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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	N/A
Name and Address of Bioanalytical Research Site	**Micro Labs Ltd** **Micro Advanced Research Centre** 58/3 Singasandra Post, Hosur Road Kudulu Anekal Taluk Bangalore, 560 068 Kamataka, India Tel no.: +91 80-25731936/7 DUNS Number: 67-760-3856
Name and address Statistical Site	N/A
Corporate address of Organization	**Head Office:** 31, Race Course Road Bangalore -560001 Karnataka, India Tel no. +91 80-22370451-57 Email: info@microlabs.in
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	**HA755** Bioequivalence study of Dolutegravir, Lamivudine & Tenofovir Disoproxil Fumarate Tablets 50/300/300 mg **HA763** Bioequivalence study of Abacavir and Lamivudine Dispersible Tablets 120/60 mg **HA767** Bioequivalence study of Efavirenz, Lamivudine and Tenofovir disoproxil Fumarate Tablets 600mg/300mg/300mg
Inspection details	
Dates of inspection	5 - 8 April 2022

Type of inspection	Initial
Introduction	
Summary of the activities	This facility primarily focused on analyzing samples collected during Bioavailability and Bioequivalence (BA/BE) studies conducted to support marketing authorization in various markets for in-house developed products. There were agreements with contract research organizations (CROs) and in-house Clinical Pharmacology Units for conducting the clinical phase and statistical part of the studies.
General information about the company and site	Micro Labs is a privately held company founded by Late Mr. G. C. Surana, now under the leadership of Mr. Dilip Surana & Mr. Anand Surana. The company was established in 1973. Micro Labs is a pharmaceutical company present across the entire pharmaceutical value chain from research and development, active pharmaceutical ingredients, and finished formulations to marketing and distribution in India and overseas. The Bioanalytical facility on the second floor of Micro Advanced Research Centre was established and started its operation in February 2017 after receiving approval from CDSCO in January same year.
History	The facility was not previously inspected by WHO. For study approval, the site has been inspected by US FDA in November 2018.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: Regarding the analytical operations, coverage was provided to confirm practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the study data and analytical method validation was conducted, along with comparison of the source data to the study reports.
Scope and limitations	
Out of scope	Micro Labs Limited, Micro Advance Research Centre was only responsible for the bioanalytical part of the studies in the scope of inspection. The clinical and pharmacokinetic parts of the studies in the scope of this inspection were carried out by RA Chem Pharma Limited, Clinical Research & Biosciences Division.

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BE	bioequivalence
	BDL	below detection limit
	CAPA	corrective actions and preventive actions
	CC	calibration curve
	CPU	clinical pharmacology unit
	CRA	clinical research associate(e)
	CRF	(electronic) case report form
	CRO	contract research organization
	CTM	clinical trial manager
	CoA	certificate of analysis
	CSR	clinical study report
	DQ	design qualification
	ECG	electrocardiogram
	GAMP	good automated manufacturing practice
	GCP	good clinical practice
	GLP	good laboratory practice
	GMP	good manufacturing practice
	HPLC	high-performance liquid chromatograph
	LC-MS/MS	liquid chromatography–mass spectrometry
	IB	investigator's brochure
	ICF	informed consent form
	ICH	International Conference on Harmonization
	(I)EC	(Independent) Ethics Committee
	IMP	investigational medicinal product
	IQ	installation qualification
	LIMS	laboratory information management system
	LLOQ	lowest limit of quantification
	LOD	limit of detection
	MS	mass spectrophotometer
	MVR	monitoring visit report
	NRA	national regulatory agency
	OQ	operational qualification
	PIS	patient information sheet
	PQ	performance qualification

	PQS	pharmaceutical quality system
	QA	quality assurance
	QC	quality control
	QRM	quality risk management
	SAE	serious adverse event
	SAR	serious adverse reaction
	SOP	standard operating procedure
	STP	standard testing procedure
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

Part 2	**Summary of the findings and comments**

General section

1. **Organization and management**

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

The CRO was accredited by CDSCO on 6 Sep 2021 for five years

The CRO had an organization chart depicting the key positions and the names of responsible persons. The organization chart was kept up to date. All the personnel involved in bioanalytical operations with their designation were represented in the organogram dated and signed on 29 Mar 2022.

There was a list of signatures of the authorized personnel performing tasks during each study. The responsibilities of the test facility management for the bioanalytical part of the trial were established to ensure that the principles of GCP were compiled within the CRO.

The number of staff counted to 51 at the time of inspection, and Dr Shivanand Dhanure managed the Test facility as Senior Vice President. The Company had working hours from 9 am to 6 pm.

2. Computer systems

There were a sufficient number of computers to enable personnel to perform data entry and data handling, required for calculations and compilation of reports.

A list of software and computerized systems used in the studies was provided.

A change request for system upgrade of chromatography software system replacement of the Hard disk with SSD (solid-state drives) hard disk was provided for each of the eight LC-MS/MS instruments, on the respective form. The change request included information about the reason for the change, relevant documents to be updated, and the closure date. The software system was adequately qualified and validated by the vendor, and the post-testing reviews were carried out by the designated personnel, incl. QA Head.

The system validation documentation comprised of:

- Evaluation and planning
    - Validation plan
    - Vendor assessment
    - Validation risk assessment
- System design
    - User and functional requirement specification
    - Design specification
- Test planning
    - Test plan
    - Traceability matrix
- Testing
    - IQ, OQ and PQ
    - Execution of test cases
    - Discrepancy resolution
    - Approval of test execution documents
- Post execution activities
    - Summary report
    - Final document review
- Project completion
    - Change management
    - Retirement planning
    - Deployment

There was access control to the trial-related information entered and stored in computers. The access control method was specified through password protection, and a list of people who had access to the database was maintained. Secure and unique individual-specific identifiers and passwords were used.

There were SOPs in place for each software program used to perform activities of a BE study. SOP for Access control of LC/MS/MS system, and SOP for Operation, calibration, and maintenance of LC-MS/MS System were reviewed and discussed.

Software programs used, storage of data, and the procedure for backups and long-term archiving of all relevant electronic data were described in SOP for Data backup and restoration. The data from the backups were regularly archived, preferably before rewriting was done. The backup was provided through the backup software system, i.e., UR backup software. The folder for storing the user data was created on the server, and the data was also backed up on the tape cartridge as a daily, weekly, and monthly backup. The cartridges were a Barium ferrite type of magnetic particle with a durability of over 30 years, as per the Systems hardware data sheet.

The user access and privilege assignments were provided through an active directory administered by the Head Office. Once a new form for a new user, approved by the Head of the department, was received, a request would be sent to the Head Office to create a user ID and password through an active directory. The same route was used to deactivate an ex-user.

As soon as the backup activity was completed, the data was stored on the instrument, and the screenshots were provided. Before sending tapes to an offsite location, data was restored to the server, and the IT administrator verified it. A complete restoration of randomly selected projects was required to be performed annually to confirm the size and readability of the backed-up information. The restoration documentation of 5 Jan 2022 was reviewed.

The data was transferred from software systems in use to a UR backup software system. A validation plan for UR Backup Software system was provided, together with a 21 CFR Part 11 Compliance assessment. The entire validation was done by in-house IT personnel. PQ documentation, validation plan, matrix traceability, etc., were reviewed and found acceptable.

SOP for Disaster Management was available. The SOP described a holistic strategy focusing on prevention, preparedness, and risk mitigation of different types of disasters/events that might occur, such as electricity failure, earthquake, fire, cyber-attack, etc.

iXLc application efficiently managed Microsoft Excel Spreadsheets to calculate analytical run acceptance limits. This tool allowed the organization to control and centralize the management of Excel Spreadsheets with an associated audit trail. The Excel sheets were therefore adequately validated.

The validation documentation of the HR system to register the arrival and departure of employees, i.e., the Micro-portal system, could not be presented during the inspection. Nevertheless, the system was demonstrated to show that the data in the system could be modified, but all changes were captured on the system's audit trail. In addition, another digital authentication system was applied to register the movement of laboratory staff within the facility. The staff presence during the conduct of the studies in the scope of inspection was randomly verified through this system.

Observations made in relation to Computerized systems were sufficiently addressed in the respective CAPA plan.

3. Quality management

The CRO had appropriate QA and QC systems with written SOPs to ensure that data were generated, documented, and reported in compliance with the Standard Testing Procedures, GxP, and the applicable regulatory requirements.

Quality management system comprised of Quality manual, Standard Operating Procedures, plans, and policies. A Quality manual was available.

The Quality Assurance Unit (QAU) was a unit that functioned independently of the personnel involved in the studies:

The QA unit was responsible for:
- verifying all activities undertaken during the study;
- ensuring that the quality management systems, were followed, reviewed and updated;
- determining that the protocol and SOPs were made available to study personnel and were being followed;
- checking all the study data for reliability and traceability;

- planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with the SOP ML-BA-QA-002/03, and following up on any corrective action as required, to determine if all studies were conducted in accordance with the applicable requirements;
- performing vendor audits in accordance with SOP ML-BA-QA-003/03, effective 4 Dec 2021;
- verifying that the bioanalytical report accurately and completely reflected the data from the study and the methods and procedures followed;
- promptly reporting audit findings in writing to management, to the investigator and to the study director, as applicable.

Randomly selected change requests and audit reports and the respective plan were reviewed and discussed.

The process for issuance of templates and the respective logbook were discussed and verified.

Observations made in relation to Quality Management System were adequately addressed in the respective CAPA plan.

4. Archive facilities

The CRO had a storage space, which was relative humidity-controlled and pest-controlled, for archiving the study-related documentation. The archiving activity was managed in accordance with the applicable SOP. Records of document access and return were maintained.

The length of time for which study documentation, including raw data, was kept in the archive as defined in the SOP, i.e., 15 years for all the study-related documentation, 20 years for study documentation submitted to Canadian authorities, and 25 years for Belgian regulatory authorities.

Observations made in relation to Archive facilities were adequately addressed in the respective CAPA plan.

5. Premises

During the inspection, a tour of the facility was conducted. A layout for the premises was available.

The facilities were kept clean and had adequate lighting, ventilation, and, where required, environmental control. Floors, walls, and working bench surfaces were easy to clean and decontaminate. The CRO had sufficient space to accommodate the personnel and activities required to perform the studies. The bioanalytical laboratory was located on the second floor of the facility. It consisted of a Deep Freezer room, sample processing laboratories, instrument & balance room, and sample receipt room.

Entry and exit to the Premises were controlled by a digital key card or biometric authentication. The biometric authentication was disabled due to the Pandemic state. The presence of employees was recorded via a face-authentication system.

Laboratory premises were designed to suit the operations. Sufficient space was provided to avoid mix-ups, contamination, and cross-contamination. Adequate storage space was available for samples, standards, solvents, reagents, and records. The reference standards were kept in a locked refrigerator, monitored by a digital thermometer. The expiration date was adequately managed by designated QC staff.

The Laboratory premises were designed to provide adequate protection to all employees. Safety data sheets were readily available to staff before testing was carried out, and the respective binder was adequately organized.

A new fire protection system was implemented, and signs indicated that staff should wear coats and goggles. Hazardous chemicals and highly toxic samples were required to be handled in qualified and maintained safety cabinets. Containers of chemicals were fully labelled and included prominent warnings (e.g., “poison”, “flammable,” or “radioactive”) whenever appropriate. The laboratory was equipped with an oxygen-meter device to alert in case of air contamination.

Disposal of waste and environmental-friendly measures were inspected. The service agreement with Maridi Bio Industries Pvt. was reviewed. The Karnataka State Pollution Control board authorized the service provider.

The temperature & humidity of the facilities were continuously monitored by digital datalogger with the aid of RH-T transmitters and monitors of the equipment with RTD probes. The associated software systems were validated, and the respective device was regularly calibrated. The temperature deviations were adequately addressed. The excursion of temperature above acceptable limits could trigger the respective alarm system, which generated appropriate notifications to the designated personnel via email and SMS.

The facility was equipped with two diesel-electric power generators, i.e., 600 kVA each. There was also a UPS system with a total of 205 kVA to provide emergency power to a load when the input power source or mains power would fail. Synchronized clocks were located throughout the facility to document study activities' exact times.

Observations made in relation to Premises were adequately addressed in the respective CAPA plan.

6. Personnel

There was sufficient technical staff with the appropriate qualifications, training, and experience to support the study-related activities.

There were job descriptions for all personnel, including a description of their responsibilities. The job description was signed and dated by the staff member to whom it applied. Randomly selected JDs, CV, training log, and training matrix belonging to staff involved in study & QA activities were reviewed and verified.

A list of personnel involved in each study was available to be used during the inspection. Project study record was also available for the studies to document the STP training of personnel involved in the study activities. The training was provided to the employees based on a training schedule and the SOP for Induction, training, and Job Description of employees. Contract workers were also employed to perform certain activities in accordance with their respective contracts.

Bioanalytical section

The inspection included an audit of source documentation and raw data for validating bioanalytical methods and analysis of subject plasma samples, a review of the acquired electronic data, and audit trails for electronic data capture related to the BE studies. Results of calibration standards, quality control samples (QCs), and subject plasma samples in analytical runs were inspected, along with the chromatograms generated from analytical runs. The preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents were also audited.

QA personnel & other applicable staff assisting the inspection team with the review of study documents were knowledgeable, transparent, and helpful.

7. Method development, Method validation & Analysis of study samples

The bioanalytical laboratory provided a detailed description of how a bioanalytical method was developed in the notebooks issued by QA. The experiment details were noted in that notebook, and an index was provided with the respective page numbers. Based on the references, the laboratory used the in-house method development methods and made the necessary tests to finalize the methods.

Sound scientific principles were used to justify the selection of proper internal standards. The chemical and physical properties of the internal standard were as close to those of the analytes. Isotope-labelled internal standards were used in the MS methods by considering factors such as the isotope labelling positions, melting points log P, etc.

The analyses of samples were performed using LC-MS/MS system equipped with a mass detector and UHPLC. The data acquisition system with a chromatography software system was used for the quantitative determination of the analytes in the scope of the inspection.

The procedures for method development were well documented in controlled notebooks. All experiments were verified by a second person, i.e., BA Head.

Validation requirements for the analytical method of Study no. 072-18 (WHO application HA747) were verified to be adequately described in the respective protocol. There was an SOP for analytical method validation.

Data to support the stability of the samples under the stated conditions and period of storage was available before the start of the study.

Before March 2019, the CRO used manual tools to review and calculate the acceptance of analytical runs for method validation and sample analytical runs. However, this practice was amended, and the CRO applied iXLc application to verify the acceptance of batches.

A run containing 120 samples during method validation was executed to be comparable in length to those expected to be used for the analysis of samples in the respective study.

The number of freeze-thaw cycles and the duration of storage that a given blank plasma sample was submitted to were tested during the method validation to ensure that there was no degradation and/or any change in its properties. Freezing blank plasma in small volumes was considered to help limit the number of freeze-thaw cycles for any given blank plasma sample.

The results of the method validations of all three studies were available before the initiation of the study sample analyses. Nevertheless, the evaluation of the long-term stability of the analyte in the matrix was carried out after the initiation of analytical runs but before the study reports were issued, which were submitted with the validation report in their application for prequalification of the products.

Each analytical run included calibration standards (CC), quality control samples (QC), and subject samples processed simultaneously and in accordance with the bioanalytical study plan and the respective batch organization. The exact sequence of processing was documented and verified. All samples collected from a given subject during all trial periods were analysed in the same run except for repeat runs. The acceptance criteria for the analytical run were defined in different applicable SOPs, such as SOP for Subject Sample Analysis and Analytical Run Acceptance Criteria and SOP for Peak Integration and Chromatographic Acceptance Criteria. The validity of the SOPs was verified.

Randomly selected analytical runs were verified through sample processing, records of usage of equipment, sample processing checklist, sample selection verification, batch acceptance confirmation, retrieval and storage of samples from deep-freezer & respective temperature records, a record of arrival & departure of employees, and last but not least review of the applicable audit trail for both instrument and project, during the inspection.

It was ensured that the carry-over effect was avoided by applying appropriate methods during analyses of the samples. The quality of samples against degradation and/or any change of the samples' properties was appropriately protected. Samples were stored in the refrigerator if they could not be used immediately after preparation in accordance with the pertinent stability data.

Incurred sample reanalysis process was predefined in SOP for Incurred Sample Reanalysis according to the requirements. Two samples per period of all the accepted batches of analyzed samples were selected as an incurred sample; i.e., one sample which had a concentration near to the C_{max} and one sample in the elimination/ terminal phase having a concentration greater than LQC. The chromatography results were calculated to investigate the analytical issues according to the requirements.

The following documentation was also reviewed concerning the analytical runs:

- Sample processing templates and their issuance
- Reconciliation record of templates – cross verified for both used and unused templates
- STP
- Preparation and reconciliation of CCs and QCs
- Calibration curve results
- Usage of reagents/solutions/cartridges
- Equipment usage records and their qualification
- Deep Freezer logbooks and storage of samples
- Presence verification of the analyst
- Positive pressure processor logbooks
- Nitrogen evaporator logbooks
- The respective audit trails
- Acquisition time in the software
- Acceptance of IS variations
- Usage of analytical columns

Consumption of the reference standards, i.e., Lamivudine, Dolutegravir, and the respective Internal Standards and use of blank matrix in studies related to WHO applications no. HA732 and HA755 were verified. The EHS Lab provided a requisition form to document any request for expired materials' elimination, such as expired Reference Standards. The form was not a controlled document. However, it was noted that the EHS Lab had recently incorporated the process in their SOP. A form for chemicals, reagents, solvents, and drug standards disposal record was issued by QA with a unique issue number. The EHS department also verified the receipt of material on the same form.

Observation made in relation to Sample analytical runs was adequately addressed in the respective CAPA plan.

8. Sample collection, storage and handling of biological material

The specification of samples, sampling method, volume, and the number of samples were stated in the clinical trial protocol. The clinical part of the study, including a collection of samples, was carried out by another CRO in accordance with their written procedures. The samples were received in different aliquots by the sample custodians in the presence of QA personnel who properly verified the samples, including the number of samples, labelling, temperature loggers used under shipment, and documentation on respective controlled templates for record of acceptance of biological samples and logbooks in accordance with applicable procedures. Aliquot II was generally received after completion of study bioanalytical activities and was stored in a separate Deep Freezer from the first aliquots. The aliquots of biological samples were retained for at least six months after approval of the bioanalytical report.

The shipment documentation, including notification from the CRO, invoice, courier documentation, data logger printouts with specific ID numbers, sample verification document for periods I and II (Aliquot 1), as well as entries in the respective freezer logbook were reviewed and verified for study 034-19.

Purchase, receipt, quantity, quality, and usage of the matrix plasma, used for the preparation of CC and QC were documented. Type of matrix, batch number, date of collection and type of anticoagulant (K_2EDTA), name of the supplier, expiry date, and storage conditions were adequately recorded in the documentation and respective logbooks. The consumption of matrix plasma was recorded, and the documentation for reconciliation of matrix plasma, as well as consumption of QC and CCs, was available. The records of pooled matrix plasma usage in preparation and use of QCs and CCs for study 034-19 were reviewed and verified.

9. Data processing and documentation

Integration settings were predefined in the respective Standard Test Procedures, based on data from method validation activities, and were science-based and justifiable. The smoothing factor was usually kept at 5, i.e., low enough not to mask possible interferences and changes in peak geometry.

The process and criteria for acceptance and exclusion of CC standards was described in the respective SOP.

A trend of the internal standard signals was evaluated, and a range for acceptable internal standard peak areas was defined. Affected samples were re-assayed.

The audit trail of all computerized systems used for validation sample analyses and evaluation was fully activated and reviewed. Sample handling, processing, and evaluation were documented on controlled forms/templates. Analytical raw data were available and accessible in their original format. Each data point was traceable to a specific sample number and collection time point.

An adequate number of samples were tested as part of incurred samples reanalysis. The difference between the initial and repeated values was evaluated according to the appropriate SOP.

The data Entry process from the source data to the study report was discussed. The bioanalytical results and source documents were sent to the QC team for verification. The QC team identified deviations, and a form, i.e., Quality Control observations form as per the applicable SOP was completed and sent back to the analyst. After correcting errors, the study data underwent a thorough QA-verification before report writing.

A designated group was responsible for preparing the study report by transferring the study data into the report prior to the QC and QA verification. The report writing group was also responsible for eCTD submission.

Observation made in relation to Data processing was adequately addressed in the respective CAPA plan.

10. Good laboratory practices

The facility was equipped with eight LC-MS/MS instruments, two balances, three centrifuges, three Deep freezers (-65 °C & -20 °C), and two refrigerators.

Key sample storage systems were adequately qualified, calibrated, and maintained. A temperature mapping was carried out for each cold storage facility. There was an adequate monitoring system to control the temperature of the critical stage areas and key sample storage systems, such as freezers. The daily monitoring and all the alarm checks were documented. A system was in place to ensure timely and appropriate action following an alarm. The automatic alarm was tested to check its functionality during the inspection.

Appropriate repairs and/or transfer of samples to other equivalent storage units were considered whenever necessary, e.g., due to malfunction of the storage facility or other applicable reasons.

Balances, other measuring devices, equipment, and instruments were regularly calibrated, maintained, and verified to fit their intended purpose. The documentation for calibration, qualification and verification of randomly selected equipment was reviewed to confirm they were appropriately qualified and calibrated in accordance with the applicable SOPs.

Chemicals, reference substances, reagents, solvents, and solutions were labelled to indicate identity, purity, concentration (when appropriate), expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available.

Observation made in relation to Good Laboratory Practices was adequately addressed in the respective CAPA plan.

11. Study report

The study reports included a report on the trial's bioanalytical part, which contained a description of the bioanalytical method used and the respective report. The reports were approved (signed and dated) by the responsible personnel.

Analytical results were presented in a tabular form in the bioanalytical report. Additionally, precision, accuracy, and linearity data for each calibration curve standard and all QC samples were submitted. The Bioanalytical report was prepared as per SOP for Preparation and approval of the bioanalytical report.

Miscellaneous	
Samples taken	***Not applicable***
Assessment of the CRO master file	The company's CRO master file was provided and reviewed.
Annexes attached	***Not applicable***

Part 3	**Conclusion**

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, as well as the corrective actions taken and planned, the studies were considered to have been conducted at an acceptable level of compliance with WHO GCP guidelines at ***Micro Labs Ltd, Micro Advance Research Centre;*** located at ***58/3 Singasandra Post, Hosur Road, Kudulu Anekal Taluk, Bangalore, 560 068, Kamataka, India***.

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

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

Part 4	**List of guidelines referenced in the inspection report**

1. Guidance for organizations performing in vivo bioequivalence studies. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9.
   Short name: WHO BE guidance or ***TRS996 Annex 9***
   https://apps.who.int/iris/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y

2. Good clinical laboratory practice (GCLP), WHO on behalf of the Special Programme for Research and Training in Tropical Diseases. Geneva, 2009
   Short name: WHO GCLP
   https://apps.who.int/iris/handle/10665/44092

3. Guidelines for good clinical practice for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995 (pp. 97–137).
   Short name: WHO GCP
   WHO_TRS_850.pdf

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

5. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009.
   Short name: OECD GLP
   https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/mc/chem(98)17&doclanguage=en

6. Standards and operational guidance for ethics review of health-related research with human participants. Guidance Document. Geneva, World Health Organization, 2011.
   Short name: WHO Ethics Committee Guidance
   https://apps.who.int/iris/handle/10665/44783

7. Guidelines for the preparation of a contract research organization master file, WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 7.
   Short name: WHO CROMF Guidelines or ***TRS No. 957, Annex 7***
   https://www.who.int/publications/i/item/WHO_TRS_957

8. 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 storage and transport guidance or ***TRS 961 Annex 9***
   https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1&isAllowed=y

9. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
   Short name: Glove use information leaflet
   https://www.who.int/publications/m/item/glove-use-information-leaflet-(revised-august-2009)

10. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Republication of multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series No. 992, Annex 7 with a new appendix 2. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-first Report Geneva, World Health Organization, 2017 (WHO Technical Report Series, No. 1003), Annex 6.
Short name: TRS 1003 Annex 6
http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf

11. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://apps.who.int/iris/handle/10665/331814

12. 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 1033, Annex 4
https://apps.who.int/iris/handle/10665/340323

13. Declaration of Helsinki, World Medical Association Declaration of Helsinki, Ethical principles for medical research involving human subjects, Bulletin of the World Health Organization, 2001 (79(4)).
Short name: Declaration of Helsinki
https://apps.who.int/iris/handle/10665/268312

14. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
Short name: ICH M10
https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf.

15. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://digicollections.net/medicinedocs/documents/s23697en/s23697en.pdfcines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1