World Health Organization

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

Part 1	**General information**		
Laboratory Details			
Name of Laboratory	Sipra Labs Limited		
Address of Inspected laboratory site	7-2-1813/5/A, Adjacent to post office, Industrial Estate, Sanathnagar, Hyderabad - 500018, Telangana, India		
GPS Coordinates	Latitude: 17.4583 Longitude: 78.4436		
Inspection details			
Dates of inspection	8 -12 March 2019		
Type of inspection	Initial		
Introduction			
Brief description of testing activities	***Type of analysis***	***Finished products***	***Active pharmaceutical ingredients***
	Physical/ Chemical analysis	pH, Solubility, Density, Viscosity, Conductivity, Water content (Karl Fischer), (Micro, Semi-Micro determination), Loss on drying, Refractive Index, Specific optical rotation, Limit tests, Saponification value, Iodine value, Acid value, Ester value, Peroxide value, Melting Point, Specific gravity, Residual solvents, Dimensions, Uniformity of dosage units (Mass, Content), Dissolution, Disintegration (Tablets, Capsules), Hardness, Friability, Nitrogen determination, Heavy metals, Osmolality, Particulate matter (Visible & Sub visible), Clarity and	pH, Solubility, Water content, Melting point, Refractometry, Loss on drying, Limit tests, X-ray diffractometry, Thermal analysis (DSC, TGA), Optical rotation, Conductivity, Density, Specific gravity, Viscosity, Osmolarity, Heavy metals, Limit tests, Sulphated ash, Acid insoluble ash, Residual solvents, Nitrogen value, Osmolality, Particulate contamination, Appearance, Clarity and Degree of opalescence of liquids, Degree of coloration of liquids, Test for extractable volume of parenteral solution, Distilling range, Acid value,

		Degree of opalescence of liquids, Degree of coloration of liquids. Total organic carbon, Appearance, Test for extractable volume of parenteral solution, Particle size, Re-dispersibility/ Reconstitution time, AA.	Ester value, Hydroxyl value, Iodine value, Peroxide value, Saponification value, Total organic carbon, Residue on ignition, Particle size, Freezing point, Drop point, Boiling point, Unsaponifiable matter, Organic volatile impurities, ICP-MS, AA.
	Identification	IR, HPLC (UV-Visible, PDA, RI detection, Electro chemical), TLC, AA Spectrophotometry and basic tests, GC (FID, TCD), UV-Vis Spectrophotometry, Chemical reaction, LC/MS, Capillary Electrophoresis, Residual solvents, Determination of degradation products, LC/MS/MS, Optical rotation.	IR, HPLC (UV-Visible, PDA, RI detection, Electro chemical), TLC, AA Spectrophotometry and basic tests, GC (FID, TCD), UV-Vis Spectrophotometry, Chemical reaction, FT-IR, GC/MS, LC/MS, CHNS Analysis, Residual Solvents, Determination of degradation products, LC/MS/MS, Optical rotation.
	Assay, impurities and related substances	HPLC (UV-VIS, PDA, RI detection), GC, UV, AA and FTIR spectrophotometry and volumetric titrations, Determination of related substances and impurities by comparison with a reference standard, Polarimetry, Determination of degradation products, Gravimetric analysis, Residual Solvents, Potentiometry, LC/MS, Coulometry, ICP-MS, GC/MS, TLC (Semi-Quantitative), Optical rotation, Potentiometric titration, Electrophoresis, Capillary electrophoresis, Nitrogen determination, Ethylene oxide residual	HPLC (UV-VIS, RI detection), GC, UV, AA and FTIR spectrophotometry and Volumetric titrations, Determination of related substances and impurities by comparison with a reference standard, Polarimetry, Determination of degradation products, Residual solvents, Gravimetric analysis, Potentiometry, LC/MS, Coulometry, ICP-MS, GC/MS, TLC (Semi-Quantitative), Optical rotation, Potentiometric titration, Electrophoresis, Capillary electrophoresis, Nitrogen determination,

		analysis, Water determination, Amperometry.	Ethylene oxide residual analysis, Oxygen flask combustion, Composition of fatty acids, Water determination, ICP-MS, Thermal analysis (DSC).
	Micro-biological tests	Sterility test, Microbial purity, Bacterial endotoxins test (LAL), Microbial assay of antibiotics, Microbial limit tests, Disinfectant efficacy of preservatives, Test for pyrogens, Anti-microbial effectiveness, Microbiological examination of non-sterile products, Identification of microorganisms.	Microbial purity, Microbial assay, Sterility test, Microbial limit tests, Test for pyrogens, Bacterial endotoxins test (LAL), Microbial assay of antibiotics, Preservative efficacy test, Anti-microbial effectiveness, Microbiological examination of non-sterile products, Identification of microorganisms.
	Bacterial Endotoxin Testing (BET)	Detection and quantification of endotoxins from gram negative bacteria, Determination of maximum valid dilution.	Detection and quantification of endotoxins from gram negative bacteria, Determination of maximum valid dilution.
	Stability testing	ICH Conditions	ICH Conditions
General information	The laboratory was established in 1994 to provide quality testing services and contracted research to Indian and global Pharma and biotech companies. Sipra is a contract test laboratory that conducts chemical analysis on a wide variety of products. The facility also includes a microbiological testing suite. The laboratory is also conducting testing of food and bioequivalence studies, including clinical trials. The analytical lab of Sipra is equipped to perform API, formulation testing, impurity testing, stability testing, method development and validation of pharmaceutical products as per ICH, USP, IP, BP, EP, JP guidelines. Sipra also conducts advanced pharmaceutical product characterization tests such as XRD, TGA, DSC, Particle size distribution, Surface area measurements, Elemental analysis, Mass spectroscopy, surface morphology, Rheology etc.		
History of previous inspections	The laboratory was not previously inspected by WHO. In the last three years, it was inspected by DCGI and the Ministry of Health of Ukraine.		

	Earlier, it was also inspected by the USFDA and the Australian authority. A warning letter with no 320-15-13 on 23 Jul 2015, with reference to the inspection performed on 24 February to 1 March 2014, was issued by the USFDA, and as a result, the organization was classified as unacceptable. However, an EIR was issued on 4 Aug 2016 as part of organization's effort to make its regulatory process and activities more transparent to the regulated industry.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Management & Quality Management System Documentation and Records, including data processing and archiving Personnel & training Premises and Equipment including Validation, Qualification and Calibration Contracts Method validation and verification Laboratory Practices, including evaluation of test results Safety Reference standards – Reagents - Water
Restrictions	Not applicable
Out of Scope	Only divisions involved in quality control of pharmaceutical products were in the scope of inspection.
Abbreviations	**Meaning**
ACPH	Air changes per hour
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
CoA	Certificate of analysis
FPP	Finished pharmaceutical product
FTIR	Fourier transform infrared spectrophotometry or spectrophotometer
GC	Gas chromatography or Gas chromatography equipment
GMP	Good manufacturing practices
HPLC	High-performance liquid chromatography (or high-performance liquid chromatography equipment)
KF	Karl Fisher titration
LIMS	Laboratory information management system
MB	Microbiology
MR	Management review
NC	Non-conformity
NCA	National control authority
NCL	National control laboratory
NRA	National regulatory agency
OOS	Out-of-specifications test result
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review

PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
RS	Reference standards
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometry or spectrophotometer

Part 2	**Summary of findings and recommendations**

1. Organization and management

The laboratory had an organogram dated 12 Dec 2016. A separate organogram for QA-unit was also available. The total number of company's staff accounted to about 200 at the time of inspection, from which 30 staff were working for the Analytical, Microbiological and QA departments. The laboratory was headed by Dr V. Satyanarayana as Managing Director and comprised of the 10 divisions:

- General Administration
- Marketing
- Supply chain
- Analytical
- Pre-clinical Toxicology
- Clinical
- Formulation and analytical R and D
- Food, Beverage and packing materials
- Bio-technology
- Corporate (central) Quality Assurance

The laboratory had arrangements to ensure that its management and personnel were not subjected to commercial, political, financial and other pressures or conflicts of interest that might adversely affect the quality of their work. The laboratory had a policy in place to ensure the confidentiality of information contained in marketing authorizations and test reports in accordance with SOP for Assurance of integrity and confidence. A policy for participation in appropriate proficiency testing schemes was included in the QM.

The laboratory was last accredited in accordance with 17025:2017 by NABL on 5-6 Aug 2017. A list of inspections and accreditations performed in the laboratory by national, regional and external audits in the last three years was provided.

The Company's working hours were established from 9:00 – 17:30, including Saturdays.

A Business continuity plan was presented as a part of ISMS. The risks were identified, assessments were made and measures/actions to be taken were considered in the plan.

The deficiencies identified on the Organization and Management were adequately addressed in the QCL's CAPA plan.

2. Quality management system

The laboratory had an independent Quality Assurance (QA) unit consisted of a Head CQA and CQA Executive for the coverage of all QMS activities. Additionally, a QA-representative was present at each division to perform quality assurance related activities. The QA unit reported directly to the Managing Director.

A quality manual defining the quality management system was available.

A list of SOPs was available. SOPs were adequately managed in accordance with the applicable SOP.

The activities of the laboratory were systematically and periodically audited internally. Management reviews were performed on a regular basis, covering audit reports, complaints and proficiency test, in accordance with the respective SOP. A logbook for recording of management review details, i.e. topics, date, time venue, agenda, attendance and minutes of meeting was available. The last management review was performed on 5 Mar 2019. Additionally, QMS trend analysis was discussed in a management review meeting on 26 Feb 2019.

An internal audit schedule for year 2019 was provided. The plan was arranged by division and activities to be audited were assigned on a monthly basis. The scheduled period and actual date of audits were both recorded on the plan. The Audit report dated 6 Dec 2018 was reviewed, and the independency of auditors was verified.

SOP for Change control system was reviewed. It was also verified whether the complaint management was carried out according to SOP for Handling of customer complaints. Complaints were required to be classified based on predefined categorizations. There were two logbooks to record the complaints upon their receipt:

- Logbook for registration of critical and major complaints
- Logbook for registration of minor complaints

Complaints were addressed in Management review meetings.

The deficiencies identified on the Quality Management System were adequately addressed in the QCL's CAPA plan.

3. Control of documentation

All SOPs and quality system formats were maintained manually. SOPs were prepared and controlled as per respective SOPs for Document Control. Each controlled document had a unique identifier, version number, date of implementation, reference to the previous version. The laboratory notebooks and forms and formats were issued and controlled by the QA with clear identification of document and page numbers in them. The documents, including SOPs were controlled by issue and inventory system. The obsolete master copies of the SOPs were archived and stored as per applicable SOP, while the obsolete user copies were retrieved and destroyed immediately. A Master list of SOPs was available.

All the laboratory notebooks and worksheets in use were taken back by the issuing officer (i.e. QA) as soon as they were full, or the relevant project was completed. They were also verified for their intactness and completeness. They were then archived and stored for the duration as mandated by the relevant regulations as stated in the applicable SOP.

4. Records

Records were made of analytical tests, including calculation and derived data, method validations / verifications, instrument use, calibrations and maintenance and sample receipt, in logbooks containing consecutively numbered pages. The records were complete and signed, alterations were commented on and duly signed and dated, and generally cross referenced to appendices containing the relevant recordings, e.g. chromatograms and spectra.

Records were kept in an archive for a period of 7 years for a pharmaceutical product. Access to the archive was restricted to authorized personnel and well documented.

5. Data processing equipment

A computer system matrix with information regarding instrument, software name and version, operating system, user access controls, existence of audit trail and data storage location was available. USB outlets on the computers were disabled. Computers were not connected to external networks. Electronic data was protected from unauthorized access. Procedures were established and implemented for making, documenting and controlling changes to information stored in computerized systems. It was verified whether computer generated, time-stamped audit trails for electronic records were maintained and reviewed as part of the decision-making steps.

Records on hardware configuration, installation and changes (incl. software updates) were kept for computerized systems, and were randomly selected and reviewed during the inspection.

The SLIMS (Sipra Laboratory Information Management System) data system was used for handling of sample and laboratory testing information.

HPLC instruments, operated by Openlab control panel with user specific credentials were visited. The Audit trail was reviewed after completion of each run by the designated Reviewer and was demonstrated. Manual integration was not allowed. Logbooks for the usage of HPLC and the respective SOP were available.

Electronic data was backed up using a specific software installed on each data-system to provide an automated backup at appropriate regular intervals, which was upon each modification/generation of data. A quarterly backup was also provided on types through the respective software system. Superseded versions of software were archived for at least 5 years in a retrievable and readable electronic format. Restoration of backed up data took place every 6 months in accordance with applicable procedure. The Restoration of backed up data on 07 March 2019 was supported by evidence, i.e. screenshot by indicating "Restoration completed", including size and number of folders.

Concerning spreadsheets (e.g. Excel®), all cells including calculations were locked so that formulas could not accidentally be overwritten. Free access was given to only those cells to be filled in with data. Preparation and validation of Excel sheets were performed in accordance with the respective SOP. The sheets were made available in the SLIMS data system, and their validity was established as 2 years. An option was in place to blacken the excel sheet as soon as it expired.

During validation of the computerized systems, the frequency, roles and responsibilities regarding the review of original records (including audit trails) were established based upon a documented and justified risk assessment.

The deficiencies identified on the data processing and computerized systems were adequately addressed in the QCL's CAPA.

6. Personnel

The laboratory had sufficient personnel with the necessary education, training, technical knowledge and experiences for their assigned functions. The laboratory maintained the records of all technical personnel, describing their qualifications, training and experience.

Job descriptions of randomly selected staff were reviewed. In general, their job descriptions were well-structured.

Staff were trained in accordance with the SOP for Training program and were assessed on completion of training. A presentation regarding the recent training metrics along with the pertaining assessment was provided by the Head of Analytical division.

The deficiencies identified on personnel were adequately addressed in the QCL's CAPA.

7. Premises

The laboratory facilities were of suitable size and design to suit the functions and to perform the operations to be conducted. Separate storage facilities were maintained for the secure storage of samples, retained samples, reagents, laboratory accessories and reference substances, if necessary under refrigeration (2-8 °C) and frozen (-20 °C). The environmental conditions of these rooms were monitored daily by a hygro-thermometer and controlled. The refrigerator used for RS and customer supplies was monitored by a Graphtec datalogger.

The laboratory had separate rooms for storing flammable substances, fuming and concentrated acids and bases.

Changes of the chilling units were in process. The change control process was adequately followed, and a change control was raised, including a risk assessment, where all storages with temperature sensitive products had been identified with exception to the room used for storage of Media powder in the microbiological laboratory.

The Waste management process and facilities were inspected. The facility was designed to direct the chemicals to an effluent sump with a capacity of 10 kL, located in a collection point handled by Waste Management Agency. Bio-waste was collected in designated containers, recorded in a logbook by an external management.

Rodent and pest control was carried out on regular basis by technicians from housekeeping unit in accordance with the respective SOP. Training documentation was presented.

Division for microbiological testing

Microbiological testing was performed in a contained laboratory unit on the 3rd floor as reflected in the provided layout. Access to the laboratory facilities was restricted to designated personnel by access cards. The biometric access was not yet activated. The section was designed to suit the operations to be carried out and there was sufficient space for activities to avoid mix ups, contamination and cross contamination. Laboratory activities such as sample preparation, media and equipment preparation and enumeration of microorganisms were segregated by space to minimize the risk of cross-contamination. Sterility testing was performed in a dedicated area. Anemometer measurements were used in formulae to calculate the actual ACPH used for the categorization of the rooms. For the initial qualification of rooms, the ACPH calculation and viable particle monitoring were taken into consideration in accordance with predefined specifications.

Separate air supply to the laboratory was ensured through Grill units throughout the division. Air supplied to grade A was via terminal HEPA filters and LAF benches.

An Environment monitoring programme, i.e. the use of active air monitoring, air settling/contact plates, temperature and pressure differentials, was in place.

The respective procedures and reports were reviewed, i.e.:

- Monthly microbial monitoring in the microbiology room was carried out in accordance with the applicable SOP. The preprinted bound logbook used for record of monitoring dated 8 Feb 2019 was reviewed. Information regarding the location of plates, type of plate, area grade, exposure time, incubator ID, plate count was recorded in the logbook. Negative and positive control test results were also recorded in accordance with the respective SOP.
- SOP for Procedure for air borne particle count and the last report were reviewed. The procedure took place every 6 months. The procedure also included the organization's specification regarding clean room parameters, such as particle count, air flow velocity,

pressurization and containment or leakage; depending on the environment or the equipment being tested, where leaks were not desirable. An extensive cleaning procedure was also a part of procedure for airborne particle count to be tested by microbial air and surface testing to ensure the effectiveness. The number of locations for particle count and air sampling for at least two hours before taking particle count were specified and verified. An Airborne particle sampling record with information about time, period of sampling, dated 28 Feb 2019 was reviewed. 24 points were tested in microbiological laboratory.

- Differential pressure was read from the display on the Pressure Gauge and recorded on a template. The acceptable range was predefined considering the air flow from more restricted area to less restricted.

The deficiencies identified on the premises were adequately addressed in the Laboratory's CAPA plan.

8. Equipment, instrument and other devices

The equipment, instruments and other devices used for the performance of tests, calibrations, validations and verifications were visited to determine whether they met relevant standard specifications. In general, they were qualified and/or regularly calibrated.

Each instrument was uniquely identified. Labels indicated the status of the calibration and the date when recalibration was due. DQ, IQ, and OQ of one of four Static Pass Box (sample handling box) by vendor dated 27 Jan 2010 were reviewed. Balances were checked daily using suitable calibrated test weights. Requalification was performed annually using certified reference weights.

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

The following instruments'/devices' calibration / validation / maintenance / logbooks for usage were reviewed:

- Calibration certificate of thermo-hygrometer
- Calibration certificate of refrigerator
- Calibration certificate of analytical balances, Calibration certificate of LabIndia tablet Disintegration tester– calibration was performed every 6 months in accordance with the respective SOP. The apparatus was infrequently in use.
- Calibration certificate of glass thermometer
- Calibration certificate of digimatic calipers used during calibration of abovementioned disintegration tester
- Daily and periodical calibration of five balances located in balance room, from which one was microbalance and four analytical balance. Two balances were under maintenance. Calibration of weights performed by service provider SIMCO was also reviewed and verified. SOP for calibration policy for analytical balances was reviewed.

- Digital Anemometer
- 6 monthly HPLC calibration report dated 18 Feb 2019 was performed in accordance with the applicable SOP. The stopwatch used for HPLC instrument qualification was calibrated by the service provider SIMCO on 17 Mar 2018.
- Autoclave validation was carried out according to the applicable SOP every 3 months, last performed on 2 Jan 2019. Annual calibration was performed using "Heat indicator" to ensure that the load 1-3 was processed.
- LAF filter integrity test using calibrated TDA 2H Aerosol photometer on 23 Apr 2018.
- Dissolution apparatuses which were either not in use or undergoing preventative maintenance
- Three HPLCs instruments
- UV-Vis equipment
- FTIR instrument
- X-ray diffraction
- Millipore Elix 35 & Milli-Q, last calibration.

Columns used for mass spectrometry were kept in the sample room and their inventory and usage was recorded in a logbook with information on sample registration number, number of usages and cumulative use.

There was one autoclave for sterility purposes located in the sterile facility and there was a second one for decontamination purposes in BioMedia decontamination area.

The deficiencies identified on the equipment were adequately addressed in the provided CAPA plan.

9. Contracts

The laboratory had a procedure in place for the selection and purchasing of services and supplies.

The laboratory had subcontracted the following testing to the following companies/organizations.

- Oxygen testing; to the Central Government Indian Institute of Chemical Technology
- NMR analysis of samples; to Sapala Organics Pvt. Ltd.

Contracts were signed and defined the contracted work and established the duties and responsibilities for each party. The competence of the contracted organizations was assessed, and records of these assessments were kept. Provisions regarding confidentiality and retention of documentation were considered.

SOP for Purchase process was reviewed. A list of approved vendors based on the service they provided, was available.

The deficiencies identified on the contracts were adequately addressed by the QCL.

10. Reagents

The reagents used were of appropriate quality and correctly labelled. Labels of the reagent contained: content, manufacturer, date received and date of opening of the container, concentration, if applicable, storage conditions, expiry date and retest date, as justified. Reagent solutions prepared in the laboratory contained the required information which included name of the reagent, date of preparations and initials of technician or analyst, expiry date or retest date, as justified, concentration, if applicable. Volumetric solutions prepared in the laboratory were also properly labelled.

The expiry date used for reagents and reference standards were the same as established by the manufacturer on the original label, unless otherwise instructed by the provider. "Expiry / use before date" issuance was described in SOP for Maintenance of laboratory fine chemical and reagents. A list was provided to determine to "use before" periodicity for chemicals without an expiry date. An overview of reagents was kept on a validated Excel sheet with conditional formatting where the relevant information regarding the Expiry date was recorded and subsequently monitored. Additionally, labelling was generated by using a template where the internal expiry date was automatically calculated.

Media used for microbiological testing were prepared in the microbiological laboratory and stored in a refrigerator in that area labelled with batch no, date of production. Media plates were valid 7 or 14 days depending on the type of media. The record of media consumption was kept in a log and sterilization of media in autoclave and consistently documented. SOP for Microbiological media preparation and Growth promotion test was reviewed. Growth promotion test records were documented in a logbook with sufficient information including the result of negative control and the GPT result (also considered as positive control). A logbook for the usage of the counter was also available with information regarding count of microorganism. The CoAs for Media powders used for the preparation of the media were uploaded in the system together with the rest of the documentation. CoAs for MacConkey Agar was randomly selected for review. Each batch of media powder was tested for both GPT and negative control.

The quality of water was regularly verified to ensure that the various grades of water met the appropriate specifications. SOP for monitoring and maintenance of water purification system was reviewed.

The deficiency identified on the Reagents was adequately addressed in the provided CAPA plan.

11. Reference substances and reference materials

1. Reference substances and reference materials

Reference substances, including customers' supplies were stored separately in the sample storage room at the analytical laboratory under the supervision of designated staff. A current list of pharmacopoeial Reference substances and primary standards to be periodically monitored, i.e. the first week of each month was provided. For RSs from suppliers such as Sigma the supplier expiry date was used throughout their entire shelf-life. The Reference standards were properly labelled. Expired RS were removed and recorded in a log for "Expiry chemical removal", with information regarding the RS ID no, name, expiry date and removal and disposal note, which was identified with a number, signature and date which could be linked to the logbook.

Official, pharmacopoeial standards were used for the purposes described in the corresponding monographs.

The identification number was quoted on the analytical worksheets whenever the reference substance was used.

2. Reference cultures

Reference cultures were available for establishing the acceptable performance of media and evaluating ongoing performance (positive control). Sufficient traceability was provided. Reference cultures were purchased from Bio Ball (A well-known French company with subsidiary in India) as 4th generation and used once to provide reference stocks. Microorganisms which could be stored in -20 °C and were consistent with USP requirements were preferred to be provided. Reference stocks (reconstituted fluids) were kept stored in aliquots deep-frozen in a -20 °C walk-in freezer for a maximum of 14 days. Reference standards could not be sub-cultured. Microorganism tests were carried out per lot to ensure their validity. Each lot consisted of 20 vials which was sufficient for 10 months live culture preparation. Disposal of stocks was well-described in SOP for Maintenance and verification of Bio Ball Multishot-550 Culture suspension.

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

Refer to section 8 of this report.

13. Traceability

The traceability of samples from receipt, throughout the stages of testing, to the completion of the analytical test report was generally ensured.

The deficiencies identified on the traceability were adequately addressed in the Laboratory's CAPA plan.

14. Incoming samples

Sipra was an independent CRO which was not associated with any manufacturing organization. Product and material samples were received by courier from clients, including pharmaceutical manufacturers, API manufacturers, RD centers and regulators. The organization was not involved in collection and selection of samples.

The process of receipt of samples was reviewed by supervising the receipt of a package during the inspection. The package was accompanied by a letter, a quotation by Sipra based on a request for analysis per respective specification and a barcode which was registered in the SLIMS system. The package was checked for possible damage followed by verification of the name and batch number, prior to inward-outward registration when an inward ID no was issued to be noted on the sticker on the sample. The sample shipping condition was not monitored unless it was required to be shipped under frozen conditions, in which case a datalogger was provided and datalogger ID was mentioned on shipping documentation.

After verification of the documentation in first stage, the samples were sent for a pre-registration check based on a checklist and the test request, followed by completion of the sample registration in SLIMS. The description of the sample, specification to be used for testing and required storage condition were recorded upon the registration of sample and a registration number was generated on a label with the respective barcode. The barcoded label was affixed on the sample and contained information about registration number, date, name of sample and batch number. A custodian was available to carry the entire sample consignment to the sample room located at the analytical laboratory on the third floor. Only defect samples would be retained in the sample receipt room until a resolution had taken place.

Samples in the sample room were stored in racks under controlled environmental conditions. A designated analyst verified whether the quantity of testing samples was adequate to be recorded in the SLIMS. If acceptable, all samples would be transferred to the laboratory for testing purpose and the remaining samples would be returned to the storage room only after completion of the test. Returned pharmaceutical samples were retained for one year after completion of test per the local legislation.

Samples might be deleted from list of “Samples received for testing” due to customer request or other applicable reasons in writing.

The deficiencies identified on the incoming samples were adequately addressed in the Laboratory’s response to the inspection report.

15. Analytical worksheet

Information on samples, test procedures, calculations and results were recorded in the required fields in the analyst logbook / analyst work sheet templates and other related logbooks/templates. Analytical worksheets from different units relating to the same sample were assembled together.

The records in the analyst logbook contained the necessary information, i.e. sample registration ID and name, date on which the analysis was started and completed, reference to specifications and full description of the test methods by which the sample were tested, including the limits; identification of test equipment used; reference substances, reagents and solvents employed; interpretation of the results and the conclusion whether or not the sample was found to comply with the specifications.

All values obtained from each test, including blank results, were immediately entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, were attached or were traceable to the electronic record file or document where the data was available.

The completed analytical worksheets were signed by the responsible analyst and verified, approved and signed by the supervisor. For corrections the old information should be deleted by putting a single line through it; it should not be erased or made illegible. Alterations were signed by the person making the corrections the date for the changes inserted. The reason for the change were also to be given, when necessary.

16. Validation of analytical procedures

The procedures employed for testing were suitable for the intended use, as demonstrated by validation, if appropriate. When pharmacopoeial methods were used for a FPP for the first time, it was demonstrated that no interferences arose from the excipients present. For an API, it was demonstrated that impurities coming from a new route of synthesis were adequately differentiated. Although the pharmacopoeial method was adapted for another use, it was further validated for such a use to demonstrate that it was fit for purpose.

Appropriate system suitability tests were employed prior to the analytical tests for verification of pharmacopoeial methods and/or validated analytical procedures.

A clear definition for repeat analysis was described in the SOP for Analytical events in analytical sequence or results.

17. Testing

Test procedures were described in detail and allowed analysts to perform the analysis in a reliable manner. Current editions of Pharmacopeia were electronically available for compendial methods. Deviations from the test procedures were approved and documented.

The sample analysis was required to be started within 15 days from the registration of the sample or earlier if the sample integrity might be compromised, in accordance with SOP for Sample process control. An Excel sheet was exported from SLIMS, populating all the information regarding the samples including the number of excursion days, ensuring that the laboratory was compliant. Clients were notified if the deadline was exceeded.

The deficiencies identified on testing were adequately addressed in the provided CAPA plan.

18. Evaluation of test results and OOS investigation

SOP for OOS investigation was in place describing the conduct of investigations of OOS test results. The Head of department / designee and divisional QA were responsible to conduct a laboratory phase investigation of an OOS result. OOSs were categorized in 10 different categories in the applicable SOP.

Doubtful results (suspected OOS result) when identified, were rejected only if they were clearly due to an identified error after review by the supervisor and the analyst of the procedures applied during the testing process. There were also adequate procedures in place when the outcome of the investigation was inconclusive. The SOP gave clear guidance on the number of retests allowed (based on statistical principles). Once an error was identified, corrective and preventive measures were recorded and implemented. All individual results (all test data) with acceptance criteria were reported. The repeat of tests was done by a second analyst, as experienced and competent as the first one. OOSs were chronologically recorded in a logbook with information about the date of record, OOS ID no, sample registration number and name, OOS parameter, analyst name, original OOS result, check result 1 and result 2, closing date and Group leader / QA Executive verification.

Analytical test reports were issued by the laboratory based on information recorded in analytical worksheets. When investigative testing was performed, the estimated uncertainty of quantitative results was also given.

The test reports included the following information:

- the background and the purpose of the testing;
- reference to the specifications and methods used;
- the results of all tests performed;
- the statement whether the sample complied with the requirements.

The following OOS investigations/records were reviewed:

- Disodium edetate BP, with sample registration no P/18/03132/1-3
- D-Biotin, with sample registration no P/18102366/2 recorded as an analytical event
- Al hydroxide gel, different samples that failed the correlation coefficient limit.

The deficiencies identified on the OOS investigation were adequately addressed in the Laboratory's CAPA plan.

19. Certificate of analysis

A certificate of analysis was prepared for each sample/batch of a substance or product and contained series of information depending on the sample analysis requisition, among others

- the results of the tests performed with the prescribed limits
- a conclusion as to whether the sample was found to be within the limits of the specification
- the analytical test methods
- the date on which the tests were completed.

20. Retained samples

Refer to section 14 of this report.

21. Safety

Staff were wearing laboratory coats, including eye protection. Special care was taken in handling highly potent, infectious or volatile substances. Highly toxic and/or genotoxic samples were handled in safety cabinets. Safety showers were installed. Rubber suction bulbs were used on manual pipettes. Safety data sheets were available before testing was carried out.

Miscellaneous	
Assessment of the Laboratory Information File	An updated LIF was provided and submitted on 28 Jan 2019.
Annexes attached	N/A

Part 3	**Conclusion – Inspection outcome**

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, ***Sipra Labs Limited***, located at ***7-2-1813/5/A, Adjacent to post office, Industrial Estate, Sanathnagar, Hyderabad - 500018, Telangana, India*** was considered to be operating at an acceptable level of compliance with WHO GPPQCL Guidelines.

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

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

Part 54	List of WHO Guidelines referenced in the inspection report

1. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1.
   Short name: WHO GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

2. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.
   Short name: WHO TRS No. 961, Annex 2
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

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

6. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO GMP guidelines*** or ***TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

7. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.
   Short name: WHO TRS No. 957, Annex 3
   http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

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

13. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
    http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. ***Short name: WHO TRS No. 981, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14***
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. ***Short name: WHO TRS No. 992, Annex 3***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.
Short name: WHO TRS No. 937, Annex 4
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1