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Prequalification Team Inspection services
WHO INSPECTION REPORT
Bio-Equivalence Study

Part 1	**General information**
Organization details	
Company information	
Name and Address of Clinical Research Site	QPS Bioserve India Private Limited 6-56/6/1/A, NH 9, Opposite IDPL Factory, Balanagar, Bhavani Nagar, Moosapet, Hyderabad, Telangana 500037, India
Name and Address of Bioanalytical Research Site	QPS Bioserve India Private Limited Plot No: 47, Second Floor, IDA Balanagar, Balanagar, Hyderabad – 500037 – INDIA QPS Bioserve India Private Limited 6-56/6/1/A, NH 9, Opposite IDPL Factory, Balanagar, Bhavani Nagar, Moosapet, Hyderabad, Telangana 500037, INDIA
Name and address Statistical Site	QPS Bioserve India Private Limited Plot No: 47, Second Floor, IDA Balanagar, Balanagar, Hyderabad – 500037 - INDIA
Corporate address of Organization	QPS Bioserve India Private Limited Plot No: 47, Second Floor, IDA Balanagar, Balanagar, Hyderabad – 500037 - INDIA
WHO product numbers covered by the inspection/ Product names/ Study numbers/ Study titles	*Study no: 661/16* 400 mg Tablets *Clinical Facility, bioanalytical and Pharmacokinetic/Biostatistics:* QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad – 500 037, Telangana, India *Study no: 776/15* Tablets 80/480 mg *Clinical Facility, bioanalytical and Pharmacokinetic/Biostatistics:* QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad – 500 037, Telangana, India

	Study no: 671/16 120 mg dispersible tablets *Clinical Facility, bioanalytical and Pharmacokinetic/Biostatistics:* QPS Bioserve India Pvt. Limited, # 6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad – 500 037, Telangana, India Study #:650/08 It was withdrawn from the scope of the inspection, since the application was inspected in 2010 by WHO. The CAPA plan was followed up.
Inspection details	
Dates of inspection	3-6 October 2017
Type of inspection	Routine inspection
Introduction	
Brief summary of the activities	QPS Bioserve is a Contract Research Organization (CRO) that provided a broad range of GxP compliant services for the pharmaceutical industry. QPS Bioserve in India performs clinical study activities covering a wide range of formulations, including, bioanalysis, clinical phase, statistical / pharmacokinetic analysis and X-rays
General information about the company and site	QPS Bioserve is a subsidiary of QPS Holdings, LLC which was a global enterprise located in 5 countries, with 12 locations. The company was initially founded under name of Quest Pharmaceutical Services in 1995. The CRO started their business in 2004 with constant development. Their facilities recently were extended, with a new bioanalytical lab department, expecting to start from November 2017.
History	The Company was the subject of number of inspections, by various authorities, since 2005. Previous inspection by WHO was performed in 2010. The organization was inspected by USFDA 10 times, EMA once, UK-MHRA once, as well as numbers of inspections by CDSCO
Brief report of Inspection activities undertaken	
Scope and limitations	
Scope	Bioanalytical and clinical activities in context with the abovementioned applications submitted to WHO
Out of scope	N/A

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
	HPLC-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
	SUSAR	suspected unexpected serious adverse reaction
	ULOQ	upper limit of quantification
	URS	user requirements specifications

Part 2	**Brief summary of the findings and comments (where applicable)**

General section

1. Organization and management

The CRO consisted of both Clinical and Bioanalytical facilities. The bioanalytical facility was moved to a new building with new equipment, which was planned to be fully utilized from November 2017. The old facility was still in use.

The organization had means to perform bioanalytical method development and bioanalytical validation practices, as well as designing and conducting the pertaining clinical trials.

The centre was generally in compliance with the national requirements and adequately equipped by 10 LCMS/MS instruments, operating with applicable software, such as Analyst, AB Sciex.

The CRO presented an organization chart depicting key positions and the names of responsible persons. The CRO Master file was also available.

2. Computer systems

Computer system qualification was reviewed.

Instruments used in applications' method validation and sample analysis, was verified, together with the functionality of the software database.

Configuration security was verified to ensure the proper access control, security data, verification of audit trails, as well as secure storage of the data to be protected against alteration, inadvertent erasures or loss.

Issues raised during the inspection were resolved in the company CAPA.

3. Quality management

Their Quality management system was designed to meet the regulatory requirements. Quality Assurance department was responsible for preparation, implementation and maintenance of the organization's SOPs and other quality documentation. A complete index of their SOPs was provided.

The quality management system was studied by review of SOPs in connection with the respective procedures.

All SOPs were subject to review every second year. If no revision was necessary, a review document would be prepared to keep the record of the review. The respective version remained valid. An SOP would be revised to a new version, only if a revision was made.

A business continuity plan and disaster recovery plan was in force at the organisation at the time of the initiation of the trials.

Audit plans were provided and reviewed to verify the independency of the QA department. Audit plans were scheduled and organized by tasks required in BE-studies. The planned activities were carried out properly.
Additional clinical laboratory internal audits were also performed according to their procedures and pertaining check lists.

Issues rose relating to this section, during the inspection were addressed adequately in the CAPA provided by the CRO.

4. Archive facilities

The new premises dedicated a room with sufficient space to allow appropriate archiving, equipped by chemically functional fire extinguisher. Paper documentation was stored in cabinets, with measures taken to prevent damages from rodents. The access was restricted to provide appropriate security.

5. Premises

Facility tours were performed on 3rd and 4th day of inspection.

The premises were well maintained and well organized with adequate space and facilities necessary to carry out the activities in a logical order.

The CRO consisted of two buildings:

1- Clinical and Bioanalytical Unit with the following departments
    a. CPU Unit 1 with 58 beds
    b. CPU Unit 2 with 34 beds
    c. Screening section, including physical examination room, blood and urine sampling section, ECG and X-ray rooms.
    d. Medical lab
    e. Pharmacy section
    f. Sample storage area; equipped by 3 freezers -20 °C and 2 deep-freezers -70 °C and walking freezer, monitored by centralized alarm system Eurotherm. The range of freezer temperature monitoring for deep freezers were set up from -58 °C to -82 °C.
    g. Study sample analysis laboratory, equipped by 10 liquid chromatography tandem mass spectrometry systems, balances in dedicated space, monochromic lights, and other required devices.
    The water for use in laboratory processes was provided using Millipore filtration. The device was used for preparation of stock solutions and other required purposes.
    h. Laboratory for method development
    i. Sample Archival

2- Main building and Bioanalytical Unit, to be fully utilized from November 2017

Access to restricted areas was enabled by biometric identification. Unauthorized test was performed. Individual card access was also possible.

Laboratory premises were designed to suit the operations to be carried out, to avoid mix-ups and contamination with adequate storage space for samples, solvents, reagents and records. All containers of chemicals reviewed, were sufficiently labelled.

6. Personnel

The CRO had sufficient numbers of skilled personnel to perform the bioanalytical activities. Organizational charts were provided.

An SOP training matrix was provided, organized by organizational departments and each department was divided to the designated groups, clarifying, for which set of SOPs, each group was required to be trained.

Furthermore, there was a list of employees with employee code, name, designation and department, date of joining and qualification. The list was signed and dated.

The training process was reviewed and verified.

Issues raised during the inspection were resolved in the company's CAPA.

Clinical section

7. Clinical phase

The Clinical phase was divided in two steps:

1- Screening
Process started with biometric verification of subject's identification in the internal database VMS, followed by testing subject's comprehension skill. If the subject was eligible to sign ICF, the next step would be to sign the generic ICF.
Process was followed by height and weight measurement, calculation of BMI, physical exam, blood and urine sample taking, ECG test and X-ray. The X-ray would not be necessary if X-ray image was available within last 180 days. The subject was given a wrist band with the subject number to be identified during the process.

2- Enrolment
On the day of enrolment, prior to starting the study procedures, the eligible subject was invited to receive information, read and sign the study specific ICF. The subject was biometrically identified in the database system named OVIS which also covered other CROs registered in the system to avoid multiple participations of subjects.

In addition, the following departments were inspected:

- Pharmacy: Storage and central monitoring of temperature were verified.
  Once a study was completed, the remaining investigational drugs were counted and stored in locked "disposition locker". The access to these lockers was restricted. The key was available upon request by QA Head.
  Drug accountability for retained drugs in selected studies was verified. Retaining time period was established by the protocol.
- CPU: CPU was visited.
  The CRO was mainly enrolling male subjects, and hence the CRO was advised to consider enrolling both genders in their studies, due to potential physiological/pharmacological variations in both sexes, as well as protocol specifications.
  CPU had 92 beds, equipped with alarms, connected to the monitoring room. Restrooms were visited.

  The unit encompassed an Emergency Unit equipped with required devices, such as defibrillator, Oxygen, ECG machine etc. The monitoring of form and refrigerator temperature was also verified.

Additionally, an agreement was in place between the CRO and BBR Multi-Speciality Hospital in case of Emergency inevitabilities. The agreement applied to the provisions of medical support and required medical treatments as assessed by medical team at the hospital was reviewed.

Systems were in place to allow the subjects to alert the CRO staff in case of need. The study site had rooms and areas appropriate for execution of the clinical activities. Equipment used was appropriately labelled with calibration date and predefined intervals.

Observations made during the inspection were addressed adequately by providing corresponding CAPA.

8. Clinical laboratory

The Qualification documentation for ECG used in screening phase was available.

Annual calibration of selected equipment was reviewed and verified.

Calibration certificate for balance used in screening phase was confirmed.

Haematological tests and urine analysis were performed during the clinical trials as specified in the study protocol. Samples were labelled properly.

9. Ethics

The independency and qualification of Ethics Committee members responsible for review and approval of clinical studies, performed by QPS Bioserve were inspected and verified. The chairman's CV was reviewed

All CVs, appointment letters and Consent forms to be a member of EC, as well as confidentiality and conflict of interest agreements for EC members were reviewed and verified to be valid, signed and dated.

10. Monitoring

Monitoring of clinical studies was performed according to the corresponding SOP to ensure that the study was conducted according to the protocol and regulatory requirements.

11. Investigators

Qualifications and job description of Principal Investigator and investigator responsible for the study in the scope of inspection were reviewed.

The investigator's practice was visited while performing the physical exam for screening pre-enrolment stage.

12. Receiving, storage and handling of investigational drug products

Information concerning the receipt, storage, handling and accountability of IMP at every stage of the trial was available.

A detailed record of receipt of IMPs and Reference products was present.
Evidence for shipment to the site was verified by QPS Bioserve. The condition of transport was verified by data-logger under ambient storage.
Letter from sponsor - sending of reference and test products was available.

CoAs (Certificate of Analysis) for reference and test product were reviewed and confirmed:

Drug accountability form was reviewed and confirmed.

Randomization schedule was reviewed and verified.

Temperature log for storage of the drugs in the pharmacy for a selected period was verified.

Drug used during dosing process was labelled properly and the activity was performed according to the protocol and respective SOP.

13. Case report forms

The completed CRFs were reviewed, as well as the date and time of subject registry to verify the existence of the subjects. CRFs were designed in accordance with the requirements for the particular studies.

Moreover, the dispensing details for period I and period II of selected subjects were checked, as well as the time for check out and check in, to verify that the information was corresponding with the time registered in the registry log book.

The result of breath alcohol analyser test was recorded on a template for all subjects with the device ID number.

The ECG printouts were verified to be relating to individual subjects, both cross the subjects and also cross the time points for each subject. ECG print outs were done on thermal.

14. Volunteers, recruitment methods

The selection of study subjects was performed in advance.

There were two sets of ICF for study:

1. Consent for screening
2. Study specific consent form

For more details please see section 7 Clinical Phase.

15. Food and fluids

This part was not inspected.

16. Safety, adverse events, adverse event reporting

There was no evidence of adverse event reported.

Bioanalytical section

17. Method development

A detailed description of how the bioanalytical method was developed was available to ensure that the method was created in a manner that would minimize the potential errors.

18. Method validation

Validation requirements for the analytical methods were described in the corresponding protocol. Method validation of four studies in the scope of the inspection where randomly reviewed to verify the reliability of the method used in the sample analysis.

During the inspection, source documentation and raw data for validation of bioanalytical method and analysis of subject plasma samples, as well as audit of the electronic data, audit trails for electronic data capture and handling of data related to the PK study were reviewed. The preparation and results from calibration standards (CC), quality control samples (QC), internal standards pertaining solutions and reagents and subject plasma samples in analytical runs were inspected, along with the chromatograms generated from analytical runs, including their respective parameters.

The analytical standard log was kept for Analyte usage.

The log was recorded to show what standard was used for, and how much was used, as well as the remaining balance.

Documentation was selected to verify the stability of the samples under the stated conditions and period of storage. Examples of documentation verified during the inspection were as follows:

- Recovery test was reviewed. The results were verified. Calculations for CV% were performed on a validated Excel sheet.
- Before any analytical run, a suitability test was performed. Analytical report was confirmed.
- Precision and Accuracy test for Qualification of QCs: LLOQ, LQC, AQC, MQC and HQC performed as well as calibration curve with r=0.9993 Linear regression
- Calibration curve standards record was confirmed.
- Preparation of the working solutions prepared, using 8 calibration standard concentrations: CC1 to CC8.
- Two aliquots were run by two different analysts to confirm the Precision and Accuracy test.
- Bench top stability documentation.
- Calibration curve was reviewed and verified. The reviewed run concerned BTS, FTS and PSS.
- Freezing and Thawing were performed in 5 cycles with different sets
- Preparation of the matrix for the Specificity test, as well as the pertaining working solution.
- The pipettes' ID used in this study was not recorded in the validation report. However, pipette performance check-activation for pipettes used in the method validation, was documented.
- Back calculation of stock solution preparation records
- Matrix effect performed, using 6 different lots, with triplet samples, for both LQC and HQC.
- Collection and testing of plasma samples used for preparation of CC and QC
- Whole blood stability test.
  Analytical report was reviewed to confirm the time points used in this test and the time of preparation and run of the samples. Time points, system suitability test and other pertaining documentation were verified.
- System suitability test was performed.
- Preparation of working solutions to be used for LQC (276 tubes), HQC (276 tubes) and the result of pertaining analytical runs.
- Verification of interference test.
- Qualification of QCs
- Calibration of standards and calibration curves
- Precision and accuracy performed in two runs
- Carryover effect
- Matrix effect and recovery
- Selectivity of OTC and concomitant medication interference test finalised

- Lipemic effect and haemolytic effect as well as dilution integrity
- Rejected runs such as Reinjection reproducibility
- QC intra and intraday precision range
- Stock solution stability and working solution
- Freeze and thawing tests
- System suitability test demonstrated for 7 days at refrigerated conditions
- Cmax list for the two assays were provided.
- Long term stability, OTC and concomitant medication interference test were performed in one run.

Issues raised in relation with this section were all addressed and CAPA provided and accepted.

19. Sample collection, storage and handling of biological material

Procedures for collection, preparation, transport, shipping and storage of samples were documented. Samples were labelled clear with unique identification codes.

Records of storage and retrieval of samples were maintained.

Anticoagulant, shipment records for receipt of samples were verified.

20. Analysis of study samples

The results of the method validation were available before the initiation of study sample analysis.

The runs for sample analysis and the results for selected subjects, as well as preparation of respective CCs were reviewed and verified.

It was confirmed that each analytical run included calibration curve standards. The exact sequence of processing was documented. QCs were dispersed throughout each batch. The acceptance criteria for the analytical run were predefined.

All the reanalysis were verified to be in line with the corresponding SOP “Reanalysis of Study samples”.

Documentation on qualification of CC’s and QC’s and incurred samples was confirmed.

Sample reanalysis and rejected runs were investigated to be according to the applicable requirements.

Results of sample analysis of incurred samples were verified against SOP for Reanalysis of study samples.

21. Data processing and documentation

Electronic raw data and paper raw data, including notebooks and various documents were reviewed during the assessment of trials' conduct. Documentation regarding all trials selected for inspection was organised and labelled properly with an Index.

22. Good laboratory practices

A complete list of instruments used for applications was provided. Equipment and devices were properly marked with unique identification number, together with the calibration date and next calibration date where applicable.

QC and QA were applied to all steps related to the study sample analysis.

There was a log book for usage of all laboratory instruments.

The laboratory was well-organized. Monochromatic lights were used in the area. There was a dedicated area for micro balances.

Calibration of thermometers and other equipment was documented.

Deep freezers were adequately qualified, calibrated and maintained. They were equipped with alarm systems and temperature monitoring.

Chemicals, reagents and solutions were labelled to be identified with correct concentration and date of expiry, as well as storage condition. Information concerning source, preparation date and stability was available on specific forms and templates used according to the QMS.

SOPs were in place for the operation, use, calibration and check of equipment, with corresponding record of activities.

Pharmacokinetic, statistical calculations and reporting section

23. Pharmacokinetic, statistical calculations

Cmax list for all trials were provided and compared to the raw data.

Issues raised in this context were addressed adequately in the CAPA provided by the CRO.

24. Study report

This part was not inspected.

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 study was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at CRO QPS Bioserve India Private Limited.

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 CRO, 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 guidelines referenced in the inspection report

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. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 9
   Short name: WHO BE guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf

2. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth report.* World Health Organization, Geneva. WHO Technical Report Series, No. 992, Annex 7, 2015, pp. 347–390
   Short name: WHO multisource guidance
   http://apps.who.int/prequal/info_general/documents/TRS937/WHO_TRS_937__annex7_eng.pdf

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
   http://apps.who.int/medicinedocs/en/d/Js5516e/19.11.html

4. WHO guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
   Short name: WHO TRS No. 996, Annex 5 WHO GDRMP guidance
   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

5. WHO Handbook on Good Laboratory Practice/OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Organization for Economic Co-operation and Development. ENV/MC/CHEM(98)17. 26.Jan 1998.
Short name: WHO GLP
http://www.who.int/tdr/publications/documents/glp-handbook.pdf

6. The Good Automated Manufacturing Practice (GAMP) Guide – A risk-based approach to compliant GxP computerized systems (GAMP5). ISPE – International Society for Pharmaceutical Engineering, December 2009.
http://www.ispe.org/gamp-5

7. Guidelines on Bioanalytical Method Validation EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.* Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

8. WHO Operational guidelines for Ethics Committees that review biomedical research (7). WHO, TDR/PRD/ETHICS/2000.1
http://www.who.int/entity/tdr/publications/documents/ethics.pdf?ua=1

9. Good Practices for Computerised Systems in Regulated "GXP" Environments, PIC/S Guidance, Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme, PI 011–3, 25 September 2007.
http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

10. US FDA Code of Federal Regulations Part 11
http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

11. EU guidelines to Good Manufacturing Practice and Medicinal Products for Human and Veterinary Use Annex 11, Computerized systems
http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf

12. Handbook – Good Laboratory Practice (GLP): quality practices for regulated non-clinical research and development – Annex I: The OECD Principles on GLP, 2nd ed., 2009. This document will be referred to as "GLP". http://www.who.int/tdr/publications/documents/glp-handbook.pdf

13. 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://apps.who.int/prequal/info_general/documents/TRS961/TRS961_Annex9.pdf

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14. Guidelines for the preparation of a contract research organization master file, WHO Technical Report Series, No. 957, 2010, Annex 7
Short name: WHO TRS No. 957, Annex 7
http://www.who.int/medicines/publications/TRS957_2010.pdf

15. Glove use information leaflet, Patient Safety, Save lives clean your hands, WHO, revised August 2009
http://www.who.int/gpsc/5may/Glove_Use_Information_Leaflet.pdf

16. WHO Good Clinical Laboratory Practices (GCLP)
http://www.who.int/tdr/publications/documents/gclp-web.pdf