World Health Organization

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

Part 1	**General information**		
Laboratory Details			
Name of the laboratory	Commission of Analytical Control and Coverage Extension (CCAYAC) Quality Control Laboratory		
Address of inspected laboratory	Calzada de Tlalpan No. 4492 Colonia Toriello Guerra Demarcación Territorial Tlalpan. C.P. 14050. Ciudad de México Mexico Phone (5255) 5080-5200 ext. 12000 and 12043 Email ccayac@cofepris.gob.mx		
Dates of inspection	14 – 17 November 2022		
Type of inspection	Routine inspection		
Introduction			
Brief description of testing activities	*Type of analysis*	*Finished products*	*Active pharmaceutical ingredients*
	Physical/ Chemical analysis	pH, water content (Karl Fischer), loss on drying, dissolution, uniformity of dosage units (mass, content), disintegration, Friability	pH, water content, loss on drying
	Identification	HPLC (UV-VIS, DAD, fluorescence, detection), TLC, UV-VIS spectrophotometry, FTIR	HPLC (UV-VIS, DAD, fluorescence, detection), TLC, UV-VIS spectrophotometry, FTIR
	Assay, impurities and related substances	HPLC (UV-Vis, DAD fluorescence detection), TLC, UV-VIS spectrophotometry, FTIR, volumetric titrations	HPLC (UV-Vis, DAD fluorescence detection), TLC, UV-VIS spectrophotometry, volumetric titrations
	Micro-biological tests	Sterility test, Total Microbial Counts, test for specified microorganisms,	Sterility test, Total microbial Counts, test for specified

		bacterial endotoxins test (LAL), microbial assay of antibiotics	microorganisms, bacterial endotoxins test (LAL), microbial assay of antibiotics
General information	As the National Reference Laboratory, the CCAYAC was part of the Federal Commission for the Protection Against Sanitary Risks (COFEPRIS by its acronym in Spanish). The Laboratory's fundamental task was to carry out laboratory analyses of products for human use and consumption subject to sanitary control, such as vaccines, medicines, medical devices, food, beverages, and children's toys, to name a few. The Laboratory issued results reports that support the decisions of the rest of the Institution's Administrative Units, as well as coordinate the expansion of coverage through a network of auxiliary regulatory laboratories sanitary. It was an entity with legal responsibility. In 1929, the Central Analysis Laboratory was established in the Liège building, which later became the Ministry of Health headquarters. In 1956, the Directorate of Institutes and Laboratories was formed, bringing together five administrative units, including the Central Analysis Laboratory. It was renamed the National Health Laboratory and began operating in its current facilities. In 1976, it was renamed the National Public Health Laboratory. Initially, the Laboratory focused on analysing food and antibiotics. Over time, it expanded its areas of analysis to include medicines, narcotics, other toxic substances, beauty products, and biological product control. It also engaged in laboratory animal production. Due to changes in regulations, such as the repeal of the Sanitary Code of the United Mexican States in 1984 and the introduction of new import procedures in 1991, the National Public Health Laboratory became part of the Undersecretariat for Health Regulation and Development. This allowed it to address various aspects of health regulation authorized by the Ministry of Health. The Ministry of Health, to protect the health of the population against sanitary risks, created, by presidential decree, on July 5, 2001, the COFEPRIS, a decentralized body of the Ministry of Health with administrative, technical, and operational autonomy. The National Laboratory of Public Health was integrated as one of its organizational units. On April 13, 2004, the COFEPRIS regulations were published in the Official Gazette of the Federation, the purpose of which was to establish the organization, operation, and scope of competence of the Commission as an administrative body and in which the Laboratory National		

	Public Health changed its name, thus creating the Commission for Analytical Control and Extension of Coverage (CCAYAC).
History	The Laboratory underwent an inspection by the WHO in April 2013 and received a qualification on November 13, 2013. In addition, the Laboratory was audited by various Mexican accreditation bodies as per the list provided in the LIF.
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 Laboratory Practices Reference standards – Reagents - Water
Restrictions	The Laboratory documentation and personnel primarily used Spanish, as it is the official language of Mexico. Additionally, the inspection team had the support of two official interpreters, provided by CCAYAC, to facilitate communication during the inspection.
Out of Scope	Atomic Absorption Spectrophotometer (AAS) testing was excluded from the scope since the laboratory did not perform any respective test.
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
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

1. Organization and management

A presentation was provided explaining the activities of the organization in detail.

A Mexican accreditation body had certified the Laboratory in accordance with ISO 17025:2017. The certification was extended on 20 Oct 2022

The organization and management structure of the Laboratory, including responsibility, authority, and interrelationship of the personnel, were specified in the organizational chart implemented in the LIF. The chart was authorized on 3 Mar 2021. The total number of staff accounted for 68 at the time of inspection. The Laboratory was headed by the Commissioner for Analytical Control and Expansion of Coverage (CCAYAC), and the Executive Director of Analytical Control. The Laboratory was comprised of various departments. The following departments were in the scope of this inspection:

- Management of analysis and development of immune and biochemical tests
- Management of analysis and development of physicochemical and toxicological tests
- Department of analysis and development of microbiological tests
- Quality Management – under the Direction for innovation which was independent form the analytical laboratory. The department was responsible for the quality management system of the Laboratory, as well as internal audits.
- System maintenance management

The CCAYAC provided its services with total impartiality, objectivity, transparency, and confidentiality, adhering to strict compliance with current national and international regulations. All personnel were required to conduct themselves with ethics, responsibility, honesty, professionalism, impartiality, and confidentiality in the development of their activities and at all times. Senior Management made a commitment to ensure that the Impartiality and Confidentiality Policy was properly documented, widely known, thoroughly understood, effectively implemented, and consistently maintained by all CCAYAC personnel. Furthermore, they ensured that the policy was communicated to stakeholders for their awareness.

The deficiency in relation to Organization and management was addressed in the respective CAPA plan. The response was found to be satisfactory.

2. Quality management system

A quality manual defining the quality management system was available.

The QMS documentation was described through documental pyramid:
- Manuals
- Plans and programs
- Procedures, methods, catalogues & criteria
- Equipment and work instructions
- Registers

CCAYAC had the policy to participate in international proficiency testing schemes, collaborative studies, and/or inter-laboratory testing, carry out an annual performance evaluation of the methodologies, and participate in the External Quality Control Program organized by WHO/PAHO. The list of proficiency testing from 2014 to 2022 was available. The results since 2018 were all recorded as satisfactory. The documentation was randomly selected and reviewed.

Management review

The Management review was performed in accordance with SOP for the review of the QMS by the management.

The documentation for the most recent MR, dated 31 Mar 2022, including agenda, participant list and the respective report was reviewed and discussed. The output of the Management review was implemented in accordance with SOP for Actions for the improvement.

Internal audits & handling of Nonconformities

CCAYAC had policies and procedures to perform internal and external audits, implement corrective and preventive actions and attention of complaints in accordance with SOP for Audits.

The audit plan for 2022, the internal audit report for the analytical laboratory, and the registration and handling of the respective NCs were reviewed and discussed.

The laboratory used the SOP for Attending non-conformities, trial work/nonconforming output, and corrective actions for handling non-conformities, also those raised during audits.

The non-conformities were logged in an Excel sheet with a specific ID number, information about the audit, description, actions, status, deadline, etc. All the non-conformities related to 2021 were closed, and those related to 2022 were closed within the deadline. Only those with a deadline of December 2022 were still pending. The Excel lists were organized by year and reviewed by the responsible staff to ensure the completion of the implementation of the corrective actions.

Complaints
When the customer was unsatisfied with the Laboratory's results, the complaint was handled following the SOP for responding to complaints and recommendations and the SOP for Conducting verification tests.

The Laboratory had not received any complaints since 2013.

Change control:
The change control was described in the QM and a form was used to record any change control request.

Risk Management:
The Laboratory had an SOP for Managing risks and opportunities.

The deficiencies related to the QMS were addressed in the corresponding CAPA plan.

3. Control of documentation

The Laboratory had established and maintained a system of procedures to control all documents concerning preparation, revision, distribution, return, and archiving. A master list identifying the current version status and distribution of documents was available. Each controlled document had a unique identifier, version number, date of implementation, and reference to the previous version. The documents were released by the Department for Quality Management, available to all staff through the internet, and managed by Control of the Quality Management System, using a software system.

An SOP was established to include the authorization process for copying and the proper identification of copies derived from official and controlled documents. Relevant staff was trained on new and revised SOPs; the personnel acknowledged by signature that they were aware of applicable changes.

4. Records

Records were made of analytical tests, including calculation and derived data, method verifications, instrument use, calibrations and maintenance, and sample receipt in template forms. The records were complete and signed, alterations were commented on, and references were made to appendices containing the relevant recordings, e.g., chromatograms and spectra. The specifications used were consistent with the information currently held in the dossier. Access to the archive was restricted to authorized personnel.

The Laboratory controlled all documents required by the QMS in accordance with SOP for creating or updating, disseminating, issuing, and managing the Quality Control System documents. The SOP established the guidelines to review, authorize and edit the documents, as well as to allow identifying changes needed. The documents were legible, identifiable, and available at through a designated software system to prevent the inadvertent use of obsolete documents.

All documents were kept for two years in the archive facility, 2-3 more years in CCAYAC´s concentration archives, and then they were sent to the historical archive of the Health Department, according to the SOP for Record control and the SOP for File handling. The applicable SOP managed the request and retrieval of documentation from the archive facility. The process was reviewed and discussed.

The deficiencies related to the Records were addressed in the corresponding CAPA plan.

5. Data processing equipment

An inventory of all computerised systems was available with information about determination, software name, version, software ID, the associated equipment, the location and administrator.

The SOP for Control of records and Work Instructions for Access control, user levels, authorization of changes, and backup of information from analytical computer systems were followed to protect the systems' data integrity.

To ensure that the Quality Management System (QMS) documents were accessible to all CCAYAC personnel, a program was implemented for the control and regular updating of these documents.

Records on installation and operational qualification related to Empower software systems, which were components of test equipment, were available and reviewed. These records were entered in the logbook of the test equipment.

Electronic data was protected from unauthorized access using unique usernames and passwords.

Procedures were established and implemented for making, documenting, and controlling changes to the information stored in computerized systems in accordance with the applicable SOP.

Electronic data was backed up every three months according to the respective SOP.

Concerning spreadsheets (e.g., Excel®), all cells, including calculations, were locked so that formulas could not accidentally be overwritten. Free access was only given to cells to be filled in with data. Calculation algorithms were tested with another validated software or by a pocket calculator. A known dataset was used to verify the software in accordance with the respective SOP. The sheets were made available in a secured directory.

The deficiencies related to the Data processing systems were addressed in the corresponding CAPA plan.

6. Personnel

The laboratory had sufficient personnel with the necessary education, training, technical knowledge and experiences for their assigned functions. Staff undergoing training was assessed on completion of the training. The Laboratory maintained current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications. The laboratory maintained also records of all technical personnel, describing their qualifications, training and experience.

7. Premises

CCAYAC had separate areas for the different testing activities, in compliance with the regulations in force and the Good Laboratory Practices requirements. The Laboratory had a Samples Reception area, a Headquarters area, a Physicochemical analysis area, a Microbiological analysis area, an Immunological and Biochemical analysis area, and a Reference Materials area.

The laboratory facilities were of suitable size to suit the functions and to perform the operations to be conducted in them. If necessary, separate storage facilities were maintained for samples, reagents, laboratory accessories, and reference substances under refrigeration (2-8°C) and frozen (-20°C).

There was biometric access to the restricted areas.

The environmental conditions of the rooms were monitored and controlled using thermo-hygrometer devices. Gases were stored in a dedicated area, isolated from the main building. The Laboratory provided separate rooms for storing flammable substances, volatile substances, microbiology-prepared media, and concentrated acids and bases.

The section for sterility testing was separated from the rest of the facility to provide aseptic conditions. The premises, services, and equipment were subject to the qualification process.

The deficiencies related to the Premises were addressed in the respective CAPA plan.

8. Equipment, instrument and other devices

The equipment, instruments, and other devices used for the performance of tests, calibrations, validations, and verifications were inspected to verify whether they met relevant standard specifications.

The volumetric equipment was regularly checked.

For details, refer to section 12 of this report.

9. Contracts

The Laboratory had an SOP for the Acquisition of goods and services in place for selecting and purchasing services and supplies.

The National Regulatory, i.e., COFEPRIS, had a list of authorized laboratories as third parties to perform any test request for which the CCAYAC did not have the resource to complete the sample analysis. The list contained the name of the laboratory, its address, and the scope of its testing/activities. The third-party laboratories were evaluated and approved through the Sanitary Authorization Commission.

Contracts were signed and defined the contracted work and established duties and responsibilities for each party. The service agreement between COFEPRIS and the waste management company was randomly selected and reviewed.

10. Reagents

The reagents and growth media used were of appropriate quality and correctly labelled. Labels of reagent contained: content, manufacturer, date received, concentration, if applicable, storage conditions, expiry date, and retest date, as justified. Reagent solutions prepared in the laboratory were marked with name of the reagent, date of preparations and initials of technician or analyst, expiry date or retest date, as justified, and concentration, if applicable. Volumetric solutions prepared in the laboratory contained information about name, molarity, date of preparation and initials of technician, date of standardization and initials of technician, and standardization factor.

The water quality was verified regularly to ensure that the type I and type II water met the appropriate specifications.

The deficiencies related to the Reagents were addressed in the corresponding CAPA plan.

11. Reference substances and reference materials

The processes for handling reference substances, materials and cultures were reviewed:

a) Reference substances and reference materials

The Laboratory used compendial Reference substances and Working standards provided by the manufacturers. The compendial RS was periodically monitored according to the provided provisions. They were stored in desiccators to avoid deterioration of their quality. Official pharmacopeial standards were used for the purposes described in the corresponding monographs.

The following information was kept on the labels of reference substances or the accompanying documentation and the register, i.e., Excel spreadsheet with access control, as appropriate: name and description of the material, batch or control/identification number, source, date of

receipt or preparation, intended use, the date the closure is first opened, use of the reference substance in the respective form, expiry date or retest date, location of storage and storage conditions, certificate/batch validity statement of compendial reference substances, and safety data sheets.

The 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.

b) Reference cultures (RC)
Reference cultures were required to establish the acceptable performance of media (including test kits), validate methods, verify the suitability of test methods, and assess or evaluate ongoing performance. Traceability of the RC was kept relatively to the relevant culture collection, e.g., ATCC, when establishing media performance for a test kit and method validations.

To demonstrate traceability, the laboratory purchased reference strains of microorganisms from commercial suppliers for which relevant properties were available on the respective certificate.

Reference strains were sub-cultured once to provide reference stocks or used directly after resuspension. Reference stocks were stored in deep-frozen aliquots, in the refrigerator, or lyophilized. Working stocks were sub-cultured up to five generations (or passages) from the original reference strain

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

Equipment underwent qualification following a plan established by the laboratory. Each instrument was uniquely identified. Labels indicated the status of the calibration and the date when recalibration was due.

Balances were checked daily using internal calibration and regularly using suitable test weights. Requalification was performed annually by accredited external laboratories.

Records/logbooks were kept for items of equipment with information to identify the device, current location, maintenance carried out, history of damage, malfunction, modification, or repair. The use of the instrument was also recorded.

The inspection team reviewed the available performance verification and calibration documentation for the following randomly selected instruments and devices, aiming to ensure the suitability of the equipment for its intended use:

- Dissolution tester
- The disintegration apparatus
- UV-Vis spectrophotometer
- UPLC system
- FTIR/NIR
- Incubator
- Thermo-hygrometers
- LAF
- Refrigerator for reference strains
- Autoclaves for sterilization
- Analytical balance
- Karl Fischer
- pH meter
- TLC lamp
- Friability
- Column used for the sample analysis
- Micropipette
- Microplate reader for LAL testing and the respective materials/devices

Th deficiencies related to the Equipment and Devices were addressed in the respective CAPA plan.

13. Traceability

Test results were traceable, and ultimately to primary reference substances.

Calibrations or qualification of instruments were traceable to certified reference materials and to SI units (metrological traceability) with some exceptions.

The deficiencies related to Traceability were adequately addressed in the QCL's response.

14. Incoming samples

The laboratory was not responsible for the sampling of materials/products.

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

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

The laboratory reviewed the test requests before receiving samples to ensure that the laboratory had the resources to meet them and that the selected tests/methods could meet the customers' requirements.

All delivered samples and accompanying documents were assigned a registration number. A 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.

Before testing, the samples were stored safely, considering the sample's storage conditions. The samples were sent to the laboratory by the responsible person. The laboratory received only one portion of the sample. The owner kept one portion, and the National authority responsible for sampling kept the other portion in case of a dispute.

The staff performed a visual inspection and labelling of samples in the sample reception area to ensure that labelling conformed with the information contained in the test request. The sample temperature was monitored upon sample arrival.

All tests were performed after receipt of the test request.

15. Analytical worksheet

The analysts recorded information about samples, test procedures, calculations, and results in analytical worksheets completed by raw data. Analytical worksheets from different units related to the same sample were assembled. The analytical sheets were produced and made available using the Microsoft® Publisher software system, and the date of printing was automatically created on the template to control the generation of the document. In addition, a sequential number was stamped on each page of the analytical record.

The worksheets contained the following information:

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

All values obtained from each test, including blank results, were immediately entered on the analytical worksheet. All graphical data received from recording instruments 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, approved, and signed by the supervisor. For corrections, the old information was deleted by putting a single line through it; it was not erased or made illegible. Alterations were signed by the person making the corrections, and the date for the changes was inserted.

The test methods, including the microbiological tests were conducted based on Pharmacopeia methods, namely FEUM (Farmacopea de los Estados Unidos Mexicanos), USP and other applicable pharmacopeial methods.

The deficiencies related to the Microbiological test methods were addressed in the corresponding CAPA plan.

16. Verification of analytical procedures

The procedures employed for testing were suitable for the intended use, as demonstrated by verification in accordance with SOPs for "The transfer of analytical methods", for "Internal verification or validation of physicochemical methods and medical devices", and for "Verification or internal validation of microbiological methods".

When pharmacopeial methods were used for an FPP for the first time, it was demonstrated that no interferences arose from the excipients present. Although the pharmacopeial method was adapted for another use, it was further validated for such use to demonstrate that it was fit for purpose.

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

The deficiencies related to Verification of analytical methods were addressed in the respective CAPA plan.

17. Testing

The laboratory used the pharmacopeia monographs, i.e. FEUM-Mexican Pharmacopeia, USP, BP, and if all the details were not specified in the monograph, the additional detail was mentioned in the analytical sheet. Test procedures allowed analysts to perform the analysis reliably.

The laboratory used the validated analytical methods from the manufacturer if a compendial monograph was unavailable.

Deviations from the test procedures were approved and documented on the analytical sheets in a specific space designated for that purpose.

18. Evaluation of test results and OOS investigation

SOPs for the investigation and confirmation of out of specification (OOS) results for physicochemical tests, and for microbiological tests were in place describing the conduct of investigations of OOS test results. When a questionable result or suspected out-of-specification (OOS) result was identified, the supervisor and analyst conducted a review of the testing procedures that were followed during the testing process.

Doubtful results were rejected only if an error could clearly be identified.

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 first one.

Analytical test reports were issued by the laboratory based on information recorded in analytical worksheets.

The test reports further included the following information:

- the background and the purpose of the testing;
- reference to the specifications and methods used;
- the results of all tests performed (or numerical result with the SD of all tests performed);

The statement whether the sample complied with the requirements was reported by the National Regulatory in accordance with the local requirements.

Randomly selected samples' analytical sheets and the respective OOS investigation were thoroughly reviewed and discussed to verify the process of sample analysis and OOS investigation.

The deficiencies related to the Evaluation of results and OOS investigation were addressed in the QCL's CAPA plan.

19. Certificate of analysis

The issuance of certificate of analysis was not the Laboratory's responsibility. Certificates were issued by the National Regulatory Authority.

20. Retained samples

The Laboratory was not responsible to retain samples.

21. Safety

Staff was wearing laboratory coats, and goggles were available when applicable.

Rubber suction bulbs were used on manual pipettes. Safety data sheets were available before testing was carried out. Adequate spillage kits were provided at the chemical storage area.

The waste disposal procedures were designed to minimize the possibility of contaminating the environment.

The deficiencies related to the Safety were adequately discussed and addressed in the Laboratory's CAPA plan.

Miscellaneous	
Assessment of the Laboratory Information File	Laboratory Information File was provided according to Guidelines for preparing a Laboratory Information File, WHO Technical Report Series, No. 961, 2011, Annex 13
Annexes attached	N/A

Part 3 – Conclusion / Inspection outcome

Based on the areas inspected, the people met, and the documents reviewed, including the CAPA plan provided for the observations listed in the Inspection Report, ***Commission of Analytical Control and Coverage Extension (CCAYAC)***, located at ***Calzada de Tlalpan No. 4492, Colonia Toriello Guerra, Demarcación Territorial Tlalpan. C.P, 14050. Ciudad de México, Mexic***o is considered to be operating at an acceptable level of compliance with WHO GPPQCL 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. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1.
   Short name: WHO GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   https://www.who.int/publications/m/item/who-good-practices-for-pharmaceutical-quality-control-laboratories---trs-957---annex-1

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
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS No. 970, Annex 2
   chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs970-annex2-gmp-wate-pharmaceutical-use.pdf?sfvrsn=39eb16b8_0

4. 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
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. 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/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

6. 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://apps.who.int/iris/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1

7. 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
   http://apps.who.int/iris/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1

8. 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://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs957-annex3-gmp-pharmaceutical-products-containing-hazardous-substances.pdf?sfvrsn=bd8e1374_5&download=true

9. 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
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. 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
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.
    Short name: WHO TRS No. 961, Annex 9
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3.
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. 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
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