World Health Organization

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**Prequalification Team Inspection Services**
**WHO PUBLIC INSPECTION REPORT**
**Quality Control laboratory**

| **Part 1** | **General information** |
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| **Laboratory Details** | |
| Name of the Laboratory | Dalian Institute for Drug Control (DIDC) |
| Address of inspected Laboratory | No 888A, Huanghe Road, Shahekou District, Dalian City, Liaoning, 116021, China. |
| GPS Coordinates | North 38 55 0<br>East 121 33 12 |
| **Inspection Details** | |
| Dates of inspection | 15 – 17 May 2024 |
| Type of inspection | Initial inspection |
| **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, dissolution, uniformity of dosage units (mass, content), friability, viscosity, extractable volume for parenteral preparations, color of solution, clarity of solution, particulate(matter) contamination, particle size, osmolality | pH, refractometry, optical rotation, loss on drying, water content, heavy metals, acid value, iodine value, limit tests, nitrogen determination, viscosity, peroxide value, saponification value, unsaponifiable matter, hydroxyl value, distilling range, melting point, congealing point, thermal analysis, color of solution, clarity of solution, particulate(matter) contamination, osmolality, solubility, sulphated ash, residue on ignition |
| Identification | HPLC (UV-Vis, DAD, RI detection), GC (FID), TLC, UV-VIS spectrophotometry, FTIR, HPLC-MS, AAS, ion chromatography, basic tests | HPLC (UV-Vis, DAD, RI detection), GC (FID), TLC, UV-VIS spectrophotometry, FTIR, HPLC-MS, AAS, ion chromatography, basic tests |

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|---|---|---|---|
| | Assay, Impurities and related substances | HPLC (UV-Vis, DAD, RI detection), GC (FID), UV-VIS spectrophotometry, AAS, FTIR, TLC, HPLC-MS, ion chromatography, volumetric titrations, gravimetric analysis, optical rotation, potentiometric titrations, nitrogen determination, determination of related substances/impurities and degradation products, residual solvents | HPLC (UV-Vis, DAD, RI detection), GC (FID), UV-VIS spectrophotometry, AAS, FTIR, TLC, HPLC-MS, ion chromatography, volumetric titrations, gravimetric analysis, optical rotation, potentiometric titrations, nitrogen determination, oxygen flask combustion, determination of related substances/impurities and degradation products, residual solvents |
| General information | Established in 1953, Dalian Institute for Drug Control (DIDC) used to be a legal public entity subordinated to Dalian Food and Drug Administration. In 1983, DIDC was designated by the Ministry of Health as "Dalian Port Drug Test Institute of the People's Republic of China". In 2018, it had become one of the branches of Dalian Center for Certification and Food and Drug Control (DCCFDC), which is a secondary legal public entity and full funded by the Dalian municipal government.<br><br>The DCCFDC is headed by the Director and the Deputy Director. The DIDC is housed in the same building as the DCCFDCA occupying floors 4, 5, 6, 7, and 8 of the building. As a third-party laboratory, it provided technical support for government supervision and independently issue certificates of analysis.<br><br>The main laboratory activities of DIDC included:<br>• supervisory and market surveillance sampling and testing<br>• sampling and testing of crude drugs imported through Dalian Port<br>• contract testing<br>• registration test for imported drugs<br>• test for health food and cosmetics according to the management authority<br>• drugs and health food test related R&D<br>• information management and technical training,<br>• professional guidance and technical support provided for industry stakeholders (mainly manufacturers and distributors),<br>• elaborating and reviewing specifications and working on the tasks entrusted by AMRs and MPAs at national, provincial, and municipal level.<br>• microbiology testing<br><br>The clients of the laboratory included:<br>• Dalian Administration for Market Regulation (DAMR)<br>• Pharmaceutical manufacturers<br>• Pharmaceutical preparation unit of governmental hospitals within the jurisdiction | | |

- National Medical Products Administration (NMPA)
- National Institute for Food and Drug Control (NIFDC),
- Chinese Pharmacopoeia Commission (CPC)

Types of samples tested:

- Medicines (finished) (tested by Chemical Unit 1 located on 5th floor or Chemical Unit 2 located on 7th floor)
- Active substances (tested by Chemical Unit 1 located on 5th floor or Chemical Unit 2 located on 7th floor)
- Pharmaceutical excipients (tested by Chemical Unit 1 located on 5th floor or Chemical Unit 2 located on 7th floor)
- Pharmaceutical packaging materials,
- Health food
- Cosmetics (tested by Cosmetic Unit, 8th floor).
- Traditional Chinese Medicines (tested by TCM Unit, 6th floor)
- Microbiology testing (tested by the Microbiology laboratory located on the 8th floor)

For purposes of WHO Prequalification, DIDC applied for prequalification of quality control testing for medicines (excluding Traditional Chinese Medicines) and active pharmaceutical ingredients conducted at Chemical Unit 1 (located on the 4th floor) and Chemical Unit 2 (located on the 7th floor) of the Dalian Center for Certification and Food and Drug Control (DCCFDC). Microbiology testing was excluded from the prequalification application.

History

| Type of inspection | Authority | Dates | Outcome |
|---|---|---|---|
| Peer Audit for purposes of WHO Qualification of the Laboratory | WHO Laboratory Network & Services (LNS) Team | 2010<br>2011<br>2012<br>12 - 14 Mar. 2019 | Pre audits in preparation for WHO Prequalification of the Laboratory |
| Laboratory reassessment & Change assessment | China National Accreditation Service for Conformity Assessment (CNAS) | 5 - 6 Dec. 2020 | Accreditation Decision |
| Competence re-assessment for inspection body and laboratory mandatory approval & extension assessment | Liaoning Administration for Market Regulation | 25 - 26 Sep. 2021 | Certificate of Qualification |
| Laboratory reassessment & Extension assessment & Change assessment | China National Accreditation Service for Conformity Assessment (CNAS) | 2 - 4 Dec. 2022 | Accredited Testing Scope, Accreditation Decision |

| **Brief report of inspection activities undertaken – Scope and limitations** | |
|---|---|
| Areas inspected | Organization and management<br>Quality Management System<br>Personnel<br>Training and Safety<br>Documentation and Records<br>Premises and Equipment<br>Validation – Qualification –Calibration of equipment, including computerized systems<br>Laboratory Practices<br>Reference standards – Reagents, including water production |
| Restrictions | The laboratory documentation was in Chinese. Therefore, the interpreters' assistance was necessary to help the inspectors review the records. |
| Out of Scope | Microbiology testing, testing of Food, Cosmetics and Traditional Chinese Medicines (see list of activities) |
| **Abbreviations** | **Meaning** |
| ALCOA | Attributable, legible, contemporaneous, original and accurate |
| API | Active pharmaceutical ingredient |
| CoA | Certificate of analysis |
| 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 |

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|---|---|
| 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 |
| 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 (where applicable)** |
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## 1. Organization and management

The organization and management structure of the Laboratory, including responsibility, authority, and interrelationship of the personnel, were specified in the organizational chart. The total number of staff accounted for at the time of inspection was 89 with an additional 19 contract workers (workers with a contract for 3 years).

The Laboratory was accredited on 06 March 2020 by CNAS (China National Accreditation Service for Conformity Assessment) for ISO/IEC 17025:2017 valid until 05 March 2025 and CMA (Liaoning Qualification of Inspection and Testing Institutions) valid until 4 November 2027.

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. Confidentiality agreement (COI) was available and signed by staff at the time of employment. It was required that the COI be updated if any change in status of staff. As stated in the Quality Manual (11th edition, 2023), the Laboratory had a policy in place to support the confidentiality of information contained in marketing authorizations and test reports i.e.:

- A section on Impartiality Control
- A section on Confidentiality Control
- Impartiality and Confidentiality Pledge.

A quality manager was designated to ensure compliance with the quality management system. The nominated quality manager, also heads the QA Unit, had direct access to the highest level of management at which decisions were taken on laboratory policies or resources. Top management was represented by the Institute Director and Technical Director. The Job description of the QA Manager was verified which required the management of the Quality Manual and its implementation, CAPA, daily supervision of quality matters during testing activities, including the issue, and signing of the CoA's. At present, 11 authorized signatures (authorization was renewed yearly) was delegated to sign the CoA with each authorised signatory representing a specific laboratory section. Authorized signatures included heads of units (pharmacovigilance, Traditional Chinese Medicines, cosmetic unit, chemical drug unit, technical management unit, quality assurance unit and one analyst within the Chemical Drug Unit). Job descriptions were verified.
The following job descriptions were inspected:

- Technical Manager
- Quality Manager

## 2. Quality management system

To ensure quality of test results, DIDC established a quality management system. The quality management system documents included the Quality Manual, Standard Management Procedures, Standard Operating Procedures, Records and Forms. A Quality Manager was responsible for the management system documents.

The first version of Quality Manual was issued in 1990. The recent (Version 11, 2023) was referring to:

- 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).

DIDC adopted a routine surveillance, internal audit, external audit, and management review practice.

DIDC took part in 19 national and international proficiency testing schemes since 2016 in accordance with the SMP on Proficiency Testing and Intra-laboratory Comparison. Annually a list for proficiency testing was defined. The tests covered the following methodologies:

- Assay by liquid chromatography
- Related substances by Liquid Chromatography
- Dissolution
- Assay by complexometric titration
- Disintegration test
- Determination of residual solvent of drugs
- Molecular weight determination of pharmaceutical excipients
- Nitrogen determination

- Potency determination of pepsin
- Determination of refractive index
- Determination of loss on drying
- Clarity of solution of drugs
- Determination of ibuprofen in plasma by HPLC-MS
- Dissolution test of tablets
- Determination of absorption coefficient
- Determination of specific rotation of drug

Amongst the 2023 proficiency testing tests results, one test was "unsatisfactory and one was still waiting feedback. Proficiency testing results were analysed and evaluated. The outcome analysis also contributed as input to the management review. A list of participation in chemical drug proficiency testing during the past three years was provided in the submitted LIF.

The 2024 proficiency testing included:

- EDQM, UV-visible spectrophotometry with the outcome satisfactory preliminary report (-0.1; -0.6)
- WHO, Metronidazole tablets, Dissolution (11.1) and Disintegration (11.2). Results submitted.
- WHO, Metronidazole injection, Assay (11.3), Related Substances (11.4), pH (11.5). Results submitted.

Management Review

A Management review on quality issues was regularly undertaken (at least annually) in accordance with the written documentation in Chapter VIII Management System Requirements Section 9 Management Review Control, which included for discussion:

- Reports on internal and external audits including follow-up actions required to correct the deficiencies.
- The outcome of investigations carried out following complaints received, doubtful (atypical), or aberrant results reported in collaborative trials and/or proficiency tests.
- Corrective actions applied, and preventive measures introduced because of these investigations.

An annual management review plan was prepared listing the agenda points for discussion. One month prior to the meeting an agenda was issued. The latest management review meeting was conducted on 12 January 2024. The attendance list was verified which confirmed attendance of all Unit Managers. The agenda points for discussion included, Change Control (Internal & External), QMS documentations, CAPA's status, Corrective action following previous Management meetings, Update on the Technical System, Quality supervision, Workload, Complaints (internal and complaints related to suppliers), QC and CoA verification and Training (various topics). The 2024 Annual plan was available and verified.

Internal audit

Generally, DIDC performs annually two internal audits as prescribed by the Accreditation Criteria for the Qualification of Inspection and Testing Institutions, CNAS-CL01 (ISO/IEC 17025), GPCL and the Quality Manual requirements, covering elements of the management system. Internal audits were carried out by trained and qualified internal auditors, independent of the audited activity according to Internal Audit and External Audit Control SOP with the Quality Manager leading the audits. Prior to the conduct of the internal audit, a protocol plan for the audit was prepared by the Quality Manager and approved by the Director. Non-compliances identified during the audits were investigated and rectified within the specified time. The head of the internal audit section organized relevant personnel to check and evaluate the effectiveness of the corrective activities performed. The last internal audit review was held 9-12 April 2024 with a completion date of 24 April 2024. The Lead Auditor was the Quality Manager assisted by 3 sub teams each being led by an audit team lead. The 3 teams were led respectively by the Heads of the General office, Head of the Traditional Chinese Medicines unit, and QA Manager. To avoid conflict of interest, the QA manager led the section dealing with instruments, equipment, reagents etc. The head of the Chinese Traditional Medicines led the audit on the QMS. The audit was conducted using a check list.

Change Control

Change control activities were carried out following a SOP. Different types of changes were identified. The Unit Directors/Heads initiated a change investigation. Changes were classified as "General" or "Significant". A change control route form was attached to the SOP. The number of Significant changes in 2023 was recorded as 4. The change control procedure was properly initiated, implemented, and documented. The following CC activities were inspected:

-Change Control related to the integration of 2 document systems for the two chemical drug units (unit 1 and 2) in the new IT system (Empower), initiated on 28 June 2023. The change was recorded as no impact and was completed on 10 July 2023.

-Change Control related to the replacement of the Purified water distribution system initiated on 12 April 2023 and completed on 26 May 2023.

Handling of non-conformances and implementation of CAPA

Non-conformances were handled according to the written procedures for Non-conformance Control and Corrective Action Control (Non-conformities related to audit findings). The cases were categorized as general and serious non-conformances. The Technical Manager or Quality Manager was responsible to manage CAPAs. When the corrective actions were completed, the Quality Assurance Unit organized relevant personnel to validate the results of the corrective actions and confirm the effectiveness. Each unit took the necessary preventive actions for the potential problems according to Preventive Action Control procedure. A CAPA investigation initiated by an internal audit related to a missing label from the GC gas cylinder was discussed. The case was properly investigated and closed on 22/04/24.

Handling of deviation

Deviations was handled according to a written procedure. Deviations were categorized as major, minor and laboratory event. The Technical Manager or Quality Manager was responsible to manage deviations. The 2023 Deviation register was verified. The following deviation investigations were inspected:

An example of a deviation related to the wrongly preparation of a buffer solution: CAPA required training of analyst which was completed on 29/05/2023. The implementation of the corresponding CAPAs was approved on 29 May 2023. The investigated was properly initiated and documented.

Handling of complaints

Complaints were classified as internal and external. The Technical Management Unit was responsible for receiving and peer review of complaints according to the Complaint Control procedure. The investigation was managed by the Quality Assurance Unit with the contribution of the Responsible Deputy Director of the three units Technical, QA Unit or General office if applicable to the complaint. During 2020-2023, there were 9 complaints received and recorded in the complaint registry. During 2024 until the date of the inspection, no complaints were received.

The investigation records of the following complaints were discussed and available.

-A complaint related to testing of TCM and outcome of testing results of 2 ingredients. The outcome of the complaint confirmed the results as per the previous test report.

-A complaint related to the testing of a chemical product and assay results obtained. The outcome of the complaint confirmed the results as per the previous test report.

## 3. Control of documentation

The documentation system was managed by the Quality Manager in the Electronic File Management System. The approval of the documents was allocated as follows:

- Quality Manual and SMPs: Top management
- SOPs and technical records: Technical Managers
- Quality records: Quality Manager.

Concerned staff was trained on the procedures and instructions. The training records were captured in the File Management System. The general test methods of the Chinese Pharmacopoeia were captured in SOPs with the details of the test procedures and the limits for parallel test deviations.

Specifications published by CPC and NMPA were controlled and distributed to the relevant units by the Quality Assurance Unit. The specification administrator was responsible to upload the specifications to the LIMS. The general provisions on the documentation system were captured in the Quality Manual:

- Chapter VIII Management System Requirements Section 2 Documentation of Management System
- Chapter VIII Management System Requirements Section 3 Document Control.

The Standard Management Procedures covered:

- SMP of Documents Writing,
- SMP of ELN
- SMP of Electronic Files and Archiving
- SMP for archiving
- SMP of Change Control

## 4. Records

Records were kept electronically or in paper based for permanent, 10 years or 30 years archive time, depending on the nature of the document. Every analyst was equipped with a personal tablet (PDA) for data recording and document review purposes. As such, analytical tests were recorded in the electronic laboratory notebooks (ELN) using predefined forms (SMP for ELN writing). The activities were timely recorded. The records were completed containing the relevant data, information, and recordings, e.g., chromatograms and spectra.
The electronic records generated in the LIMS were backed up regularly. The IT Administrator copied the PDF files of the records from the server to a CD and passed it to an archivist for archiving the information every six months.
The quality management records available in hard copies included:

- reports from internal (and external if performed) audits and management reviews
- complaint investigations
- corrective and preventive actions
- investigation of deviations

The history of a randomly selected sample was checked (receipt log, storage conditions, tests, instruments and standards used, results, reporting, and archive) to verify the records' accuracy.
See section 17 (Testing).

Archiving
The archiving unit was located on the 6$^{th}$ floor of the building. Access to the archive was restricted to authorized personnel, as per the written procedure.
Archive management addressed archiving of documentations and the identification of different types of documents that required archiving. The decision to archive documents for long term or short term was made by the respective units. The following archiving periods were identified:

- Pharmaceutical product on the market - shelf-life plus one year.
- Investigational products and all documents addressing sample testing - 15 years.
- Documents related to testing of drugs (domestic and imported) - 6 years.

The starting time for archiving was recorded as the date the documents were received by the “General office for archiving”.
Electronic records generated in the LIMS were backed up regularly. The IT Administrator copied every six months the PDF files of the original records from the server to a CD and passed them to archivist for archiving. CD’s were archived in an access controlled magnetic cupboard. A hand over report was completed on acceptance of documents / CDs at the archive unit. An archive number was allocated to each document for purposes of traceability. The traceability of CoA, for a specific batch number in one of the Archive locations was inspected and found compliant.

**5. Data processing equipment**

An inventory of computerized systems was available (with information about unique identification, purpose, validation status, physical or storage (drive and files path), software and related documentation location, and responsible or contact person). The critical computerized systems used by DIDC included:

- Laboratory Information Management System/LIMS (Version 10, STARLIMS Company, USA),
- Waters Online Chromatographic System (Empower 3),
- Shimadzu Online Chromatographic System (LabSolutions),
- Office Application System (OA),
- Reagent Management System,
- File Management System
- iPAD software.

The LIMS of DIDC controlled the processes of acceptance, test, data collection and experimental data calculation, proofreading, deviation control, review, signing & issuing and certificate of analysis printing. The system was connected with all testing instruments with data output function. Use of instruments, reference substances, columns, were recorded in the LIMS. Each software user had a unique ID and password. Users of different duties had different privileges. The validation policy of the computerized systems was detailed in SMP for validation.

The validation of LIMS was performed by the software development company while the re-validation of the system and the ELN templates were completed by the DIDC IT staff.
The laboratory equipment was controlled (including data acquisition and management) by the following networking systems:

- Empower 3 software (Waters Online Chromatographic System) for LC Waters HPLCs and some GCs.
- LabSolutions software (Shimadzu Online Chromatographic System) for Shimadzu and Agilent spectrophotometers, and chromatographs.

Both Empower 3 and LabSolutions software had the appropriate user management system including user groups as reviewers and IT administrators. Critical functions such as data modification and deletion were restricted. An Office Application System (OA) was a commercial software in use for daily office work.
A Reagent Management System was used for the management of reagent, including preparation, inventory, usage of test solutions and reagents.
A File Management System was managing the file elaboration, review, approval, issue, search, revision, and invalidation, while the iPAD software was managing SOP access and on-site data entry.

All the systems had the permanent audit trail function enabled. The procedure for reviewing of audit trails of each applicable computerized system was sufficiently established.

The qualification and validation of the following computerized systems were reviewed to verify that the system was appropriately validated or verified as being suitable for use. During the validation of computerized systems, the frequency, roles, and responsibilities regarding reviewing original records (including audit trails) were established based on a documented and justified risk assessment.

- System name: Laboratory Information Management System/LIMS (Version 10, STARLIMS Company, USA)
- Qualification/Validation approval date: 23/12/19 (revalidation by the laboratory staff).

Procedures were established and implemented to protect the integrity of data. The relevant SOPs included the measures to ensure the integrity and confidentiality of data entry or collection and data storage, transmission, and processing. Electronic data were protected from unauthorized access, and an audit trail of any amendments was maintained. Electronic data was backed up at appropriate regular intervals according to a documented procedure.
LIMS data were saved in CDs every six months and archived by IT Administrator and archived by the General office -See section on Archiving.

Electronic data generated by stand-alone workstation were stored according to the prescribed path.
All the data files generated in the experiment process are backed up in real-time and the terminal time synchronization was realized. The LIMS server and database was fully backed-up on the 8th day of every month, with an incremental backup on Monday and Thursday. All the files were backed up to the all-in-one backup machine. The server for the Empower system automatically did an incremental backup every Monday to Friday at 00:00 and a full data backup every Sunday at 00:00. The LabSolutions system server automatically did a full data backup every day at 12:30. The stand-alone workstation performed warm backup each hour automatically with the data uploaded to the server in the boot state.

## 6. Personnel

The Director of the Institute was responsible for the overall work of DIDL. The Technical Manager and Quality Manager were appointed by the Director. The Technical Manager with the technical management group were responsible for technical work while the Quality Manager was responsible for the management of the quality functions. The organizations, positions and the reporting line was captured in the Organizational chart.

The laboratory had sufficient personnel with the necessary education, training, technical knowledge, and experience for their assigned functions. Staff undergoing training were assessed on completion of the training. Ongoing training including refresher training and on-the-job training was provided. A staff training matrix was available.

The Laboratory maintained current job descriptions for all personnel involved in tests and/or calibrations, validations, and verifications. The laboratory also maintained records of all technical personnel, describing their qualifications, training, and experience. Training in good data and record management in evaluating configuration settings and reviewing electronic data and metadata, such as audit trails for individual computerized systems used in generating, processing, and reporting data was performed.

19 Contract workers with 3 years contract were employed to perform some of the following functions: analysis, calibration/daily calibration, reference material management.

The following training records were inspected:

- Training records of an Analyst, to verify training on format and issue of CoA.
- Training records of an Analyst for the competency. The training matrix was available confirming competency in GC, HPLC, UV, Water content testing, IR, mass spectrophotometry.
- Training records of a sampler. Training included information on the 2024 DIDC testing programme, 1 April 2024 (1h) as per training log of the sampling unit. Training on sampling techniques.
- Training records of Reference material management (Contract worker) was verified. Training included eye drop volume verification, validation, water quality, management of reference material.

Consultants were not used for routine work. Consultants were only appointed for purposes of presenting training. Competency was verified through checking credentials. No formal procedure on the appointment of consultants was available.

## 7. Premises

DIDC and DCCFDC were located in the same building.
DIDC laboratory area was 4766 square meters with 2734 square meters of office and auxiliary rooms. The laboratory facilities were of suitable size and design to suit the functions and to perform the operations to be conducted.

- 4th floor - Management unit
- 5th floor - Chemical Drug Unit 1
- 7th floor - Chemical Drug Unit 2

The building construction was reinforced concrete and brick. Color steel plate partitions were adopted in interior decoration. Ventilation system was divided into two parts, the first part was for the microbiological laboratory and the second part was the laboratory area, equipped with five sets of exhaust system. Each system consisted of an exhaust blower, inverter, fume hood, storage with exhaust, universal exhaust hood, and metal exhaust hood. Rooms were equipped with continuous monitoring system. The centralised temperature and humidity requirements were defined as between 10-30ºC, and 40-75% RH. Commercialised cooling systems (additional air conditioner and dehumidifier) were used in certain area such as the balance room number 524. Separate storage facilities were maintained for the secure storage of samples, retained samples, reagents, laboratory accessories, and reference substances, if necessary, under refrigeration (2-8°C) and frozen (-20°C). The environmental conditions of these rooms were monitored and controlled.

An alarm system was connected using a mobile application for alerting staff on temperature outage. The environmental qualification (temperature) for the laboratory was verified. Annually, a temperature validation plan was prepared. The 2024 Validation report, related to the retention sample area and reference material area were verified. The mapping study on the retention sample store was inspected. The study was conducted over 48h using 14 probes for temperature and 7 probes for RH.

Worst case/hottest spot was identified with one probe was used for continuous monitoring. Ongoing temperature / humidity monitoring in the pH recording area 5th floor using an electronic monitoring device was verified. The device was calibrated annually (last calibration date 24/04/ 2024 expiry date: 23/04/25) by the *Liaoning Institute of Measurement*s. Calibration was conducted at 20°C and 40%RH against the national standard, JJF 1076-2020.

It was noted that a restroom for staff was located on each floor of the building within the laboratory section and only separated by the corridor. In terms of good laboratory practices this is not advisable.

See advisory note in Part 3 below.

All toxic/hazardous reagents used in DIDC were managed in accordance with the unified procedure as prescribed by the government. Fire extinguishers were in place for security purposes under the supervision of specified personnel. Storage of chemicals was managed by dedicated personnel, and special access accounts were set up.

Retention samples were stored in Room 422 located on the 4th floor under 10-20°C, RH 35-75% conditions, and managed by the Technical Management Unit. Apart from the ambient temperature area, there were refrigerators and freezers in place to store samples with special storage requirements. The retention periods were:

- for import samples with known expiry date: until the expiry date,
- for import samples with unknown expiry date: three years,
- samples of claims or returns: until the end of the case,
- domestic drug samples: two years,

To prevent electricity outages, appropriately sized UPS banks were located on each of the floors, (5th-8th floors). These were connected to equipment and instruments (HPLC) to ensure continuous running of the system.

## 8. Equipment, instruments, and other devices

DIDC was equipped with the appropriate type and number of instrumentation, including chromatography (HPLC, GC, ion chromatography), spectrophotometry (Infrared spectrophotometer, Ultraviolet/visible spectrophotometer, fluorescence spectrophotometer, AAS, ICP-OES), mass spectrometry (HPLC-MS, GC-MS and ICP-MS).

Other types of equipment included dissolution test equipment, pH meter, analytical balance, X-ray diffractometer, potentiometric titrator, thermal analyzer, automatic polarimeter and electrophoretic analyzer. All the equipment had a unique identifier indicated on the device and indicated in the corresponding LIMS registry.
The purchase, acceptance, qualification, operation, intermediate check, maintenance of instruments and equipment were implemented according to the SOP on Instrument and Equipment Control.

The regular preventive maintenance and the repair of the equipment (including HPLC, HPLC-MS, GC and GC-M) was contracted out for service providers. Maintenance and service records were archived in the equipment file. A series of SOPs covered the instrument operation records, maintenance and performance qualification. Cleaning of instruments and equipment was performed by laboratory staff. Each instrument had an analyst assigned to take responsibility of cleaning and regular maintenance.

Cleaning of the glassware was carried out in accordance with SMP of Glassware Cleaning, A-ZZ-2023-021 which provided for cleaning of new glassware and used glassware. Used glassware required washing with a detergent and tap water and rinsing done with purified water. Drying of glassware was performed using an oven at 105ºC for 60min. Volumetric glassware was recalibrated (every 3 years).

## 9. Contracts

The Laboratory had a procedure in place for the selection and purchasing of services and supplies, external provided products and services. The general office was responsible for handling contracts. DIDC had no subcontracting of test in the last three years. It was the intention that test items of WHO prequalification would not be contracted out. Contracts signed, defined the contracted work and established duties and responsibilities of each party. The competence of the contracted organizations was periodically assessed, and records of these assessments were kept.

The Dalian Municipality provided an annual plan to the laboratory for purposes of regulatory testing. All sample testing were compensated by the Dalian Municipality. The annual test plan was based on the Provincial annual testing plan which was based on the NMPA annual testing plan. The 2024 annual plan issued by the Dalian Municipality on 29/03/2024 was available for verification and required testing of 400 samples. There was a SOP that dealt with testing on behalf of the Dalian Municipality as and allowed for 400 batches of product to be tested. Products on the 2024 annual testing plan included Essential Drugs, Cardiovascular products, Covid treatment products and Traditional Chinese Medicines. Samples for testing for marketing release were tested within 30 days. DIDC did not have a contract with the Dalian Municipality.

Contract testing performed for manufacturers (approximately 20 manufacturers within the municipality borders of Dalian) was supported by a contract between DIDC and the applicable manufacturer. Contracts with manufacturers for purposes of post marketing testing required the need to submit samples to allow for at least 3 complete tests (no routine testing was conducted for manufacturers). If test specifications were against the Ch Pharmacopeia standards, no specifications required to be submitted. Contracts are renewed annually. As per legislation it was required that DIDC performed all animal testing. The following contract was verified:

-Between DIDC and the manufacturer, CSPS. The contract was signed on 05 Jan 2024. Contract consisted of 2 pages with annex which identified product names, test name and specifications. Subcontracting was addressed. Samples were retained by the laboratory. It was noted that contracts were not signed /dated on each page to ensure authenticity.

In the event of proficiency testing, contracts were signed between DIDC and the corresponding organizer.

Suppliers

The General Office was responsible to apply for supplier evaluation performed by Science and Technology Committee. Prior to adding a supplier to the Approved Supplier list, the supplier was evaluated informally based on the following criteria.

- Evidence of quality
- Accreditation / Manufacturer license
- Price
- Sustainability of supply
- Timelines on delivery
- Post marketing support.
- Scoresheet: more than 30 qualified

Contracts with suppliers were available.

The assessment of *Dalian Chemical Engineering;* the supplier of chemical reagents was verified. An informal evaluation on the competency of the supplier was conducted telephonically. The result of this verbal evaluation was discussed by a scientific committee prior to the supplier approval / rejection. No record on the evaluation of the supplier was available.

## 10. Reagents

Suppliers of critical consumables, supplies, and services that affected testing quality were evaluated. Records of these evaluations and lists of approved suppliers were maintained to document their suitable quality concerning the requirements of the laboratory.

Most of chemical reagents and other materials were purchased from the supplier who has been awarded the tender by the government. DIDC participates in the URS formulation before inviting bids. Each unit was required to apply for procurement as per work needs. Following approval of the application by the Institute Director, the General Office implemented the procurement procedure. Packed Products were purchased directly, while other products were purchased after price comparison according to the bid procurement process. The purchaser was responsible to check the package, appearance, labels, quantity and certificates or other documents.

Reagents were kept on the 5$^{th}$ floor with the area temperature controlled. The reagents used were of appropriate quality and correctly labelled. Labels of reagent contained the content, manufacturer, date received and date of opening of the container, concentration if applicable, storage conditions, expiry date, and retest date, and was controlled in the Reagent Management System which was linked to LIMS. Each reagent was allocated a reagent identification number on receival. Expired reagents were removed every 3 weeks.

The Material Safety Data Sheets (MSDS) of chemicals and reagents were handled as separate documents as per the written procedure. MSDS were received as a hard copy and bound in a folder which was accessible to the laboratory analysts. The possibility to upload the MSDS to the iPAD software / LIMS was discussed.

Purified water (Purified Water monograph in Chinese Pharmacopoeia) and ultrapure water (requirements of Grade I Water in Water for Analytical Laboratory Use-Specification and Test Methods GB/T 6682) were used in the laboratory. The water quality was regularly verified to ensure that the various grades of water met the appropriate specifications.

Purified water was produced by a water system consisting of a preparation system (8th floor) and distribution system. Tap water was used as water source, which was first processed through silica sand, activated carbon and water softener, precision filter, double reverse osmosis and electro-deionization (EDI) to obtain purified water. A Distribution system distributed purified water to the laboratory water points on the 5th to 8th floors, circulating 24 hours per day. The Purified water system was equipped with an automatic alarm. Conductivity was monitored every day, TOC every second week, and microbial limits monthly. Full analysis was performed every second month, which included description, acidity or alkalinity, nitrate, nitrite, ammonia, conductivity, total organic carbon, non-volatile substances, heavy metals, and the microbial limit. The laboratory was equipped with an ultrapure water generation system for use by AAS, HPLC and GC .

Reagent solutions were prepared in accordance with published pharmacopeial or other standards where available. Records were kept of the preparation and standardization of volumetric solutions.
Volumetric solutions prepared in the laboratory were labelled by the name, molarity, date of preparation, date of standardization and initials of technician, and included the standardization factor.

**11. Reference substances and reference materials**

Reference substances ware recorded in the LIMS upon receipt in the Laboratory and stored in Room 528 according to the storage requirement: ambient temperature, 8-15ºC, or 2-8ºC.

The supplier CoA, usage and stock records of *Doxycycline hyclate* active substance reference material, was verified and found to be accurate and recorded in LIMS.
The Location was identified, storage condition: 2-8ºC, certificate/batch validity statement of compendial reference substances: complied, with assigned content: 83,6%,

The respective identification number was quoted on the analytical worksheets whenever the reference substance was used. The batch validity statement was attached to the worksheet when pharmacopeial standards were used.

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

The purchase of equipment was dependent on the DQ according to work requirement. On arrival, laboratory staff performed an open-package inspection together with the supplier. Qualified instrument can be applied for using only once an instrument SOP was prepared and the successful IQ, OQ and PQ was approved by the Technical Manager.

Eleven key instruments were identified for PQ and which were supported with relevant SOPs. The engineer of the supplier issued IQ, OQ and PQ reports. The laboratory staff was required to confirm the reports and include in the instrument/equipment dossiers. Verification, calibration and PQ of the equipment was performed according to the annual plan.

Each instrument was uniquely identified. Labels indicated the status of the calibration by red, yellow, or green labels and included the date when recalibration was due.

The usage data generated during the analytical testing were available in LIMS which served as an instrument logbook.

The qualification documentation of the following equipment was discussed.

- UV-VIS spectrophotometer
- Initial qualification date: 25/04/2019
- Qualification frequency: annual, the last qualification date was: 25/04/2024
- PM was performed upon usage following the maintenance plan.
- Instrument SOPs for PQ and for operation
- HPLC with DAD, ELSD, RID, FLD
- Initial qualification date: 17/04/2018
- Qualification frequency: annual, the last qualification date was: 22/09/2023
- PM was performed upon usage
- Instrument SOPs for operation with PM.

Balances were daily checked using internal calibration and suitable standard weights. Requalification was performed annually using certified reference weights.

- Analytical balance
- Initial qualification date: 11/07/2014
- Calibration covered daily internal calibration and daily verification with calibrated weights
- Calibration frequency: annual, the last qualification date was: 15/08/23
- Instrument SOPs for operation with PM.

Equipment Records/logbooks were kept in LIMS identifying the device and current location together with information on the use of the instruments. It was noted that information on maintenance, history of damage, malfunction, modification, or repair was not recorded.

## 13. Traceability

Test results were traceable, and when appropriate to primary reference substances. All calibrations or qualifications of instruments were traceable to certified reference materials and SI units (metrological traceability). The traceability of the sample was available from receipt, throughout the stages of testing, to the completion of the analytical test report.

## 14. Incoming samples

Quality testing of samples was conducted either on behalf of a Contract Giver (Manufacturer), the DCCFDC (Dalian Administration for Market Regulation (DAMR) or the Dalian Municipality. Many tests were paid for by the Dalian Municipality. If testing was conducted on behalf of a manufacturer/contract giver, a contract was signed annually. Approximately 20 manufacturers were established within the geographic area of the Dalian Municipality. The written procedure dealt with testing of samples on behalf of the Dalian Municipality which provided for 400 batches of product to be tested.

Testing was conducted for purposes of contract testing, post marketing testing or animal testing. Testing of samples for marketing release was completed within 30 days.

Samples were received on the 4th floor at the sampling receiving area. The acceptance and distribution of samples was managed in the laboratory information management systems (LIMS). The laboratory was responsible for the sampling of materials/products. A sampling plan and internal procedures for sampling were available. The sampling was carried out to avoid contamination and other adverse effects on quality. The Sampling Unit was responsible to prepare the annual sampling protocol supporting the annual plan of drug surveillance test by the Dalian Administration for Market Regulation according to the SMP of Drug and Health Food Sampling. The sample quantity was sufficient for at least two complete set of tests.

At receiving, the Contract Reviewer was responsible to receive and check the samples. The sample received was visually inspected by the sample custodian to ensure that the labelling conformed with the information contained in the test request. The findings were recorded, dated, and signed. If discrepancies were found or the sample was damaged, the information was recorded on the test request form. Any queries were referred to the provider of the sample. After receiving the samples, the Contract Reviewer put a label on the samples with a unique sample ID and distributed to laboratories according to the test types.

A registry was available to keep records on all incoming samples and accompanying documents and record the information from receiving, distributing, and supervising the consignment of the samples to the specific units. The procedures for handling of samples from their receipt to completion of testing were performed according to the SOPs for Sample Handling Control and Test Work Control. The Contract Reviewer transferred the first part of the sample to the laboratory and kept the rest as retained in the retained sample storage area under appropriate environmental conditions.

A test request accompanied each sample submitted to the laboratory which contained the following information:

- description of the sample,
- specification to be used for testing,
- required storage conditions.

The laboratory reviewed the test requests to ensure that it has the resources to meet them and that the selected tests/methods meet the customers' requirements.

All delivered samples and accompanying documents were assigned a registration number. An (electronic) register was kept in which the following information was recorded:

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

The laboratory staff performed a visual inspection of samples to ensure that the labelling conformed with the information on the test request. All tests were performed after receipt of the test request.

The different laboratories were equipped with cabinets allocated to each laboratory analyst for samples storage awaiting testing.

The SOP on Sampling required the collection of enough sample for 2 full tests. A sample was divided in 3 portions of which:

- Portion 1 was used for full testing (immediate testing).
- Portion 2 used for confirmation testing (repeated test if required) (50% required for full testing)
- Portion 3 used for retention in case of a dispute (50% required for full testing).

For purposes of verifying the laboratory testing procedures, a sample was selected randomly and the life cycle of the sample tracked. The sample lifecycle verification was found acceptable.

The sample received could be issued to either Chemical Drug Unit 1 or Unit 2. As per the information available, the sample was issued to Chemical Unit 1. Testing specifications were identified from LIMS. Eash test result was recorded using the Electronic Laboratory Notebook (ELN) with each ELN allocated a unique ID. The status of the sample as under testing, awaiting testing or testing completed were identified on the LIMS system.

It was noted that no clear guidance on the responsibilities for sample testing between Unit 1 and Unit 2 was available.

**15. Analytical worksheet**

Electronic laboratory notebooks (ELN) were elaborated and available in LIMS, validated by Quality Assurance Unit and issued by Technical Manager. Analyst should choose and use the test item specific ELN from the LIMS.

The analysts recorded information about samples, test procedures, calculations, and results in the analytical worksheets together with all raw data. Analytical worksheets from different units related to the same sample were assembled.

The ELN 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).

All values obtained from each test, including blank results, were entered on the analytical worksheet, and all graphical data, whether obtained from recording instruments or plotted by hand, were attached or traceable to the electronic record file or document where the data was available. The completed analytical worksheets were signed by the responsible analyst and verified by a proof-reader (2nd analyst), approved, and signed electronically by the supervisor.

The specification necessary to assess the sample was defined in the test request or master production instructions (as applicable). If no precise instruction was given in the test request, the specification in the officially recognized national pharmacopeia (Ch Pharmacopeia) might be used or, failing this, the manufacturer's officially approved or other nationally recognized documentation was used. It was noted that no reference was made to the inclusion of WHO specifications / International Pharmacopeia.

**16. Validation of analytical procedures**

Analytical test method validation, verification or transfer was carried out in accordance with SMP of Test Method Validation, Transfer and Verification and Method selection, verification and control. Test methods used by DIDC usually belonged to the Chinese Pharmacopoeia but were verified before the first use. The LIMS impeded distribution of the samples without properly implemented specification/test methods.

Accordingly, method validation happened when the testing was required against a specification never used by the Laboratory. The validation was initiated by the analyst considering the parameters defined in the SOP, such as: accuracy, precision, specificity, LOD, LOQ, linearity, range and robustness which was in-line with the Chinese Pharmacopoeia 2020 volume IV General Requirements 9101 "Guideline for Validation of Analytical Method".
In case of import drug registration test, analytical test method validated by the manufacturer was transferred. No laboratory-developed methods were used.

The procedures employed for testing were suitable for the intended use, as demonstrated by the validation or verification of the appropriate method.

Validation/Verification was performed according to a protocol, including analytical performance characteristics to be verified for various analytical procedures. Characteristics to be considered for validation/verification/method transfer were defined.

Appropriate system suitability tests were conducted to verify pharmacopeial methods and/or validated analytical procedures prior to the performance of the analytical tests.

**17. Testing**

The samples were tested in accordance with the work plan of the laboratory after completion of the preliminary procedures.

Guidance on official pharmacopeial requirements was usually given in the pharmacopeia's general notices and specific monographs. However, the respective test procedures were described in detail and provided sufficient information in the individual protocol to allow appropriately trained analysts to perform the analysis reliably.

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 the Record Control SOP. The test records and reporting of the test results of the randomly selected samples was checked (receipt log, storage conditions, tests, instruments and standards used, results, reporting, and archive) to verify the records' accuracy.

**18. Evaluation of test results and OOS investigation**

An SOP (SMP of OOS Result of Test) was in place describing the conduct of studies of OOS test results. When a doubtful or suspected OOS result was identified, the supervisor and the analyst reviewed the procedures applied during the testing process.

The records of the randomly selected sample 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,

The process of invalidation of OOS was also inspected. Doubtful results were only accepted if an error could be identified.

If the investigation was inconclusive, the SOP gave clear 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 first one.

**19. Certificate of analysis**

The CoAs were generated in the LIMS upon unified form and according to SOP Certificate of Analysis Control. A Workflow diagram on the issue of the CoA was available.

After completing the test, the analyst prepared the draft CoA containing at least the following information:

- the results of the tests performed with the prescribed limits
- a conclusion as to whether the sample was within the limits of the specification
- date on which the tests were completed
- date on which the sample was received
- Batch number
- quantity of sample and
- expiry date.

The certificate of analysis was reviewed by the proofreader (2nd analyst), Unit Director and Technical Management Unit then released by an Authorized Signatory. A sealed hard copy was issued to the client. Any revision or modification to the original electronic records could be traced including the information of contents, users, and dates. The retention period of the CoAs was at least 6 years. In case the CoA need to be corrected or modified, it was managed in a controlled way. The revised certificate number would bear an additional letter “g” after the original CoA number.

Examples of certificates of analyses were verified.

**20. Retained samples**

Samples were retained as required by the legislation or by the originator of the request for analysis. The amount of retained sample allowed for one re-analysis. The retained sample was kept in its final pack.

**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 and 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 fully labelled and included prominent warnings (e.g., "poison", "flammable") whenever appropriate. 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.

| **Miscellaneous** | |
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| ***Assessment of the Laboratory Information File*** | The content was reviewed and accepted. |

| **Part 3** | **Conclusion – Inspection outcome** |
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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, ***Dalian Institute for Drug Control (DIDC),*** located at ***No 888A, Huanghe Road, Shahekou District, Dalian City, Liaoning, 116021, R.P. 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 manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

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

| Part 4 | List of 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 8
    ***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
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