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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	**Quantys Clinical Pvt. Ltd.** Plot No. 668, 671 & 672 New Area Kandla Special Economic Zone Gandhidham, Kutch, Gujarat-370230 India
Name and Address of Bioanalytical Research Site	**Quantys Clinical Pvt. Ltd.** Plot No. 668, 671 & 672 New Area Kandla Special Economic Zone Gandhidham, Kutch, Gujarat-370230 India
Name and address Statistical Site	Statistical Facility (For Randomization schedule): Endpoint Data Analytics Pvt. Ltd. B-2, 186/8, Tirumala Mansion, SR Nagar, Hyderabad-500038, India. Statistical Facility (Pharmacokinetic and Statistical calculations): Star IT Technology 905, Paradise Tower, Naupada Next to Railway Station, Thane, India.
Corporate address of the Organization	**QUANTYS CLINICAL PRIVATE LIMITED** Plot No. 668, 671 & 672 New Kandla Special Economic Zone Gandhidham, Kutch- 370230, Gujarat India Tel: 02836-253330
GPS coordinates	23.03113° N 70.13649° E
WHO product numbers covered by the inspection/	**WHO application no. NT020** Bioequivalence study of Azithromycin 500 mg film-coated tablets

Product names/ Study numbers/ Study titles	
Inspection details	
Dates of inspection	17-20 September 2024
Type of inspection	Initial
Introduction	
Summary of the activities	Quantys, a CRO established in 2016 in Kandla, Gandhidham, Gujarat, provides bioequivalence testing services to the pharmaceutical industry. The facility was approved by DCGI in 2017 and has since completed a number of clinical and bioanalytical projects.
General information about the company and site	Established in April 2016, the facility was approved by the Drug Controller General of India (DCGI) in 2017. The company is part of the Rusan Pharma organization and is overseen by its board of directors. The CRO changed its name from Quest Care Private Limited to Quantys Clinical Private Limited on 26 July 2018, following the departure of one of the partners from the board of directors. The company had several offices and partner offices globally, engaging in various activities across multiple domains.
History	The CRO had experience in handling regulatory inspections from various agencies, including DCGI, US FDA, GCC, UK MHRA, EMA, TPD Canada, BPFK Malaysia, and the Ministry of Health Turkey.
Brief report of inspection activities undertaken	The following scope and study-related activities were reviewed: The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensation and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, and a tour of the facility. Regarding the Analytical operations, coverage was provided to verify practices, qualifications of personnel, and procedures utilized during the method validations and analytical testing. A review of the clinical study data, analytical method validation, and analytical study data was conducted, along with a comparison of the source data to the study reports.

Scope and limitations	
Out of scope	Statistical facilities & pharmacokinetic and statistical calculations

Abbreviations	ADR	adverse drug reaction
	AE	adverse event
	ALCOA	attributable, legible, contemporaneous, original and accurate
	BA	bioanalytical
	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
	ISF	investigator study file
	ISR	incurred sample reanalysis
	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
	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 organization was part of RUSAN corporate. The QA team reported to the Corporate QA Head, who in turn reported to the Managing Director. Additionally, the QA team reported in parallel to the Senior Vice President of Operations.

The CRO had an organizational chart depicting key positions and the names of responsible persons. The organizational chart was dated 19 July 2024, was authorized, and was kept up to date.

There was a job description for each employee, outlining their responsibilities. It was randomly verified that each job description was signed and dated by the respective staff member.

A list of signatures of the authorized personnel who performed tasks during each study was available and was verified.

The principles of Good Laboratory Practices had sufficiently established the responsibilities of the test facility management. The CRO management was aware that, since the investigator was an employee of the CRO, some responsibilities typically assigned to the investigator similarly resided with the CRO management.

The management ensured that appropriate and technically valid SOPs were implemented and followed throughout the facility. A historical file of all SOPs was maintained and organized efficiently, allowing for easy reference and ensuring that all operational procedures were up-to-date and adhered to regulatory standards. The current version of the SOPs was provided to the inspector on a USB memory stick for reference on the first day of the inspection, upon request. This ensured that the inspector had access to the procedures in a convenient format for review during the inspection process.

The CRO demonstrated compliance with ISO 9001:2015, which focuses on quality management systems, and ISO 27001:2013, which addresses information security management through respective approvals.

The facility operated within the standard working hours of 9:00 AM to 6:00 PM.

2. Computer systems

An inventory of all computerized systems on the network was available. Any changes to the network, including the temporary addition or removal of systems, were documented following the applicable SOP and the Validation Master Plan. A list of software and computer systems used in the studies was provided before the inspection.

SOP for Computer Management was available to oversee the management of computerized systems, covering aspects such as qualification, password control, and related procedures. The validation of the computerized systems was performed in accordance with the Validation Master Plan, effective from 23 November 2022. The company had requested the respective vendor to conduct the validation of the computerized systems through a formal proposal.

The Chromatography software system used for the analysis of the analyte within the scope of the inspection was inspected. The latest version of the software was available on the market at the time of inspection. The workstations operated on Windows 10 and were networked to ensure seamless communication and data transfer between systems.

There was a sufficient number of computers available to enable personnel to perform data entry, data handling, and the necessary calculations and report compilations. The computers had adequate capacity and memory to support their intended use.

Access to the software systems containing trial-related information was controlled. The method of access control was specified, and a list of personnel with access to the database was maintained. Secure, unique, and individual-specific identifiers and passwords were used to ensure data protection and integrity.

The software programs used to perform key steps were deemed suitable and validated for their intended use. Qualification and validation certificates were provided under the user's supervision to ensure that the software was validated appropriately and developed in a controlled manner, in accordance with a QA system. New procedures were implemented to ensure that the systems were validated in accordance with the applicable requirements.

It was noted that two procedures were implemented to address the preparation of User Requirement Specifications and risk assessment: SOP for the Preparation, Review, and Approval of User Requirement Specifications (URS), and SOP for Risk Assessment. These procedures covered the GxP criticality assessment and risk assessment of information assets, such as equipment, hardware, software products, and other physical assets at Quantys Clinical Private Limited. The qualification of the selected systems was reviewed for verification.

SOPs for the usage of each software program utilized in the activities of a bioequivalence study were available.

The storage of data, as well as the procedures for backup and long-term archiving of all relevant electronic data, were specified in SOP for Backup, Archiving, Restoring, and Periodic Verification of Electronic Data, effective from 12 July 2024. This SOP also outlined the frequency of data backups and ensured the proper management of electronic records. The physical location of the servers was verified.

Observations related to the computerized systems were adequately addressed in the respective CAPA plan.

3. Quality management

The CRO had appropriate QA and QC systems with written SOPs to ensure that trials were conducted, and data were generated, documented, and reported in compliance with the protocol, GCP, GLP, and the applicable regulatory requirements.

Quality System documents included (not limited to):
- Quality Manual, Quality policy
- Protocol
- Standard Operating Procedures
- Method Standard Operating Procedures
- Policies/ Guidelines
- Instructions where applicable

A Quality Manual, effective from 29 April 2023, was provided. The purpose of the Quality Manual was to guide the department's quality procedures and was designed to fulfill the requirements for a well-documented quality system.

QA functioned independently and reported directly to Management. QA operated according to the applicable SOPs and was responsible for overseeing the overall quality systems within the organization. All procedures followed within the organization fell under the purview of QA audits. The QA department ensured that all related activities were performed and documented systematically and in accordance with approved procedures, ensuring the accuracy, reliability, and traceability of study outcomes.

The QA unit managed GCP/GLP programs, regulatory inspections, audits, and pharmacovigilance to ensure compliance with regulatory requirements. It developed SOPs, reviewed study documents, coordinated quality reviews, performed audits, verified records, and ensured proper documentation for regulatory submissions. Additionally, it oversaw archival activities and collaborated with sponsors and regulatory bodies.

Both in-process and retrospective QA verifications were performed, such as those conducted in bioanalysis during the preparation and testing of samples and standards. The quality management system had encompassed root cause analysis, trend tracking, data integrity, and CAPA implementation. The company had defined the audit trail review process by QA in the applicable SOP, along with the respective reports used for different systems and purposes. The training of QA staff to perform the audit trail review was documented in the respective training forms. The documentation was available and reviewed during a random check.

The issuance of controlled templates was conducted under the supervision of QA to ensure compliance with internal protocols. Each controlled template was stamped with a signature, a QA-initial, and a unique identification number. This unique ID was documented in the respective logbook, ensuring traceability and accountability for all issued templates.

Observations related to the QMS were adequately addressed in the respective CAPA plan.

4. Archive facilities

The archives were located on the third floor and were equipped with air conditioning, a fire detector, a fire extinguisher, and a dehumidifier. Overall, the CRO ensured the safety and integrity of the documentation through security measures.

The archiving activities were managed in accordance with the respective SOP.

Access to the archive storage areas was controlled and restricted to authorized personnel only. A list of authorized personnel was displayed at the entrance of the facility.

Records of document access and return were maintained. The retention period for study documentation, including raw data, was defined in the SOP.

The archiving procedures for trial-related documentation were verified through the successful retrieval and traceability of documents during the inspection.

5. Premises

During the inspection, a tour of the clinical facility was conducted on day 2.

The facilities were kept clean and had adequate lighting, ventilation, and environmental control. Floors, walls, and working bench surfaces were designed to be easy to clean and decontaminate.

Clinical trials were carried out under conditions that ensured the safety of the subjects. The site selected was appropriate to the potential risks involved in the studies.

The CRO had sufficient space to accommodate the personnel and activities necessary for conducting the trials. The trial site was equipped with adequate facilities, including essential equipment.

Entry to the facility was restricted and controlled through biometric access, with doors kept locked and study participants continuously supervised. Emergency evacuation procedures were in place and ensured the safety of all present. Any entry to and exit from the facility was recorded to maintain comprehensive security and traceability.

Sites where clinical activities had taken place included a pharmacy where investigational products were stored under appropriate conditions. Access to the pharmacy was restricted and controlled through access control measures. Comprehensive entry and exit records for each visit to the pharmacy were maintained to ensure the traceability and security of the investigational products.

The bioanalytical laboratory premises were designed to accommodate the operations conducted within them, with sufficient space to prevent mix-ups, contamination, and cross-contamination. Adequate storage was provided for samples, standards, solvents, reagents, and records. Additionally, the premises were designed to ensure the safety and protection of all employees.

Safety data sheets were made available to staff prior to testing. The laboratory staff was familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents they handled. It was recommended that these safety data sheets be arranged in an easily accessible order. Staff was trained to use firefighting equipment, including fire extinguishers, and was instructed to wear laboratory coats. All chemical containers were fully labeled, with prominent warnings (e.g., 'flammable') displayed, whenever appropriate.

Adequate insulation and spark-proofing were provided for electrical wiring and equipment, including refrigerators. Staff were aware of the need to avoid working alone in the laboratory. First-aid materials were available, and staff were trained in first-aid techniques. During the inspection, it was advised to ensure first-aid materials were easily accessible.

Containers holding volatile organic solvents, such as mobile phases or extraction solvents, were sealed appropriately, and volatile organic chemicals were handled under certified fume hoods. Emergency showers and eyewash stations were available in the laboratory.

The premises had suitable systems for waste disposal, fume treatment, and environmental protection following local or national regulations. Temperature control was maintained using Eurotherm and hygrothermometers, depending on the facility type. A generator and a UPS were also in place.

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

6. Personnel

A qualified team of medical, paramedical, technical, and clerical staff was available to support the trial and effectively respond to foreseeable emergencies. At all stages of the trial, including nighttime, qualified and trained personnel were in place to ensure the subjects' rights, safety, and well-being were safeguarded, and to provide care in case of emergencies. For specific activities, contract workers were employed to complement the team's capabilities.

Randomly selected current curricula vitae and training records of full-time and contract personnel involved in trial activities were reviewed for verification.

Based on the requirements, phlebotomists, paramedics, and/or consultant doctors were employed on a contractual basis through mutual agreements. They were trained and delegated specific procedures before being assigned tasks. Consultants were invited to provide and share their technical expertise as needed.

Clinical section

7. Clinical phase

The clinical phase of the studies was performed on the premises of the CRO.

The facility comprised 104 beds distributed across five clinics, supported by an Emergency Nurse Calling System and a fully equipped emergency room. It had dedicated areas for sample collection, monitoring, dining, recreation, and screening.

To ensure patient safety, the facility provided round-the-clock in-house ambulance services and used GPS-synchronized clocks for accurate timekeeping. The access-controlled walk-in pharmacy was equipped with a digital temperature monitoring system, and the clinical deep freezers set at -20°C and -70°C were available for the proper storage of temperature-sensitive materials. Additionally, systems were implemented in the accommodation areas to allow subjects to alert CRO staff if necessary.

The facilities for changing and storing clothes, as well as for washing and toilet purposes, were clean, well-organized, easily accessible, and sufficient for the number of users. Lockable toilets were equipped with alarms, and the doors were designed to allow opening from the outside in the event of a medical emergency.

Provisions were made for the urgent transportation of subjects to hospitals.

Access to the randomization list was restricted to the pharmacist in charge of the study.

The equipment used was appropriately calibrated at predefined intervals. The functionality and performance of emergency-use equipment, such as defibrillators, were verified at regular intervals.

Observations related to the Clinical phase were addressed in the respective CAPA plan.

8. Clinical laboratory

An external clinical laboratory was used for sample analysis, and it was accredited.

Hematological tests, urine analysis, and other tests were performed during the clinical trial as specified in the study protocol. The CRO received information regarding the analytical methods used in the laboratory, along with a dated list of laboratory normal ranges and the laboratory's accreditation certificate. The current and signed curriculum vitae of the Head of the Clinical Laboratory were reviewed.

The laboratory created individual paper reports for each subject and included them in the CRFs. The results were delivered to the CRO by the laboratory personnel.

The laboratory was last audited by the CRO in 2019. The audit report and the respective CAPA plan were available and reviewed.

9. Ethics

The trials were approved by the Independent Ethics Committee before any study was conducted. The committee's independence from the sponsor, investigator, and CRO was verified through its member list. The Ethics Committee used a digital platform for communication with applicants, where the required documentation was submitted and decisions were subsequently received. The IEC was given sufficient time to review protocols, informed consent forms (ICFs), and related documentation.

The volunteers were insured by an insurance company.

Informed consent form

Information for study participants was provided to them in vernacular languages (Hindi and Gujarati) and at a level of complexity appropriate to their understanding, both orally and in writing.

Informed consent was given by each subject and documented in writing before any trial-related activities began. The CRO obtained separate consent for screening, study participation, and PCR testing during the study. The information was clear: participation was voluntary, and subjects had the right to withdraw from the study at any time, without providing a reason. Reasons for withdrawal were recorded in the study documentation.

Information about insurance and procedures for compensation or treatment in case of injury or disability during the trial was available through the insurance policy.

Volunteers or subjects were allowed to discuss their concerns about potential side effects or reactions from using the investigational products with a physician before participating in the trial.

The certificates of translation and back translation of the informed consent were reviewed.

10. Monitoring

The study was monitored by a monitor employed by the sponsor. The monitor was appropriately qualified to ensure that the study was conducted in accordance with the protocol, GCP, GLP, and applicable ethical and regulatory requirements. The monitor's visit was verified through the visitor log and logbook.

Two monitoring visits were conducted during the trial for period I and period II, and two reports were issued. The monitor prepared a written report after each site visit. No observations were recorded in any of the reports. Both reports were identical in layout and content. It appeared that the monitor opted to reuse the content from the first report for the second visit, as no observations were identified, and the same activities were checked and verified during both visits.

Observations related to the monitoring were addressed in the respective CAPA plan.

11. Investigators

The principal investigator (PI) was responsible for the clinical conduct of the study, including the clinical aspects of study design, administration of the investigational products, communication with local authorities and the ethics committee, and signing the protocol and final study report.

12. Receiving, storage, and handling of investigational drug products

The information regarding the receipt, storage, handling, and accountability of investigational products at each stage of the trial was recorded. Information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, and reconciliation of any remaining pharmaceutical products was also verified. Details of the pharmaceutical products used included dosage form, strength, lot number, and expiry date.

Pharmaceutical products were stored under appropriate conditions as specified in the official product information provided by the sponsor. These conditions were monitored using a digital temperature monitoring system.

Randomization was performed by an external company in accordance with the study protocol, and records were maintained in an email stored by the pharmacist.

The investigational products were properly labeled. Compliance of all labels with the randomization list was verified once they were printed and before labeling the containers. Labels were affixed to the containers in a manner that ensured the information remained intact even if the lid was removed.

Adequate routines for labeling and documenting the administration of the investigational product were established to verify that each subject received the product dispensed for them. This was achieved by using labels with a tear-off portion. The labels were designed with two identical sections: one to be affixed to the container and the second to be pasted onto the CRF at the time of dosing.

The empty containers were labeled separately for the test and reference investigational products. They remained segregated in a secure, locked area to prevent any potential mix-ups until the dispensing stage.

Dispensing and packaging procedures were carried out in accordance with the requirements specified in the respective SOP. Dosing was performed following SOP for dosing administration.

The surface on which the product was handled was cleaned before bottles of the product were brought into the area. All product containers (full or empty), individual dosage formulations, labeling materials, contaminants, dirt, and debris were removed from the area. A second person verified that the surface and surrounding area were clear and clean

before bringing in and opening containers of the product. The investigational medicinal products were handled using appropriate utensils. Tablets were distributed into each container in accordance with the randomization list for the test or comparator product, as applicable. The two products, i.e., test and reference, were handled at different times, including the labeled containers. Every step was recorded sequentially and in detail. The surface and its surroundings were cleared and cleaned immediately before and after dispensing each product, even when handled within the same study.

Investigational product accountability and dispensing records were maintained. Each activity was documented at the time it was performed, including records of doses administered, and returned, as well as records of verification by a second person for each step.

Dosing was carried out under the supervision of the investigator and a qualified staff member to whom this task was explicitly delegated in writing. The label was checked before dosing, and the exact time of dosing was documented on the designated page of the CRF. A mouth check was performed to ensure that the subject had swallowed the investigational product for solid oral dosage forms. This check involved looking under the tongue, under the lips, in the corners of the mouth, and between the gums and cheeks, using a spatula and a penlight. Dosing was directly documented in the CRFs.

Investigational product reconciliation after dosing was verified by a second responsible person. Samples of the product in the original container were retained for inspectors' confirmatory testing for at least one year after the expiry date of the newest product. Sample retention was defined and described in the relevant SOP. Dispensed products that were not administered were also retained.

13. Case report forms

Randomly selected CRFs from the study were reviewed.

The data collected on each volunteer was specified in the trial protocol.

Copies of the clinical laboratory reports and all ECGs were included in the CRFs for each subject. Information about the inclusion and exclusion criteria, medical history, food intake, blood collection, investigational product administration, and any adverse events, etc. was recorded in the CRFs.

14. Volunteers, recruitment methods

Procedures for recruiting volunteers were specified in the SOP for the Recruitment of Volunteers and included a description of the potential methods used by the CRO for this purpose. A database was maintained to register the volunteers and their participation in the studies. Access to the database was password-protected to secure confidential information about the volunteers or subjects.

Identification of volunteers and subjects was ensured through a biometric system that utilized thumb and index finger scans, along with an ID card.

The informed consent of potential subjects was obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study. The process was video recorded, and the records were available for review. The clinical trial protocol described the criteria for subject selection, including inclusion and exclusion criteria, as well as screening procedures. A software system, OVIS, was used to determine whether any subjects had participated in a previous trial. The participation date was uploaded to this central repository to prevent over-volunteering.

The screening activities, along with the respective facility and devices used to assess inclusion and exclusion criteria, were visited, and the corresponding documentation was thoroughly reviewed. The ECG machine used for recording produced paper ECG recordings issued in a controlled manner to ensure accuracy and traceability. This ECG machine could not store data electronically.

The subjects were tested for alcohol and drug consumption using devices and kits in accordance with current practices. However, during the study, a specific device was utilized that did not include an indicator to show the amount of air blown into it.

Observations related to the recruitments were adequately addressed in the respective CAPA plan.

15. Food and fluids

Meals were standardized and adequately controlled, with a schedule established for the study days. The CRO arranged standardized meals, snacks, and drinks for the study subjects, as outlined in the clinical trial protocol and in accordance with the agreement with the catering service. The corresponding invoice was available for review.

The timing, duration, and amount of food and fluids consumed were recorded. Before samples were obtained from ambulatory subjects, they were asked about their food and

drink consumption. Standardized meals were designed by a dietitian with the appropriate qualifications, training, and experience.

16. Safety, adverse events, adverse event reporting

The study was planned, organized, performed, and monitored to ensure that the safety profile was acceptable, including for the volunteers. The principal investigator (PI), a qualified medical doctor, was responsible for making medical decisions in the event of adverse events. The PI was also tasked with notifying the relevant health authorities, the sponsor, and, when applicable, the ethics committee, particularly in the case of a serious adverse event.

Documentation of adverse events (AEs) related to out-of-range parameters was accurate and thorough. Only clinically significant events were reported as AEs, ensuring that the focus remained on issues with potential implications for patient safety and study integrity.

First-aid equipment and appropriate rescue medications were available in the ICU for emergency use at the study site. Any treatment administered to a subject was thoroughly documented, with records included in both the CRF and the supporting documentation maintained in the ICU. The CRO had adverse event registration and reporting forms as part of the CRF. This ensured that all medical interventions were tracked and could be reviewed as needed for compliance and safety purposes.

Bioanalytical section

The following records and activities were investigated for the study associated with WHO Application No. NT020, including the associated method validation projects:

- Source documentation and raw data for the validation of the bioanalytical methods.
- Analysis of subject plasma samples, along with the respective electronic data.
- Audit trails for electronic data capture and handling related to the bioequivalence studies.
- Results of calibration standards, quality control samples, and subject plasma samples from analytical runs, along with the chromatograms generated during these runs.
- Preparation of analyte stock solutions, calibration standards, QCs, internal standards, and reagents.

Furthermore, the chromatograms and their integration were verified, ensuring the absence of signals in the blank samples and no unexplained interruptions in the injected sequences. The reasons for the repeat analyses of study samples and all instrument failures were reviewed to identify any potential issues. Additionally, the provisions and documentation

of the ISRs were confirmed, ensuring compliance with the required standards and protocols.

During the review of the study documentation, the inspection team received adequate support from well-informed and transparent personnel. Access to the chromatography software systems with administrative rights was granted to the inspectors during the inspection, facilitating a thorough examination of the data and processes involved in the study.

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

The method development process was described and documented, with the use of the internal standard justified by relevant literature, a copy of which was available for reference. The initial method was developed using solid-phase extraction, and an SOP for method validation was subsequently produced. The analysis of the initial study samples was conducted using the solid-phase extraction method, as detailed in Method Summary, and was documented under SOP titled "The Estimation of Azithromycin in Human Plasma by LC-MS/MS Detection (Solid Phase Extraction Procedure)," on 07 Jan 2022.

A stable isotope-labeled internal standard, Azithromycin-13CD3, was used in the LC-MS/MS methods, and K_3EDTA was employed as an anticoagulant.

The source data for the initial method development (MD), method validation (MV), and Incurred Sample Reanalysis related to the first round of sample analysis, along with the investigation reports, sample processing details, audit trails, and the respective runs conducted between the completion of the first and second rounds of sample analysis, were thoroughly reviewed.

The consumption records for the reference standard used as the internal standard during method development, validation, and sample analysis were accurately documented in the respective logbook, and these records were verified for consistency and correctness. Additionally, the data from the chromatography software systems were thoroughly reviewed to ensure compliance with regulatory requirements and to maintain complete traceability throughout the analytical process.

All integrations were conducted using the chromatography software system. Slopes, intercepts, and correlation coefficients were determined through least squares linear regression analysis, utilizing the ratio of analyte/internal standard peak areas from the calibration curve standards. A weighting factor of $1/x^2$ was applied in the calculation of the linear regression line. Concentrations were calculated using a validated scientific calculator

and manually entered into a Microsoft Excel spreadsheet to prepare the tables. The report was generated in Microsoft Word, and all entries were verified against the raw data.

During the method validation, as outlined in SOPs for Bio-analytical method validation and for batch processing form for method validation and project sample analysis, which were valid at the time of the study, a run was conducted to determine the batch containing 173 samples of QCs and CCs. This was referred to as "Extended Precision and Accuracy," comparable in length to the runs anticipated for analysis.

The sample processing was documented in the respective forms. An investigation form was provided to record any unexpected occurrences during sample processing and the corresponding investigation, when applicable. Repeat analysis was performed in accordance with SOP for Repeat Sample Analysis, Re-injection, and Evaluation of Internal Standard Response.

The repeat analysis of the ISR run under code A was reviewed in accordance with the aforementioned SOP.

The remaining repeat samples and the corresponding results were reviewed to verify the errors and the repeat analysis. The second concentration for the sample was generally reported and used in the pharmacokinetic analysis.

Data supporting the stability of the samples under the specified storage conditions and durations was available before the commencement of the studies. The exception was the long-term stability data, which was generated prior to the issuance of the study reports.

The review of the method validation included precision and accuracy testing (P&A), dilution integrity, selectivity, matrix effect, calibration curve, autosampler carry-over, and stability tests (Bench Top stability, freeze-thaw stability, stock solution stability, whole blood stability (WBS), hemolytic effect, recovery, and injection reproducibility). Method validation and sample analysis were conducted using the respective SOPs.

The matrix used for analytical method validation was consistent with that of the study samples, including anticoagulants (K_3EDTA). The purchase documentation for the plasma (Hemolysis and Lipemic for method validation) from the suppllier, dated 21 Mar 2022, was available, reviewed, and included records of receipt and consumption of the pooled plasma. The normal plasma was provided in-house. Documentation for the batches used for the second sample analysis (second aliquot, used for analyses performed in April 2022) was also reviewed, along with the logbook for the consumption of the biological blank matrix and the receipt form for the biological blank matrix.

During batch processing, the analyst verifies the system loading, a second analyst confirms the loading was done correctly, and a third verification is conducted, followed by additional checks after the analysis is completed.

The preparation, distribution, and storage of CC standards and QC samples were performed in accordance with the applicable SOP. Each analytical run included calibration curve standards, QC samples interspersed throughout the run, and subject samples, all processed simultaneously. The exact processing sequence was predefined and documented. All samples collected from a given subject during all trial periods were analyzed within the same run. The acceptance criteria for the analytical runs were confirmed by reviewing the analytes' retention times, the accuracy of calibration standards and QC samples, peak integration, and IS peak areas, in accordance with applicable SOPs. A system suitability and stabilization test was performed prior to the start of each day's run.

Of the first 1,000 samples, 10% were used for ISR, and for the subsequent samples, 5% were selected for ISR. A total of 204 samples were incurred for ISR in this study, chosen based on concentrations around C_{max} and during the elimination phase. The acceptance criteria for ISR were defined in the SOP.

At the time of the study, a system audit trail review was not conducted for the study within the scope of the inspection. However, this practice has since been implemented, and adequate training was provided to the responsible personnel, with documentation to support this.

Observations related to the sample analysis and method validation were adequately addressed in the respective CAPA plan.

18. Sample collection, storage, and handling of biological material

The specification of the samples (blood plasma), the sampling method, the volume, and the number of samples were outlined in the clinical trial protocol and provided to the volunteers. The collection, preparation, transfer, and storage of the samples were carried out in accordance with SOP for the separation and storage of subjects' biological samples, and SOP for the collection and transfer of blood and urine samples from volunteers during screening and the study.

Actual sampling times and any deviations from the prespecified sampling times were recorded. The respective deviations were considered during the calculation of the pharmacokinetic parameters.

The labeling of collected samples was clear, ensuring correct identification and traceability of each sample. All storage conditions (e.g., freezer temperature) were controlled, monitored, and recorded throughout the storage period and during transportation. Records of the storage and retrieval of samples were maintained. Samples related to the study within the scope of inspection were duplicated into aliquots.

As per SOP for Disposal of Biological Samples, the study samples, QC samples, and pooled matrices were discarded. The respective records were reviewed, and it was noted that the study plasma samples were discarded on 8 May 2023.

Observations related to the sample collection were adequately addressed in the respecctivev CAPA plan.

19. Data processing and documentation

Integration settings were recorded under the quantitation methods of the chromatography software system. Two quantitation methods were created during the study, but it was confirmed that each method was applied consistently throughout the entire batch when used. The smoothing factor was set at 5, ensuring it remained low enough to avoid masking potential interferences and changes in peak geometry.

The criteria for acceptance and exclusion of CC standards, QC samples, and batch acceptance were defined in the applicable SOP. The source data for all analytical runs contained comprehensive information about the original first evaluation of runs, including all calibration samples when the analysis was repeated. The calibration range was appropriately truncated. Internal standard variations were used as part of the verification of result validity, and those outside the acceptable range were subject to repetition under code E.

Full audit trails were always activated on all analytical instruments before, during, and after the method validation and the studies of interest. The software system was set up in full security mode, ensuring that access to the software, data, and analytical methods was restricted to authorized personnel only.

All original analytical raw data (e.g., calculations, chromatograms, and their associated audit trails) were documented in a manner that ensured full traceability regarding the sample number, equipment used, date and time of analysis, and the name(s) of the technician(s). All audit trail files were retained for complete recordkeeping.

Each data point was traceable to a specific sample, including the sample number, time of collection, time of centrifugation, time of placement in the freezer, and time of sample analysis. This traceability ensured the ability to determine whether any aberrant results might have been caused by sample mishandling.

20. Good laboratory practices

A tour of the facility was conducted on day 3 to verify its suitability in terms of arrangement and safety.

The bioanalytical facility was equipped with LC-MS/MS systems for precise analysis. The facility also featured refrigerated centrifuges and dedicated areas for sample storage and weighing, ensuring proper handling and processing of samples.

To ensure the integrity of sensitive materials, the facility maintained an Ultra Low-Temperature Freezer (ULTF) at -70°C, controlled by digital temperature and humidity monitoring system. Additionally, the facility was equipped with ultra micro balances and integrated software for secure data processing, ensuring precise measurements and the protection of critical data.

Deep freezers for sample storage and refrigerators for storing reference standards were adequately qualified, calibrated, and maintained. An alarm system was linked to the digital thermometer, designed to trigger sound signals in case of temperature deviations. The automatic alarm system was tested during the inspection to verify its proper functionality. Daily monitoring and all alarm checks were documented within the digital thermometer application.

For the purposes of qualification verification, the temperature mapping of the Deep Freezer was reviewed to verify the hot spot and the location of the respective sensor. The mapping was conducted by a service provider. The temperature mapping process was properly executed at the time of inspection. The transfer of samples to equivalent storage units was appropriately considered during maintenance and repair, following the applicable SOP.

Balances, other measuring devices, and equipment and instruments used during the conduct of a trial were periodically calibrated and verified before use to be fit for their intended purpose.

The operation, use, calibration, checks, and preventive maintenance of equipment were described in the respective SOPs, with records maintained in accordance with applicable requirements. These activities were verified through a random review of the equipment used in study-related activities. The equipment and its components were labeled with the respective ID number, calibration date, and next calibration date. The equipment usage was properly documented in the analytical sheets and the respective logbooks for instrument usage. Additionally, the use of columns was recorded in the logbook dedicated to column usage.

The qualification/calibration documentation of the following equipment were randomly selected and verified:
- Balance
- Weight box
- Columns and the respective logbook
- Waters Xevo TQ-XS- Mass Spectrometer & Acquity UPLC coupled with MS/MS.

Chemicals, reference substances, reagents, solvents, and solutions were labeled to indicate identity, purity, concentration when appropriate, expiry date, and specific storage instructions. Information concerning the source, preparation date, and stability was available on the label or the CoA.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

This section was out of the scope of this inspection.

22. Study report

The study report included a detailed account of the bioanalytical part of the trial, including a description of the bioanalytical method used and a report on the validation of this method. Reports related to the previous method validation and sample analysis were also available.

The Principal Investigator approved the clinical study reports prior to data transfer to the statistical department. The bioanalytical reports were approved by the responsible staff and management. Monitoring and audit reports were available before the final study report's release. Data verification was performed, and the activities were confirmed through written correspondence between the QA team and other relevant teams.

Miscellaneous	
Samples taken	N/A
Assessment of the CRO master file	The CRO master file with an effective date of 10 March 2023, was reviewed during the inspection. The file contained the relevant documentation and records necessary to confirm compliance with regulatory requirements and operational standards.
Annexes attached	N/A

Part 3	**Final conclusion – inspection**

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/GLP/BE guidelines at ***Quantys Clinical Pvt. Ltd.***, located at ***Plot No. 668, 671 & 672, New Area Kandla Special Economic Zone, Gandhidham, Kutch, Gujarat-370230; 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, before 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***

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

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

4. 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***

5. 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

6. 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***

7. 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***

8. Glove use information leaflet, Patient Safety, Save lives clean your hands. Geneva, World Health Organization, 2009 (revised).
   Short name: Glove use information leaflet

9. 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

10. 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

11. 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

12. 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

13. Bioanalytical Method Validation and Study Sample Analysis M10, ICH Harmonised Guideline, Final version, Adopted on 24 May 2022
Short name: ICH M10

14. 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

15. Supplementary guidelines on good manufacturing practices: validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fortieth report, World Health Organization, 2006 (Technical Report Series, No. 937), Annex 4.
Short name: WHO No. 937, Annex 4