WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Quality Control Laboratory

Part 1: General information

<table>
<thead>
<tr>
<th>Name of QC Laboratory</th>
<th>SGS India Pvt. Ltd. (Life Science Services)</th>
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</thead>
<tbody>
<tr>
<td>Physical address</td>
<td>2nd Floor, TICEL Bio Park Ltd. Tharamani Road, Tharamani Chennai - 600113 India</td>
</tr>
<tr>
<td>Contact person and email</td>
<td>Mr J Arun e-mail: <a href="mailto:j.arun@sgs.com">j.arun@sgs.com</a> Mr Ulrich Markens e-mail: <a href="mailto:ulrich.markens@sgs.com">ulrich.markens@sgs.com</a></td>
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<tr>
<td>Date of inspection</td>
<td>19 to 21 July 2010</td>
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<tr>
<td>Type of inspection</td>
<td>Prequalification inspection of a quality control laboratory</td>
</tr>
<tr>
<td>Type(s) of testing included in the inspection</td>
<td>Physical, chemical, microbiological testing</td>
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</tbody>
</table>

Summary of the testing activities performed by the QC Laboratory

<table>
<thead>
<tr>
<th>Type of analysis</th>
<th>Finished products</th>
<th>Active pharmaceutical ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical/Chemical analysis</td>
<td>pH, refractive index, optical rotation, viscosity, water content, conductivity, density, residual solvents, limit tests, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units (mass, content)</td>
<td>pH, refractive index, optical rotation, viscosity, melting point, loss on drying, heavy metals, sulphated ash, water content, conductivity, residual solvents, limit tests</td>
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<tr>
<td>Identification</td>
<td>HPLC (UV-Vis, PDA, RI, fluorescence detection), GC (FID), TLC, UV-Vis spectrophotometry, FTIR, basic tests</td>
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<tr>
<td>Assay</td>
<td>HPLC (UV-Vis, PDA,</td>
<td>HPLC (UV-Vis, PDA,</td>
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<tr>
<td>Impurities and related substances</td>
<td>RI, fluorescence detection, GC (FID), UV-Vis spectrophotometry, AAS, FTIR, ICP-MS, flame photometry, polarimetry, potentiometry, volumetric titrations</td>
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<tr>
<td>Microbiological tests</td>
<td>Sterility test, microbial limit tests, bacterial endotoxins test (LAL), preservative efficacy test, microbial assay of antibiotics</td>
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</tr>
<tr>
<td>Stability studies</td>
<td>ICH conditions</td>
<td>ICH conditions</td>
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Part 2: Summary

General information about the company and site

SGS was founded in 1878 in Rouen, France and registered in Geneva, Switzerland in 1919 where the head Office was located. The company operates in more than 140 countries. The company SGS Life Science Services was created in Chennai in 2004 and started its operations in 2005. The company was an independent quality control laboratory of Chennai.

History of WHO and/or regulatory agency inspections

SGS India Pvt. Ltd. (Life Science Services) Quality Control Laboratory was initially inspected by WHO team on 10 to 12 December, 2009 and this was a follow-up inspection.

Site has been accredited/approved by the following institutions:
- February 2005 – Approved by Tamil Nadu State Drug Control Authority
- May 2005 – Registered by CPCSEA, Govt. of India for conducting Animal Studies
- November 2005 – Accredited by NABL as per ISO 17025:2005
- June 2006 –Preliminary audit for GLP by National GLP Monitoring authority of India
- December 2006 – Surveillance audit by NABL as per ISO 17025:2005
- February 2007 – Inspection by USFDA
- September 2007 –Final audit for GLP by National GLP Monitoring authority of India
- November 2007 – Approved by National GLP Monitoring authority of India
- April 2008 – Surveillance audit by NABL as per ISO 17025:2005
- October 2008 – Re-assessment audit by NABL as per ISO 17025:2005
- January 2009 – Surveillance audit for GLP by National GLP Monitoring authority of India

Focus of the inspection

The inspection focussed on the quality management system, physical/chemical analysis and microbiological tests, as the areas of quality control testing to be prequalified by the WHO.

Inspected Areas

The areas covered during inspection included the overall quality system to support the reliability and traceability of the results of analysis. The areas of the WHO guidelines for Good Practices for Pharmaceutical Quality Control Laboratories (GPCL) were inspected including the following items:
- Quality management system (incl. customer service, internal audits, non-conforming work)
- Documentation and records
- Personnel and training
- Premises and equipment
- Reagents and reference substances
- Sample flow and sample storage
- Validation of analytical methods, testing, evaluation of results
- Traceability
Safety

The following areas of quality control testing both for final products and active pharmaceutical ingredients were inspected:

- Physical-chemical testing such as pH, refractive index, optical rotation, viscosity, water content, melting point, loss on drying, heavy metals, sulphated ash, conductivity, density, residual solvents, limit tests, tablet hardness, friability, disintegration, dissolution, uniformity of dosage units
- Identification using chromatographic methods (HPLC, GC, TLC) and spectrophotometric methods (UV-VIS, FTIR)
- Assays and determination of related substances/impurities using chromatographic methods (HPLC, GC), spectrometric methods (UV-VIS, FTIR, flame photometry and atomic absorption), ICP-MS, polarimetry, volumetric titration, potentiometry
- Microbiological tests such as sterility test, microbial limit tests, bacterial endotoxins test (LAL), preservative efficacy test, microbial assay of antibiotics

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

- J. Arun – Director
- U. Markens – Vice President Asia Pacific
- P. Sutz – Vice President Corporate Quality
- N. Ramesh – Manager QA
- K. Senthil – Project Manager – QC
- M. Saravana Kumar – Executive – QA
- R.H. Mythili – Section in charge
- P. Priyadharshini – Team Leader

2.1 Organization and management

The organization of the laboratory was defined in an organization chart which showed the arrangements, responsibilities and reporting lines. The laboratory had appropriate technical personnel with authorities to carry out their duties. The responsibilities of personnel were defined in job description cards.

2.2 Quality management system

The quality system was implemented in 2005 and was based on ISO 17025:2005 standard. Quality assurance (QA) documents were approved and available for the laboratory employees. An organization chart was available.

Standard operating procedures (SOP) “Change Control”, “Handling of Deviations” and “Customer Complaints” were reviewed and found to be acceptable as well as several records on deviations and complaints.

The quality system was systematically reviewed by internal audits at least twice per year according to the audit schedule. SOP “Internal Audit Procedures” was reviewed and found acceptable. Auditors recorded their observations and prepared internal audit non-conformity report. After audit corrective actions were proposed and verified by the auditors.
2.3 Control of documents

There were procedures in place to generate and approve SOPs, records and analytical worksheets as well as procedures for issuing certificates of analysis. Distribution of the documents was controlled. SOP on “SOPs Management” was reviewed. Review period for the documents was at most every 3 years. The document "effective" date was assigned after imparting training to relevant staff.

SOP “Auditing Duties and Responsibilities” was reviewed and found acceptable.

2.4 Records

Training records, analytical worksheets and sample logs were available. Records included the identity of the analyst performing the preparation and testing of samples. Raw data and other records including final results were retained for 5 years after releasing the Certificate of Analysis (CoA).

2.5 Data-processing equipment

HPLCs, GC, UV, AA, ICP - MS and IR instruments were linked to computers operated by their respective software, which was connected to a central server. All raw data generated by these instruments were stored electronically and as hard copies. Back up was regularly carried out.

2.6 Personnel

Current job description cards were available; documents were signed and dated by the relevant employees.

Master list of personnel was available and presented name, designation, function, qualification experience and date of joining. Specimen signature record was available.

SOP “Orientation and Training” was reviewed and effectiveness of training was evaluated through the questionnaires. There were the following types of training:

- Introduction training for new employees
- Refresher training to update and review previous knowledge
- Retraining due to performance issues or failure to perform a procedure satisfactorily
- Role playing
- Round robin testing (the testing was passed from one person to another in a sequence)
- Split sample testing (the sample was split between two or more analysts; the test results were compared among analysts)
- Temporary staff orientation training and/or refresher training if exceed a period of 1 month
2.7 Premises

The laboratory environment was appropriate for the tests to be carried out. In general there was sufficient space available to separate different types of analysis. The laboratory premises were well maintained and clean.

The microbiology laboratory was relocated in December 2009. Access to the area was restricted to authorized personnel. The air classification of the various testing areas was appropriate. New magnehelic gauges which were capable of measuring both positive and negative pressure had recently been installed.

The SOPs “Environmental Monitoring – Microbiology Laboratory” and “Environmental Monitoring – Sterility Room” were reviewed and found acceptable. SOP “Cleaning and Maintenance of Sterility Test Room” was amended as necessary.

2.8 Equipment, instruments and other devices

The laboratory had suitable testing equipment. Operational and calibration SOPs were available for all equipment. A list of laboratory equipment was available. See also 2.12 - Calibration, validation and verification of equipment, instruments and other devices.

2.9 Contracts

The laboratory did not subcontract any tests.

2.10 Reagents

The reagents were purchased from reputable manufacturers. Approved vendors list was available. A five year expiry period was assigned to reagents after opening and 1 year to liquids.

The preparation of reagents was performed according to pharmacopoeial methods. Volumetric solutions were standardized according to the relevant pharmacopoeial methods. Liquid volumetric solutions and dry reagents were properly labelled.

A storage area for reagents had been built. Acids and bases were adequately segregated. In addition, organic solvents were appropriately stored in metal cabinets.

In the microbiology laboratory, the verification of suitability of reagents prior to use had been included in the SOP “Media Preparation and Growth Promotion”. Media was manufactured in house and stored in the testing areas at ambient temperature. Media shelf life was validated for one month. Procedure for determining of microbiological quality of water was modified as per harmonized pharmacopoeias method and validated.

2.11 Reference substances and reference materials

Pharmacopoeial (primary) and manufacturers reference substances were used for the analysis. The reference substances register was appropriately maintained. Reference materials were
properly labelled. On receipt, an identification number was assigned to each reference substance.

Reference materials were appropriately handled and stored over silica in a refrigerator. The access to this refrigerator was controlled.

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

Equipment items were uniquely identified. Labels indicating equipment calibration status and due date were affixed to all equipment and instruments.

pH meters were verified with standard buffer solutions every day. Analytical balances were verified daily with standard weights before balances were used.

Critical equipment (IR, dissolution, disintegration, HPLC, GC) was regularly calibrated.

In the microbiology laboratory, incubators, laminar air flow (LAF) cabinets and a biosafety cabinet were all regularly calibrated. Temperature mapping of incubators was performed annually. The air handling system and critical incubators were furnished with online monitoring and alarm system to indicate any failure.

2.13 Traceability

Traceability of results was assured by:

- Keeping proper records of observations
- Verifying observations, calculations and results
- Using primary reference standards
- Regularly calibrating instruments and equipment
- Performing system suitability tests as specified in relevant compendia monographs

2.14 Incoming samples

Records were kept for all incoming samples. The laboratory had a central registry dealing with registration and distribution of the samples. Records on incoming samples were properly kept. Samples numbers were generated by the LIMS.

Received samples were allocated to the designated analysts. A unique registration number was allocated to each sample and was traceable through all the operations.

Upon receipt, samples were visually checked. The amount of samples was sufficient for analysis and for sample archive.

2.15 Analytical worksheets

The analytical worksheets provided necessary information. The records in analytical worksheets were checked, signed and dated by the analysts, then checked and signed by the QA personnel. Alterations were done in a correct manner.
2.16 Validation of analytical procedures

The SOPs “Analytical Method Validation Procedure” and “Method Transfer” had been revised to include acceptance criteria for different parameters. SOP “Verification of Compendia Methods” had been written and acceptance criteria were included.

2.17 Testing

The specifications were stored in a separate room in locked cupboards.

The samples were tested in accordance with the work plan.

Test results were recorded on analytical worksheets and graphical data were attached. System suitability criteria were fulfilled when defined in the method.

In the microbiological laboratory, two steam autoclaves were used for sterilization purposes and one for the media destruction. The SOPs “Bacterial Endotoxin General Work Instruction” and “Procedure for bioburden testing of products” were reviewed and amended as necessary.

2.18 Evaluation of results

Data generated during analysis and calculations performed by analysts were reviewed by the QA personnel and entered into the LIMS by the data operator.

Test reports in general contained the required data.

The SOP “Handling out of specifications (OOS) test results” was reviewed and amended as necessary.

In the microbiology laboratory the SOPs “Biological Indicators: Ampoules and Strips, Use and Verification” and “Identification of Microorganisms” were reviewed and revised as necessary. New SOPs “Handling out of specifications (OOS) for sterility testing” and “Handling out of specifications (OOS) for microbiological testing” were prepared and amended as necessary.

2.19 Certificate of analysis

All the results were entered into LIMS and Certificate of Analysis was generated, which was then checked and approved by QA.

2.20 Retained samples

Retain samples were kept for a predefined period after releasing the Certificate of Analysis. The period was in line with WHO GPCL requirements.
2.21 Safety

Personnel at the laboratory had to wear protective clothing. Safety instructions were followed. An emergency water shower had been installed.

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 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.