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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Quality Control Laboratory

Part 1: General information

Name of QC Laboratory	SGS India Pvt Ltd (Life Science Services),
Physical address	2nd Floor, TICEL Bio Park Ltd. CSIR Road, Tharamani, Chennai 600113, India
Contact personand email address.	Mr Arun J j.arun@sgs.com
Date of inspection	26 - 28 August 2013
Type of inspection	Routine inspection
Type(s) of testing included in the inspection	Physical, chemical and microbiology testing
Summary of the testing activities performed by the QC Laboratory	

Type of analysis	*Finished products*	*Active pharmaceutical ingredients*
Physical/ Chemical analysis	pH, density, refractometry, viscosity, loss on drying, water content, disintegration, dissolution, uniformity of dosage units (mass, content), friability, tablet hardness, particulate matter test	pH, density, refractometry, specific optical rotation, viscosity, loss on drying, melting point, water content, heavy metals, sulphated ash, acid insoluble ash, acid value, iodine value, ester value, acetyl value, peroxide value, saponification value
Identification	HPLC (UV-Vis), GC (FID, ECD), GC/MS, TLC, HPTLC, UV-VIS spectrophotometry,	HPLC (UV-Vis), GC (FID, ECD), TLC, HPTLC, UV-VIS spectrophotometry,

		IR, AAS	IR, FTIR, AAS, chemical reaction
	Assay, impurities and related substances	HPLC (UV-Vis, DAD, fluorescence, light scattering detection), GC (FID, ECD), TLC, HPTLC, UV-VIS spectrophotometry, AAS, fluorimetry, volumetric titrations, amperometry, potentiometry, nitrogen assay	HPLC (UV-Vis, DAD, fluorescence, light scattering detection), GC (FID, ECD), TLC, HPTLC, UV-VIS spectrophotometry, AAS, fluorimetry, volumetric titrations, amperometry, potentiometry
	Microbiological tests	Sterility test, microbial purity, bacterial endotoxins test (LAL), microbial assay	Microbial assay
	Stability studies	ICH conditions	ICH conditions

Part 2: Summary

General information about the company and site

SGS is a Geneva Switzerland based company engaged in testing, verification and inspection of pharmaceutical products. SGS operates a network of over 1500 offices and laboratories around the world. In all, SGS has 28 facilities in 15 countries with a workforce of about 1,400 full time employees.

SGS Life Science Services (LSS) India was founded in June 1950 and currently has about 3000 full time employees. SGS India has two laboratories in India, one in Chennai and the other one in Navi Mumbai. SGS Chennai started operations in February 2005 and currently has about 70 full time employees. SGS Mumbai started operations in January 2012 with a total of 45 full time employees.

History of WHO and/or regulatory agency inspections

This was a routine WHO inspection of SGS Life Sciences, Chennai. The last WHO inspection was held in July 2010 and the laboratory was prequalified on 17.1.2011. Since then, the USFDA had inspected the laboratory in October 2010. A surveillance audit was conducted by the National Accreditation Board for Testing and Calibration (NABL) as per ISO 17025:2005 in September 2011. In addition, desktop audit verification was conducted by NABL as per ISO17025:2005 in July 2013.

Inspected Areas

This was a routine WHO inspection of SGS Life Sciences, Chennai. The last WHO inspection was held in July 2010 and the laboratory was prequalified on 17.1.2011. Since then, the USFDA had inspected the laboratory in October 2010. A surveillance audit was conducted by the National Accreditation Board for Testing and Calibration (NABL) as per ISO 17025:2005 in September 2011. In addition, desktop audit verification was conducted by NABL as per ISO17025:2005 in July 2013.

The following areas of the WHO good practices for the pharmaceutical quality control laboratories were covered in this inspection:

- Organization and management
- Quality management system
- Control of documentation
- Records
- Data-processing equipment
- Personnel
- Equipment, instruments and other devices
- Contracts
- Reagents
- Calibration, verification of performance and qualification of equipment, instruments and other devices
- Traceability

- Incoming samples
- Analytical worksheet
- Validation of analytical procedures
- Testing
- Evaluation of test results
- Certificate of analysis
- Retained samples
- Safety

List of persons (and their positions) met during the opening/closing meeting

- Mr Ulrich Markens, VP Corporate Quality & Compliance
- Mr Arun Janakiraman, Business Director
- Mr Satish Kumar, Head Laboratory Services
- Mr Senthil Kalathi, QA Manager
- Mr Srinivasan Velmurugan, Project Manager
- Mr Siva Sankara Narayanan, Assistant Manager, Microbiology

2.1 Organization and management

A management structure was in place to manage a wide variety of tests being conducted at the SGS Life Science Services (the testing of medicines, medical devices, trace element analysis for blood products as). The organization of the laboratory was defined in an organization chart. The laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were defined in job description cards. The laboratory had procedures in place to ensure confidentiality of results and protection of data.

The issues noted from this section had been adequately addressed, and the same will be verified during future inspections.

2.2 Quality management system

There was a global quality management system (QMS) in place which consisted of 6 layers. These layers were defined as Global Quality Manual, Global Policies, Global SOPs, Local Quality Manual, Local SOPs and Site Quality Documents. The global QMS was based on GxP principles and also incorporated additional certifications on local levels such as ISO17025, ISO9001 and WHO Prequalification Programme.

There was a local *Quality Manual* implemented on basis of the global Quality Manual which was reviewed in detail during the inspection (QM/002). The Quality Manual was mainly based on ISO 17025. Otherwise all relevant chapters like quality policy, responsibilities, management system, documentation system, subcontracting, complaints, control of non-conforming testing, internal audits, management reviews, personnel, environmental conditions, test methods and validations, equipment, measurement traceability and assuring the quality of test results were included.

Change Control System was described in SOP. The system is administrated by QA who assigns a change request number in the beginning. The documentation included a description of the current situation and a description of the planned change including an impact assessment and a classification into minor or major and a list of actions needed to implement the change. Change requests followed a defined approval procedure dependent on the classification. QA was responsible to verify the completion of actions prior to implementation of the change. During the inspection the documentation of the change from Star LIMS to Bluephire LIMS, the documentation for the update of the version of Bluephire R4 to R5 and the documentation of the change from various methods for temperature and humidity monitoring to the Yokogawa monitoring system were reviewed.

Internal Audits were performed according to SOP effective since 01.06.2013. An annual audit plan is generated by QA covering all laboratory areas (QC and microbiology) and audits are performed according to predefined checklists. The global QA is responsible for auditing the local QA procedures. CAPAs are documented and implementation thereof is tracked in a database.

2.3 Control of documents

The Documentation system was based on the provisions of the Quality Manual as well as on the Master SOP effective since 28.05.2013. Master copies of SOPs were kept in the archive whereas there were controlled copies available for QA, QC and Microbiological lab which were kept directly at the point of use within easy reach of the operators during performance of the different tasks. There was also an SOP for the control of records available.

2.4 Records

Different types of records were made and reviewed during the inspection including calibration records, training records, cleaning records and validation records. Usually it was traceable who performed the recorded task; however, the person actually performing the cleaning of the microbiological area is not signing the cleaning record so the training status could not be verified.

The issues noted from this section had been adequately addressed, and the same will be verified during future inspections.

2.5 Data-processing equipment

HPLCs, GC, UV, AAS, ICPMS and IR instruments were linked to computers operated by their respective software. All raw data generated by these instruments were stored electronically (HPLC backed up weekly) and as hard copies. Records were retained for at least 5 years.

A procedure was available on Data Backup, Restore Procedures, User ID and Password Management. The data were backed up daily, weekly, monthly and yearly, and these were saved. The latest monthly backup tapes were stored at regional office in Chennai.

2.6 Personnel

An organization chart showing the arrangements, responsibilities and reporting lines in the laboratory was available. Current job descriptions were available; documents were signed and dated by the relevant employees.

- Orientation and training procedure was available which provided instructions for organising and documenting trainings. A yearly training schedule for 2013 was available.
- An SOP on organogram, job responsibility, and layout together with the job descriptions (JD) of following personnel were reviewed:

i. JD of K. Senthil, QA Manager
ii. JD of Ganesh, reviewer QA
iii. JD of Monalisa Nayak, reviewer QA
iv. JD of M Satish Kumar, Head Laboratory Services

2.7 Premises

The laboratory premises were well maintained, clean and provided adequate room for laboratory activities except the space constraint. Access control to all laboratories was implemented by biometric means (finger scan). The laboratory environment was appropriate for tests to be performed. HPLCs, GC with Head Space, Balances (Micro and Analytical), UV, IR, AAS, and ICPMS were located in the main laboratory.

Laboratory had appropriate storage facilities for reference standards, reagents and solvents.

In the microbiology area there were three separate areas. Access to the area was limited to authorized personnel. Each area was accessed via an airlock with a double door system which prevented the opening of the access doors simultaneously. In the airlock, operators donned overshoes, hair covers and a laboratory coat. The sterility testing area was accessed via a Grade D, then Grade C area (which contained incubators for test incubation) then an additional airlock system and gowning procedure for access to the Grade B area which contained a laminar airflow (Grade A) for sterility testing. There was a separate pass through for materials and samples for sterility testing. A pressure difference of minimum 10 PA was maintained between each area. Pressure differentials were monitored and in place.
On several occasions, inadequate space issue was noted in laboratory (glassware washing area, hot equipment area, HPLC, GC area).

Cleaning of the laboratories was performed by external staff who was trained on respective procedure SOP in the local language. The cleaning records including also the fumigation records were reviewed during the inspection.

Environmental monitoring of the microbiological laboratory was performed according to SOP including settle plates, air sampling and surface sampling. Non-viable particles were assessed by an external company for the classification of the areas. The microbiological monitoring did not include the pass-box to the sterility area and

sample locations as depicted in the appendices to the SOP were not numbered in a unique way.

The issues noted from this section had been adequately addressed, and the same will be verified during future inspections.

2.8 Equipment, instruments and other devices

Equipment was calibrated and maintained according to SOP, effective since 17.07.2012 and calibration and maintenance work was documented in the manually kept calibration and maintenance schedule. Equipment is categorized taken into account availability at the different SGS laboratories and the categorization provided by USP. The Master Equipment log includes information on the name of the equipment, respective unique number, date received, vendor information, serial number, qualification status and the initial release for use. Calibration documentation for a randomly selected balance, an incubator, a dissolution apparatus, a UV spectrophotometer and an HPLC instrument was reviewed and found to be compliant with the requirements. The validation documentation of the autoclave used for sterilization of media was reviewed. All defined load patterns were included in the heat penetration studies and biological indicators were used for verification.

Alarm Monitoring System
There was an Alarm Monitoring System implemented according to change control documentation which was validated according to vendor's specifications and approved by SGS. However, this online monitoring system was not fully operated at the time of inspection so for some equipment the temperature monitoring was still performed manually, the temperature monitoring of the stability chambers respectively was still performed in parallel with Enviro Software which was planned to be replaced since it was not Part 11 compliant.

The issues noted from this section had been adequately addressed, and the same will be verified during future inspections.

2.9 Contracts

SOP on Handling and Management of Purchased Materials and Contractors was reviewed. The procedure stated three levels of evaluations (a) evaluation of subcontractors (b) laboratory instruments and equipment and (c) office stationaries. There was a contractor self-audit form which was used to obtain basic company information, their quality system, facilities, equipment and vendor qualification. It was however noted that there was no contract available between SGS LSS and other parties (Godrej, LGC Promochem and Artek Scientific) providing services (calibration, qualification and validation of autoclaves, incubators, laminar airflow, biosafety cabinet, supplier of media/cultures etc).

2.10 Reagents

SOP was describing how volumetric solutions and test solutions are to be prepared, labelled and stored. Expiry dates were defined for the routinely used solutions; all other solutions were defined to be only valid at the day of preparation. During the lab tour labels of various reagents were checked and found to be in compliance with the SOP. However, required storage conditions were not included on the labels.

The issues noted from this section had been adequately addressed, and the same will be verified during future inspections.

2.11 Reference substances and reference materials

Reference standard management was covered by SOP. The SOP stated that primary and secondary reference standards should be verified for its appropriateness before labeled and recorded in logbook. These reference standards were routinely verified for its validity (every 2 month for USPRS, working standards every 15 days).

The laboratory didn't perform any verification on the secondary working standards as most of these working standards were standardized against the primary reference standards. It is to be noted that these working standards were obtained from their customers for the analysis of their product as per their protocol.

A MS word database was maintained on computer for the inventory of these reference standards. The certificates of analysis of some of the working standards (Artemether IP, Levonorgestrel, Artemether Ph Eur. Zidovudine, Isoniazid, Rifampicin, Artesunate and Rifampicin EP) were reviewed.

2.12 Calibration, verification of performance and qualification of equipment, instruments and other devices

Examination of the relevant SOP for calibration, qualification, verification and preventative maintenance of equipment was available to guarantee consistent qualifications. Some of the calibration for following equipment was reviewed:

- SOP Inductively Coupled Plasma Mass Spectrometer
- SOP Atomic Absorption Spectrometry
- Balance
- UV spectrophotometer
- Dissolution apparatus
- HPLC

The documentation was found to be complete and traceable. There were no observations.

2.13 Traceability

Traceability of the materials did not show any particular issue from what was examined during inspection. With regard to equipment calibration all reference equipment items were traceable to NIST and certificates were available. Primary reference substances were used for testing (if not otherwise specified by the customer).

2.14 Incoming samples

Samples from customers were received at the reception and logged in a register before being forwarded to laboratory for verification and LIMS registration. Samples were then stored in a dedicated sample storage room. The room was monitored with regard to temperature manually and temperature monitoring was recorded in respective logbook. Registered samples were stored in colour coded boxes separately from samples waiting to be registered. For cool storage of samples a fridge was available which was also manually monitored for temperature.

2.15 Analytical sheet

The analytical worksheets for sample (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol Hydrochloride tablets), sample (Lopinavir and Ritonavir 50mg) and sample Ethionamide were reviewed in detail during the inspection. The transfer of raw data to the calculation sheets and the validity of the reference substances used were checked. The lot number of the actually used reference substance was not documented in the worksheet.

The issues noted from this section had been adequately addressed, and the same will be verified during future inspections.

2.16 Validation of analytical procedures

SOP on Analytical Method Validation Procedure was in place and found satisfactory. The procedure described in details the tests and acceptance criteria for method validation of both in-house and compendial methods. In addition, SOP on verification of compendial methods was reviewed. It was however noted that verification procedure didn't describe parameter to be verified including specificity requirement and acceptance criteria.

Following validation documents were reviewed:

- Analytical method validation for the determination of Bacterial Endotoxin Test (BET) for Rizatriptan Benzoate API (Dr Reddy)
- Method validation for assay by HPLC Sildenafil Dune 100mg tablets

It is to be noted that analytical methods were validated upon request from manufacturers. As samples of WHO prequalified products were received by SGS from IDA and GDF, as such no validation was done on WHO products.

2.17 Testing

SOP on the handling of out of specification (OOS) and out of trend (OOT) test results was reviewed. The SOP provided flow diagrams and checklist for the investigation of OOS. The retesting criteria using appropriate statistical tool was not part of the procedure. For more detail, refer to the section on observation.

The SOP on the handling of OOS for sterility testing and SOP on the handling of OOS for microbiological testing (BET, MLT, PET and Assay) were reviewed and found satisfactory.

In addition, some of the OOS for sterility failure were reviewed and found satisfactory in general.

2.18 Evaluation of results

The procedure for evaluation of test results was reviewed during the inspection of the analytical worksheets for sample (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol Hydrochloride tablets), sample (Lopinavir and Ritonavir 50mg) and sample Ethionamide. The transfer of raw data to the calculation sheets was checked. The formulae used for the calculation in the excel sheets had been checked manually. The formula check was documented and found to be appropriate. There were no observations.

2.19 Certificate of analysis

Certificates of analysis were reviewed during the inspection of the analytical worksheets as listed in above section. Certificates included as required by the WHO guideline: the registration number of the sample, date of receipt, the name and address of the laboratory testing the sample, the name and address of the originator of the request for analysis, the name, description and batch number of the sample, the reference to the specification, the test results, a conclusion as to whether or not the sample was found to be within the limits of the specification, expiry date or retest date if applicable, date on which the tests were completed and the signature of the head of laboratory. There were no observations.

2.20 Retained samples

The retention samples were stored in a store room which houses several stationary items and parts of MilliQ water etc. The area was found non-conducive for storing retention samples. In addition, adequate quantity of retention samples were not stored, instead leftover after the analysis were stored as retention samples. The issues raised were addressed satisfactorily and will be verified during future inspections.

2.21 Safety

In general, the laboratory was equipped with adequate safety equipment such as shower, eye washer and laboratory kit. While inspecting the glassware washing area, it was noted that there was no exhaust provided for adequate ventilation.

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, **SGS India Pvt Ltd (Life Science Services), Chennai, India** was considered to be operating at an acceptable level of compliance with in compliance with WHO Good Practices for Pharmaceutical Quality Control Laboratories.

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

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