	Validation master plan
VS	Volumetric solution

Part 2	Summary of findings and recommendations

1. Organization and management

The Top Management, consisting of the Director General, Deputy Director, Technical Manager and Quality Manager, was responsible for the overall activities of the laboratory.
The departments involved in the WHO-PQ program included:
Functional departments

- Executive Office,
- Business and Technology Department,
- Human Resources Department,
- Quality Management Department,
- Equipment Purchasing and Maintenance Department,
- Information Technology Department

Testing departments

- Chemical Drugs Testing Department，
- Analysis and Testing Research Department,
- Microbiological testing Department,
- Pharmacology and Toxicology Department.

The organization and management structure, including responsibility, authority, and interrelationship of the personnel, was specified in the organizational chart. The total number of staff at the time of inspection accounted for 315 persons with 47 managers and 259 analysts.

The Laboratory had arrangements to ensure that its management and personnel were not subjected to commercial, political, financial, and other pressures or conflicts of interest that might adversely affect the quality of their work. A written procedure dealt with COI at the time of appointment and when there was a change in staff positions. The requirement was to address COI on appointment and when there was a change in status such as marriage status or change in position within the organisation. Annually, a COI was signed. The Laboratory had a policy in place to ensure the confidentiality of information contained in marketing authorizations and test reports.

The Job description for the Quality Manager was verified which confirmed the responsibilities for quality management including audits, CAPA investigations and complaints.

The Shenzhen Administration for Market Regulation was responsible for the authorization of drug products in the geographic area of the municipality with SZIDC, an affiliate, performing testing of medicines, medical devices and cosmetics in the region.

Communication within the laboratory was conducted through an application developed by the Guangdong Province which facilitated communication between all governmental organisations within the province.

2. Quality management system

The management system was developed, implemented, and maintained according to the applicable national legislation, international guidelines and standards. The current version of the Management Manual, was issued on 30 June 2023 and implemented on 10 July 2023. The main referred documents and standards were:

- Administration Measures for Qualification Accreditation of Inspection and Testing Institutions, Administration Measures for Supervision of Inspection and Testing Institutions and other relevant laws and regulations, Accreditation Criteria for the Qualification of Inspection and Testing Institutions (SAMR Notice 2023 No. 21),
- Accreditation Criteria for the Competence of Testing and Calibration Laboratories (CNAS-CL01: 2018, equivalent to ISO/IEC 17025:2017),
- World Health Organization (WHO) Good Practices for Pharmaceutical Quality Control Laboratories (WHO Technical Report Series No.957, 2010).

The CNAS laboratory accreditation covered the microbiological testing of drugs, including sterility testing; detection, isolation, enumeration, and identification of microorganisms (bacteria, yeast, and mould); and bacterial endotoxin testing according to the Chinese Pharmacopoeia.

Routine surveillance, internal audit, external audit, and management review practices were implemented.

The testing units actively participated in national and international proficiency testing (PT) programs (29 tests) and national collaborative chemical reference substance calibrations (15 tests). The PT program covered the following methodologies:

- Liquid chromatography,
- TLC,
- Polarimetry,
- Volumetric titration,
- Gas Chromatography,
- Conductivity test of Water for Analysis,
- Determination of Relative Density and pH,
- Determination of the dissolution,
- Total Aerobic Microbial Count of drug,
- Determination of Nitrogen Content,
- LOD determination of drug,
- Optical rotation,
- Refractive index,
- PCR-RFLP,
- Sterility Testing.

The Laboratory maintained close cooperation with the WHO International Pharmacopoeia (Int. Pharmacopoeia) and the Chinese Pharmacopoeia Commission (Ch Pharmacopoeia) and was involved in the revision of various drug standards and the validation of standard testing methods.

In 2020, SZIDC won the bid to become China's first global drug testing laboratory in the United Nations Development Program (UNDP) for long-term cooperation.

Management Review

A Management review of quality issues was regularly undertaken (at least annually) in accordance with a written procedure, which included:

- reports on internal and external audits or inspections and any follow-up required to correct deficiencies.
- the outcome of investigations carried out as a result of complaints received, doubtful (atypical), or aberrant results reported in collaborative trials and/or proficiency tests.
- corrective actions applied, and preventive measures introduced as a result of these investigations.

The last review was held on 17 Jan 2024 with the requirement to initiate CAPA by 23 Jan 2024. At the time of the inspection (24 May 2024), none of the CAPA had been completed.
It is noted that the SOP did not address timelines for CAPA to be completed. The Quality Management issued an inquiry on the status of CAPA every 6 months. If required, an extension of timelines could be considered. The Quality Management was required to follow up CAPA until completed.

The Quality Manager prepared an agenda for the meeting of 17 January 2024 in February 2023. As per the January 2024 Agenda the following topics were discussed: Technical Management, Quality Management, and Administrative Management. The Management Review meeting notes together with action points were made available on 19 Jan 2024. The meeting was chaired by the Director, an attendance list was made available.

Internal audit

The requirements for internal audits were captured in a written procedure. Internal audits were performed at least annually covering the main areas of the management system. Internal audits were conducted according to an SOP by qualified and trained internal auditors who were independent of the activities to be audited. The internal audit program for 2024 was available with the annual audit planned for Nov-Dec 2024. The Audit programme for 10 Nov 2023 was evaluated which included the guidelines against which audit would be conducted. A report dated 24 Nov 2023 was available. When identifying risks and opportunities associated with laboratory activities, the Risk Management Program would be initiated to analyse the impact, develop and implement measures to control the risks and opportunities, and evaluate their effectiveness.

Change Control

Change control activities were carried out following a written procedure. The SOP made provision for 8 different types of changes. The changes implemented since the last WHO inspection (2017), classified as Major, were discussed. The changes were initiated, implemented, and documented.

Handling of deviation and implementation of CAPA

Deviations were handled according to an SOP and classified based on

- significance (severity and impact) as general or critical and
- frequency as temporary or permanent change.

The Corrective Action Control Program, implemented to prevent reoccurrence, was controlled via the Change Control procedure.

Deviations were applied for, identified, and recorded on a deviation form. After the second reoccurrence of the same deviation, a Change Control procedure was initiated. The identified deviations included non-conforming operation with the management system, outcome of external proficiency testing, interlaboratory comparisons and internal quality control activities. Follow-up audits validated the implementation and effectiveness of the corrective action taken. The Deviation log for 2023 was verified which listed 2 deviations of which one related to cosmetics. It was noted that the deviation policy lacked the requirement for a CAPA investigation and subsequent implementation.

CAPA handling

CAPA implementation was addressed by a written procedure. All CAPAs were handled by Quality Management except CAPAs triggered by internal audits. The Team responsible for Internal Audits was responsible for follow up actions and implementation monitoring.

Handling of complaints

Complaints were handled and investigated according to the Complaints Handling Program and were classified as:

- related to testing results.
- other, not related to testing.

In the event of a complaint on testing results, the customer may request for a retest to be conducted by the Institute or by the Provincial Laboratory. If retesting of a sample was required, the Institute handled the matter as a new test request. During 2023, 15 complaints on testing results were recorded with 9 complaints related to medicine. No complaints were received in 2024. No trending of complaints was done due to the small number of complaints received.

3. Control of documentation

The document management system consisted of two tiers: the Management Manual and the Standard Operation Procedures (SOP).

The documents were prepared, approved, revised, and issued based on the Document Control of the Management Manual and Files and Documents Control Procedure.

The Management Manual was prepared by the Quality Management Department under the leadership of the Quality Manager, reviewed by the Top Management, and issued after authorized by the Director General.

SOPs were prepared by the relevant departments under the leadership of the Quality Management Department, to be approved by the Director in charge. The SOPs were reviewed periodically (at least every five years) and modifications were made where necessary. SOPs were available for each testing process, from sample reception to test report issuing. 201 SOPs were issued related to chemical drugs testing, of which 87 management SOPs, 11 testing method SOPs, 103 equipment operation and maintenance and performance qualification SOPs.

The testing procedures were implemented in accordance with the Testing Work Procedure. Testing standards and methods were selected and prepared according to the Management Manual as well as the Test Methods Control Procedure.

The main technical standard documents related to chemical drugs testing were the National Standards, Chinese Pharmacopoeia, pharmacopoeias of other nations and regions, national registration standards and tentative standards.

The Business and Technology Department oversaw updating, distributing, and managing technical standard and method documents. The testing departments were responsible for preparing SOPs, records, forms, and templates of related testing work.

Experimental data, such as data on the electronic balance, were transferred automatically, and any operation in the system was recorded, tracked, and audited.

4. Records

The testing process and corresponding test reports were completed and generated through the LIMS system. Each person related to the test had an individual account and password to access LIMS, with different authorization for business reception, testing, retesting, checking, review, report generation, signing, issuing, and printing.

Experimental data, such as weighing data from electronic balances, were collected automatically. Any operation in the system were recorded, tracked, and audited and managed according to the following procedures:

- Technical Records Control Procedure,
- Data Control Procedure,
- Computer, Network and Information System Management Procedure,
- Records and Files Management Procedure.

After the testing being finished the test report was submitted to the reviewer then approved by the department director before being signed by the authorized signatory. The test reports were prepared with details and requirements in compliance with the Management Manual and the Test Reports Management Procedure.

The CoA was printed, signed and stamped by the Business and Technology Department before issued to the customer.

The history and records of the randomly selected sample, *Cefetomet Pivoxil HCl Dispersible tablet* was checked (receipt log, storage conditions, tests, instruments and standards used, results, reporting, and archive) to verify the records' accuracy.

See section 17 (Testing).

A separate Archive facility was available. The area and storage cabinets were access controlled. A fireproof door gave access to the area. Archiving was managed according to the SOP "Record and Archive management" which identified different types of documents with corresponding archiving timelines. Documents classified as "Testing" which included Test reports, CoAs, Contracts and sample records required archiving for 15 years. IT disks required archiving for 30 years.

5. Data processing equipment

An inventory of computerized systems was available (including information about unique identification, purpose, validation status, physical or storage (drive and files path), software and related documentation location, and responsible or contact person.

Three servers used chromatography systems:

- Empower-3 for Waters and Agilent
- Chromeleon and VP Station for Dionex and Shimadzu

The data processing equipment were controlled according to the Data Control Procedure, and the Computer, Network and Information System Management Procedure. Commercial software was validated by the suppliers while the in-house developed software was validated by the IT Department. Access to the IT systems required a unique user password. Data entries were locked with any revision recorded in an audit trail.

The user management including user groups, privileges, and audit trails of a randomly chosen HPLC were discussed.

6. Personnel

The personnel were managed in accordance with the Management Manual and the SOP "Management of Personnel Training, Competence Confirmation and Authorization". The laboratory had sufficient personnel with the necessary education, training, technical knowledge, and experience for their assigned functions. Generic job descriptions for key positions were available addressing responsibilities and qualification requirements. Records on technical personnel describing qualifications, training, and experience were available.

Staff training was divided into initial training aimed at personnel joining the institute, transfer training aimed at staff transferred from one position to another, and ongoing training which included routine, refresher, and on the job training. Training details included job responsibilities, work content, quality standards, operation standards, testing skills and work procedures. Contents, examination results and evaluation of the training effectiveness were recorded in the Educational Training Record of each staff member.

Training in good data and record management in evaluating the configuration settings and reviewing electronic data and metadata, such as audit trails for computerized systems used in generating, processing, and reporting data was performed.

The training records of the following staff members were verified:

- Technical Manager -Drugs: he was appointed during December 2023 and he previously held the position as Technical Director- TCM.
- Two Physical Chemical Laboratory analysts.

A policy on the appointment of consultants was available addressing recognition as an expert, experience, and signing of a contract.

7. Premises

The total construction area of Site I was 62,000m^2. The laboratories in the scope of the PQ covered a total area of 4485m^2 on the 1st, 3rd and 4th floors of buildings "A" and "B", and the 8th and 9th floor of building "D". The related laboratories included the physical/chemical laboratory, instrument laboratory, reagent room and storeroom, sample retention room, sample room, and all the functional laboratories required for drug microbiological testing. An up-to-date layout of the premises was available.

The buildings were constructed of reinforced concrete, steel-framed ceilings with aluminium alloy plating, emulsion paint-coated walls, and non-slip tile flooring. The experimental furniture used acid and alkali-resistant ceramic surfaces and steel frames. Fume cupboards that can automatically control airflow were available.

Laboratories included chemical, physical, electronic, instrumental, light resistant and microbiology.

Temperature and humidity were controlled monitored and recorded. Based on the requirements for different storage specifications of tested samples, the sample retention rooms were divided into normal, cool and cold zones with the temperature and humidity requirements defined and maintained appropriately.

The Equipment Purchasing and Maintenance Department was responsible for organizing and managing cleaning work according to the Facilities and Environmental Conditions Control Procedure. The construction of the microbiology laboratory met biosafety (BSL) level II specifications.

8. Equipment, instruments, and other devices

The Laboratory was equipped with all instrumentation relevant to chemical drugs testing in the scope of PQ, including chromatographic equipment such as HPLC, GC; spectrographic equipment like IR, UV/VIS, AAS; microbiological testing equipment such as isolator, biosafety cabinet, incubator and refrigerator equipped with real-time temperature monitoring device, microbiological identification equipment based on different principles, clean bench, autoclave sterilizer, ultra-low temperature freezer, optical microscope, electronic balance, pH meter, etc; Other equipment included a dissolution tester, particle detector, refractometer, polarimeter, melting point apparatus, disintegration apparatus, and moisture meter.

The Equipment Purchasing and Maintenance Department was responsible for preparing regular inspections and maintenance plans, as well as organizing a logistics management company to maintain, repair and manage the facilities, including the tap water and sewer system, air conditioning system, electricity, lighting system, lab furniture, water generator and compressed air system. Instruments and equipment were operated and maintained according to

- The Management Manual,
- The Equipment Management Procedure,
- Instrument specific SOPs.

The designated operators (analyst) from the Testing Departments together with the equipment controllers were responsible for the maintenance plan and for timely maintenance activities. Maintenance records were captured in the LIMS and backed-up electronically.

The volumetric flasks were adequately identified and maintained.

9. Contracts

A procedure was in place for the selection and purchasing of services and supplies. The Business and Technology Department was responsible for investigating the competence of the subcontractor considering the following: personnel, equipment, test environment, quality management and other capabilities such as criteria of accreditation/authentication. Test reports provided by the subcontractors were included in the testing documentation together with an indication of the source data. The supplier evaluation and the purchase of materials were described in Purchasing Control Procedure for Products and Services. The list of approved suppliers was revised taking service quality and usage experiences into account.

10. Reagents

Materials and reagents were stored in their respective warehouses according to their properties indicated on the label or MSDS.

Waste was collected by the Testing Department and managed by the Equipment Purchasing and Maintenance Department according to Environmental Protection Procedure. Waste was disposed of by specialized companies legally authorized to perform such services. Hazardous reagents were stored in a dedicated warehouse with video monitoring, ventilation devices, explosion-proof equipment and fire extinguishers. Hazardous substances were purchased, checked and accepted, stored and distributed following the related national laws and regulations, and the Management Manual, including:

- The SOP on Purchasing Control Procedure for Product and Services,
- The Reagents and Testing Solutions Management Procedure,
- The Laboratory Safety Management Procedure.

All testing departments had a reagent room managed by a nominee.

The MSDS of chemicals and reagents were available and uploaded to LIMS to allow analysts access.

Water supply was assured by the purified water system and ultrapure water generators. Purified water was used for general physical/chemical testing, glassware cleaning and as a source for ultrapure water. The ultrapure water was used for AAS, HPLC, GC and other sensitive analyses. The following procedures managed water quality:

- The procedure for the Operation and Maintenance of the Purified Water Generator,
- The procedure for the Preparation, Testing, Storage and Use of Experimental Water,
- The Experimental Water Testing Procedure.

Purified Water was tested daily for conductivity, with a test against the water specification done monthly. A total of 48 sample points were identified.

The media used for microbiology testing were mainly in dry powder and commercially available. The plates used for environmental monitoring were in-house prepared media or ready-made contact plates. All the media, culture and auxiliary consumables discarded were chemically disinfected or decontaminated by an autoclave dedicated to waste sterilization.

11. Reference substances and reference materials

The reference substances and reference materials were purchased, prepared, handled and stored as prescribed in Reference Materials Management Procedure. Reference materials for control of medicines were ordered by the Equipment Purchasing and Maintenance Department mainly from the National Institutes for Food and Drug Control (NIFDC).
When receiving, the following were checked:

- CoA and specifications,
- lot number (compared to the CoA and specifications),
- appearance, character (compared to the CoA and specifications),
- expiry date (compared to the CoA and specifications),
- sample amount received (compared to the delivery note),
- source.

Nominated personnel was responsible for the management and inventory of reference materials and substances. Usage was timely registered in LIMS including the name, lot number and source information.
The register for reference substances was available. The handling and usage records of randomly selected reference materials were discussed. The respective identification number was quoted on the analytical worksheets whenever the reference substance was used.

12. Calibration, verification of performance, and qualification of equipment, instruments, and other devices

New equipment was purchased by the Purchasing and Maintenance Department upon the requirements provided by the initiating department according to the Equipment Management Procedure. No equipment can be put into use unless qualified.
Equipment was handled in the LIMS in accordance with:

- Procedure for Measurement Traceability of Equipment,
- Equipment Management Procedure.

The calibration, verification protocols, schedule and records of the following equipment were discussed.
Balance
Balances were checked daily using suitable test weights and annually by an external company. The calibration protocol and records of a laboratory balance were verified. The instrument label indicated the annual performance qualification by the external company as per Performance Protocol procedure.

HPLC
The procedure and qualification documentation of a Waters HPLC were reviewed. The criteria and the records were matching.

13. Traceability

Test results were traceable, when appropriate, ultimately to primary reference substances. All calibrations or qualifications of instruments were traceable to certified reference materials and SI units (metrological traceability)

14. Incoming samples

Sampling and testing were mainly conducted in support of the domestic drug surveillance testing plan prepared by the National Medical Products Administrations and assisted by the SZIDC Supervision and Sampling Department as per the procedure "Sampling of the Management Manual, and Sampling Control". Samples were received, handled, and tested as per procedure "Handling of Test Items of the Management Manual, and Samples Management" which required that on receipt, a testing identification number be generated by LIMS. A sample label was attached containing the identification information. Amongst others, the following information was recorded in the registry:

- number of samples,
- registration number of the sample,
- date of receipts,
- expiry date,
- unit to which the sample was forwarded.

The sample quantity received was divided into three equal portions: one for full testing, and two for retention. In case of special circumstances, the controller can reduce the amount of the sample. Two sample portions were stored in the retention room following receipt, with one portion sent for testing to the specific unit together with the test request. Samples were stored in the sample storage lockers of each analyst awaiting testing.

For purposes of verification, *Cefetomet Pivoxil HCl Dispersible tablet* was traced. The product, was sampled on 29/8/2023 and the sample was received on 31/08/2023. Storage condition was indicated as "cool place".
The sample statuses indicated in the LIMS were:

- to be tested,
- under testing,
- retention storage,
- finished testing.

15. Analytical worksheet

The project for elaborating and implementing the electronic laboratory notebook (ELN) was ongoing. The ELNs already available in LIMS were validated by the Quality Assurance Unit and issued by the Technical Manager. Analyst should choose and use the test item specific ELN from the LIMS.

The worksheets contained the following information:

- the date on which the analysis was started and completed.
- reference to specifications and complete description of the test methods by which the sample was tested, including the limits; identification of test equipment used; reference substances, reagents, and solvents employed.
- interpretation of the results and
- the conclusion of whether or not the sample was found to comply with the specifications.
- any deviation from the prescribed procedures (approved and reported).

16. Validation of analytical procedures

The SOP described the Selection Validation, Verification and Transfer of Methods, and Test Methods Control Procedure. A general policy for validation of analytical methods is mentioned under point dealing with Validation of analytical procedures. As such, compendial test methods were validated for the intended use. Method verification/validation was applicable prior to testing in the following cases:

- for test methods used first time,
- non-compendial methods (including self-developed methods),
- methods used outside their intended scope,
- standard methods amplified and modified,
- transferred validated methods.

The method verification/validation was based on the approach of the Chinese Pharmacopoeia Guidelines for Validation of Analytical Method Adopted in Pharmaceutical Quality Specification. The analytical tests were subjected to verification/validation which included:

- identification,
- quantification or limit test of impurities,
- content determination of active ingredients in drug substances,
- dissolution and release test of pharmaceuticals.

The characteristics to be validated were depending on the purpose of the test and included accuracy, precision, specificity, limit of detection, limit of quantitation, linearity, range and ruggedness.

For microbiology testing, the validation methodology was mainly based on the Guidelines for the suitability of the microbiological test method as per the Chinese Pharmacopoeia (2020 edition, General rules <1101>, <1105>, and <1106>). Test method suitability included positive and negative controls. Non-standard methods should be validated prior to use, which was not applicable at the time of the inspection. The method was used only after the verification result and conclusion have been reviewed and approved. The records related to the verification of an HPLC impurity and assay method were available and discussed.

17. Testing

The specification necessary to assess the sample was defined in the test request. If no precise instruction was given in the test request, the specification in the officially recognized national pharmacopeia was used or, failing this, the manufacturer's officially approved or other nationally recognized specification.

The samples were tested in accordance with the work plan of the laboratory against the corresponding specification. Usually, the product specification and the test methods described in the Chinese Pharmacopoeia were followed. Where system suitability criteria were defined in the method, they were fulfilled. Any deviation from the test procedure was approved and documented. Test records were managed according to a SOP. During the inspection, the test records and reporting of the test results of randomly selected samples was checked (receipt log, storage conditions, tests, instruments and standards used, results, reporting, and archive) to verify the records' accuracy.

For purposes of verifying the testing records of a randomly selected sample were discussed focusing in particular on the following:

- sample receipt, sample distribution,
- CoA preparation, contents, approval,
- specification with criteria and test methods,
- method verification,
- and laboratory worksheets,
- test raw data, chromatograms, injection table, instrument method,
- handling of chromatography columns,
- calculations,
- data transport between the electronic data processing devises and the LIMS,
- competency of the analyst,
- user privilege,
- system suitability testing and evaluation.

18. Evaluation of test results and OOS investigation

The records of randomly selected samples were reviewed to verify the accuracy of records, including:

- Qualification of analysts and equipment,
- Preparation of reagent solutions,
- Adequacy of reference standards, Analytical worksheets,
- Traceability, evaluation of test results,
- Information on the CoA.

For the test records discussed see the relevant section.

When the test result was found out of the specification, the analyst initiated an investigation according to Procedure for Out of Specification Results Investigation.
The investigation covered amongst others the following: qualification of the analyst, analytical procedure, testing sample, laboratory environment, instruments & equipment, reagent, reference materials, testing process, original records and calculations.

If the investigation was inconclusive, the SOP gave guidance on the number of retests allowed (based on statistical principles). Once an error was identified, corrective and preventive measures were recorded and implemented. All individual results (all test data) with acceptance criteria were reported. The repeat of tests was done by a second analyst, as experienced and competent as the initial analyst.

Microbiological tests were supported with negative and positive controls (add standard strain) for sterility. In case of an abnormal control, a Microbiological Data Deviations (MDD) investigation was carried out.

19. Certificate of analysis

The CoAs were generated in the LIMS using a unified format containing at least the following information:

- the results of the tests performed within the prescribed limits.
- a conclusion as to whether or not the sample was within the limits of the specification.
- date on which the tests were completed.

After testing was completed, the draft CoA was submitted to the reviewer for reviewing, and then reviewed and approved by the department director before being signed by the authorized signatory. The Management Manual and the Test Reports Management Procedure described the process. The CoA was printed and stamped by the Business and Technology Department before issued to the customer.

20. Retained samples

Samples were retained as required by legislation or by the client. A sufficient amount of retained sample was kept allowing at least one reanalyses. The retained samples were kept in its final pack for period of time:

- generally, up to 1 year after the product expiry date,
- up to 2 years after testing or 2 years after the expiry date in case of OOS samples.

Temperature and humidity conditions of the retention sample room were monitored and recorded. The alarm system sent an automatic e-mail notification to two staff members via the Government internal network portal in case of out of specifications.

21. Safety

General and specific safety instructions reflecting identified risks were available to each staff member and regularly supplemented as appropriate (e.g., with written material, poster displays, audio-visual material, and occasional seminars). Staff was trained to use fire-fighting equipment, including fire extinguishers, fire blankets, and gas masks. Staff was wearing laboratory coats, including eye protection. Special care was taken in handling highly potent, infectious, or volatile substances. Highly toxic and/or genotoxic samples were handled in safety cabinets.

Safety data sheets were available for chemicals. First-aid materials were provided, and the staff was instructed in first-aid techniques, emergency care, and the use of antidotes. Containers of chemicals were labelled and included warnings (e.g., “poison”, “flammable”) whenever appropriate. Rules on the safe handling of cylinders of compressed gases were established, and staff were familiar with the relevant colour identification codes. Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and the need for safe and complete disposal of mercury and its salts were implemented.

All the media, culture and auxiliary consumables leaving the microbiology laboratory were decontaminated either by autoclave dedicated to waste sterilization or through chemical disinfection.

22. Microbiology

The microbiology laboratory was in Building D, 8th floor. The construction of the microbiology laboratory met biosafety (BSL) level II.

To ensure the accuracy of the microbiology test results, environment monitoring and the microbial identification program were in place in accordance with the guiding principles of the Chinese Pharmacopoeia, and data on a randomly selected sample was verified.

Culture media was prepared according to the SOP Management Procedure for Quality Control of Culture Medium by analysts using qualified purified water. Apart from the sterilization indicators used for each sterilization run, biological indicators were also placed in places difficult to sterilize.

The media used for microbiology testing were mainly in dry powder form and commercially available. The plates used for environmental monitoring were prepared in-house or were ready-made contact plates.

The sterilized media was stored under specified conditions with temperature monitoring with the suitability test conducted according to the Guidelines for the suitability of the culture medium in the Ch Pharmacopoeia (2020 edition, General rules <1101>, <1105>, and <1106>) which included: pH, sensitivity, growth promotion, recovery of target organisms. Key equipment such as sterilizing cabinet, incubator, balance, and pH meter, were calibrated, qualified and properly maintained to ensure the quality of the culture media. All prepared and sterilized media were stored under defined storage conditions and the shelf-lives had been verified with the reference media labelled with an open date and expiry date.

Validation data on the sterilization method using chemical and biological indicators was available. Data on Loading patterns using two configurations, one for liquids and one for solids were available. Sterilized products were identified. The sterilization data on TSB, with identification XX, oven (identification XXX) was verified. Incubation in incubator XX was verified and found acceptable. Material was transferred from the corridor into the various Clean Areas (Class B) using a pass box. It was noted that the pressure differentials were only monitored when the pass box was in use.

Endotoxin testing was conducted in a dedicated room. Working standards were prepared and standardized against a National standard. Standards were stored at appropriate storage conditions with control standards at 2-8 ^{0}C and national standards at -20 ^{0}C.

Microbiology results were uploaded manually to the LIMS system. Interpretation of results was captured by the analysts and verified by a second analyst. Gel clot reading was checked every 5 minutes.

Sterility testing of sample, *Cefodizime Sodium sterile powder for injection* was verified. Incubation started on 25/04/2024 and concluded on 9/05/2024.
Endotoxin testing of sample, *Cefotoxin powder for injection* was verified.
Results of microbiology testing were appropriately concluded and signed off.

Miscellaneous	
Assessment of the Laboratory Information File	The Laboratory Information File was provided for the inspectors and contained all the relevant sections and data.
Annexes attached	N/A

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, ***Shenzhen Institute for Drug Control (Site I)*** located at ***No.28, Gaoxin Central 2nd Avenue, Nanshan District, Shenzhen, 518057, Guangdong, China*** was considered to be operating at an **acceptable level** of compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories guidelines.

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

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

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report, Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4. ***Short name: WHO GPPQCL Guidelines, TRS No 1052, Annex 4***
https://www.who.int/publications/i/item/9789240091030

2. 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

3. 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

4. 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-

5. 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 GMP guidelines or ***TRS No. 986, Annex 2***
   https://www.who.int/publications/m/item/trs986-

6. 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

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. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
   Short name: WHO TRS No. 961, Annex 6
   https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex6-gmp-sterile-pharmaceutical-products.pdf

9. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.
   Short name: WHO TRS No. 961, Annex 7
   https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs961-annex7-transfer-technology-pharmaceutical-manufacturing.pdf?sfvrsn=2e302838_0

10. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 96, Annex 9)
    ***Short name: WHO TRS No. 961, Annex* 9**
    https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

11. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report, Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
    Short name: WHO TRS No. 943, Annex 3
    https://www.who.int/publications/m/item/trs943-annex3

12. 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
Short name: WHO TRS No. 1010, Annex 8
https://www.who.int/publications/m/item/Annex-8-trs-1010

13. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report, Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2.
Short name: WHO TRS No. 981, Annex 2
https://www.who.int/publications/m/item/trs981-annex2

14. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report, Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3.
Short name: WHO TRS No. 981, Annex 3
https://www.who.int/publications/m/item/annex-3-trs-981

15. WHO guidelines for preparing a laboratory information file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report, Geneva. WHO Technical Report Series, No. 961, 2011, Annex 13.
Short name: WHO TRS No. 961, Annex 13
https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/quality-control/trs961-annex13-guidelines-preparing-laboratory-information-file.pdf?sfvrsn=54d1f397_2

16. 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

17. 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

18. 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

19. Good chromatography practices. 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 Good chromatography practices
https://www.who.int/publications/m/item/trs1025-annex4

20. Good manufacturing practices: guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third report, Geneva, World Health Organization, 2020 (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

21. WHO model certificate of analysis. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second report, Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 4.
Short name: WHO TRS No. 1010, Annex 4
https://www.who.int/publications/m/item/trs1010-annex4

22. 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

23. Guidelines on pre-approval inspections. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report, Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 7
Short name: WHO TRS No 902, Annex 7
https://www.who.int/publications/m/item/trs902-annex7

24. Prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first report, Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 3
Short name: WHO TRS No 1003, Annex 3
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