World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Quality Control Laboratory

Part 1: General information

Name of QC Laboratory	Stabicon Life Sciences Pvt. Ltd.
Physical address	Plot No. 28, Bommasandra Industrial Area (Sub-layout), 4th Phase, Jigani hobli, Anekal Taluk, Bangalore - 560 100, India
Date of inspection	10 - 12 September 2013
Type of inspection	Initial
Type(s) of testing included in the inspection	Physical, chemical, microbiological testing
Summary of the testing activities performed by the QC Laboratory	

Type of analysis	Finished products	Active pharmaceutical ingredients
Physical/Chemical analysis	Average Weight, Uniformity of Weight, Weight per ml, Minimum volume, pH, Water content by KF, Loss on Drying, Friability, Disintegration Time, Tablet Hardness, Divisibility Test, Dissolution by UV, Chemical & HPLC and Uniformity of Dosage units	pH, Water content by KF, Loss on Drying, Chlorides, Sulphates, Heavy Metals and general limit tests
Identification	TLC, HPLC,	TLC, HPLC,

	GC, UV-Visible Spectrophotometric and basic chemical tests	GC, UV-Visible Spectrophotometric and basic chemical tests
Assay, impurities and related substances	Assay by HPLC (UV-VIS, DAD & RI Detectors), Assay by Gas Chromatography Assay UV-VIS Spectrophotometer Assay by Titration Related Substances by HPLC, GC & TLC Related Solvents by GC Preservatives by HPLC, GC & UV	HPLC(UV-VIS, DAD & RI detection), Gas Chromatography (FID) UV-VIS Spectrophotometer, Volumetric titrations, Determination of Related Substances and Impurities by comparison with a Reference Standard
Microbiological tests	Microbial limit tests Preservative Efficacy Testing Pathogens, Microbiological Assay (Antibiotic Assays & Vitamin Assay)	Microbial limit tests Pathogens, Microbiological Assay (Antibiotic Assays & Vitamin Assay)
Stability testing	Storage & Testing of samples at different conditions as per ICH	Storage & Testing of samples at different conditions as per ICH

Part 2: Summary

General information about the company and site

Stabicon Life Sciences Pvt. Ltd (further on as SLS) was established in 2010 at Bangalore, India. The main focus of Laboratory business is conducting Stability Programs and Analytical Method Development & Validations as per various National & International Regulatory requirements.

Previously SLS was located at 3BM, 416, 3rd Block, HRBR Extension, Bangalore – 560 043, Karnataka, INDIA. SLS moved to Plot No.: 28, Bommasandra Industrial Area (Sub-layout), 4th Phase, Jigani Hobli, Anekal Taluk, Bangalore – 560 100 at the end of January 2013. As of the date of inspection, the chemistry laboratory was operational; the microbiology laboratory had not yet fully commenced activities.

In their activities SLS had not been involved in market surveillance testing, SLS had operated as a contract laboratory for manufacturers of medicines.

The Laboratory has consent to operate from Karnataka State Pollution Control Board through Combined Consent Order No. KSPCB / CFE / SR / 2012-13 / H1714 dated 07th March 2013.

History of WHO and/or regulatory agency inspections

SLS expressed its interest in prequalification in August 2011 and this was the first inspection performed by WHO inspection team within the Prequalification procedure.

- SLS is licensed by the local Karnataka Drugs Control Department for the Testing Laboratory.
- SLS was approved by Health Canada (Health Product and Food Branch) for its previous facility with respect to cGMP requirements
- New facility was re-audited by Health Canada due to change in facility address. Inspection report had not been received till the date of this inspection.

SLS had undergone an Inter Laboratory Comparison Testing with at least 3 other laboratories which are accredited by NABL (ISO/IEC 17025:2005). SLS had participated in Inter Laboratory Comparison Testing Program for the following Tests:

- Assay by HPLC & UV
- Dissolution by HPLC & UV
- Disintegration tests
- Water by K Fisher
- Loss on drying

SLS had planned to participate in Proficiency Testing conducted by LGC Standards Proficiency Testing, UK through LGC Promochem, India which will commence in March 2014.

Focus of the inspection

The inspection focussed at the WHO good practices for pharmaceutical quality control laboratories (GPPQCL).

Inspected Areas

The inspection covered the following sections of the WHO GPPQCL text

- Organization and management
- Quality management system
- Control of documentation
- Records
- Data-processing equipment
- Personnel
- Premises
- Equipment, instruments and other devices
- Contract
- Reagents
- Reference substances and reference materials
- 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

2.1. Organization and management

On the national level, SLS was legally authorized to perform the tests mentioned above. The SLS had managerial and technical personnel with the authority and resources needed to carry out their duties. The organization and management structure of the Laboratory was defined.

2.2 Quality system

The quality management system (QMS) covered all the departments of SLS. The QMS was based on the ISO 17025:2005 requirements. In addition, it followed the requirements of the WHO Good Practices for Pharmaceutical 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, Pharmaceutical Quality System ICH Q10 and international regulatory requirements.

QMS was established and specified the following:

- To provide timely Analytical Testing Services
- To establish, implement & maintain effective QMS
- To follow Good Professional Practices
- To ensure that all personnel are familiar with Quality Documentation and commit to continually improve the effectiveness of QMS

- To provide all required to maintain the Laboratory to its standards of QMS
- To continually improve the effectiveness of the management system through review meetings.

The Quality Manual (QM) was a high level general document covering all activities and processes.

Quality Policy (QP) was part of the QM. QP was affirmed in a statement from the Management.

Customer service: the main customers were finished product manufactures in India, US, UK, EU, SA, Canada and Thailand. Customers were allowed to audit laboratory facilities and procedures.

Complaints:
Procedure "Handling of customer complaints" was reviewed. Customer complaints could be received in written or verbal form. QA Manager was responsible for handling of complaints. Complaints were logged in the complaint register. In 2012 there were no customer complaints registered. One complaint was registered in 2013. According to the procedure, complaints should be trended. QA was responsible to follow up CAPAs and ensure the feedback to the customers.

Internal audits:
Self-inspections were performed as per SOP "Quality audits". QA Manager was responsible for overall implementation of the procedure. Audits observations were classified as:

- Critical
- Major
- Minor

Internal audits were carried out by QA and QC personnel twice per year. QC and QA Managers attendance certificates for a training course Laboratory Quality Management System & Internal audit as per ISO 17025:2005 were presented to the inspectors. Last internal audit was carried out on 5 August 2013 and audit report was presented to the inspectors. The audit had been conducted with help of a check list covering elements of QMS and technical requirements. Non-conformities were recorded in Audit Observation form. Afterwards summary of internal audit was written and approved by the President Technical – operations. Specific form was used to record individual internal audit non-conformities. This form consisted of:

- Description of non-conformity
- Corrective actions (CA) proposed by the auditee
- Responsibility & time required for CA given by the auditee
- CA taken given by the auditee
- CA verified & comments if any signed by the auditor Quality manager

Non-conformities and CA taken were discussed during the Management review meetings. Internal audit report was not reviewed by the inspectors.

Non-conforming (NC) work/Corrective and preventive actions (CAPA):
A CAPA procedure was reviewed. Person responsible for preparing a CAPA plan was Department head or designee. QA Head was responsible for maintaining the CAPA register, issuing CAPA request and reviewing of CAPAs, evaluating effectiveness of CAPA and issuing interim and final reports. The procedure was applicable for:

- Deviations / non-conformance
- Audit observations
- Inspection and test data (analytical data and test data review)
- Equipment calibration and maintenance
- Training records
- Change control records
- Laboratory deviations
- Equipment malfunctions
- QS review findings
- Complaints
- Regulatory changes
- Legal claims
- Customer audits

Management review: The management review was carried out twice per year. The procedure was explained in the quality system procedure. Management team consisted of:

- Chairman
- Director – Operations
- Manager QA
- President - Technical
- Manager QC
- Section Heads/ Group Leaders

The latest management review had been performed on 7 August 2013. Before the meeting notification was sent to all management team members and contained proposed agenda for discussion. Minutes of the meeting were signed by all participating members and approved by the President – Technical Operations. Internal audits findings were discussed in details and responsible person for CAPAs as well as target date was specified. Review contained also Key Personnel Indicators Measurement (KPI) what was not described in the procedure. It was recommended to specify KPI procedure in written document.

Change control (CC):
Procedure “Change control management” was spot checked. The procedure was applicable to changes to facilities, materials, equipment, computerized systems and/or processes used in the testing of pharmaceuticals or other life science products and materials. CC register was presented to inspectors.

According to the procedure, CC should be classified as:
- Critical
- Major
- Minor

IQ, OQ and PQ and calibration reports of shifted equipment's were available for inspection.

2.3 Control of documentation

Procedure "Design & control of document" was spot checked.

An updated master list of quality system procedures and master list of documents – SOPs were available and presented to the inspectors. Document review/changes and distribution record of the document were attached to the document master copy. Documents were reviewed at least every 2 years.

2.4 Records

Retention time for the different types of quality and laboratory records was defined 5 years. Records were kept in documentation archive. Archive room ensured secure storage and retrieval of documents. Access to the archive room was restricted to designated personnel. The Laboratory explained that in the near future they are planning to purchase movable document storage racks and to move archive to another room.

2.5 Data-processing equipment

Procedure "Back-up & restoration, archival & retrieval of laboratory electronic data management" was reviewed. IT administrator was responsible for data back up and restoration. Performed back-ups register was shown to the inspectors.

2.6 Personnel

Procedure "Training of personnel" was reviewed. There were several types of training defined in the procedure:
- GxP
- On-going training
- Refresher training (for employee who was absent for more than 6 months and less than one year)
- Orientation training (for new employee)
- Retraining (for employee who was absent for more than 1 year)
- Role playing
- Split sample testing

Training effectiveness was evaluated by:
- Written tests/questionnaire
- Role playing by trainee and trainer
- Observing the trainee
- Presentation by trainee on the topic on which the trainee was trained.

Evaluation of effectiveness was documented in Employee training cards/files. Training records were maintained in a training binder.

Employee training card and training file for QC officer (analyst instrumental section) was spot checked. Training evaluation questionnaire for training on the procedure "Reference standards" was reviewed.

"Analyst qualification" procedure was reviewed. The analyst was to analyse an already analysed sample and results were compared. Acceptance criteria for % variance of results between analysts were specified.

Training files were kept by the QA department. Training schedule for 2013 was shown to the inspectors.

Job descriptions:
The following job descriptions (responsibilities) were spot checked and found to be adequate:

- Assistant Manager QA. Senior Executive QA had overall responsibility for implementation &monitoring of QMS in absence of QA Manager
- Assistant manager QC
- Senior executive QC. This person was responsible for maintenance of reference standards, working standards, stock standard solutions and Material Safety Data Sheets.

Job responsibilities were signed ("Read & Accepted") by the designated person.

2.7 Premises

Chemistry section:
The chemical laboratory facilities were acceptable in size and suitable for performing of analyses. Surfaces and finishing were suitable for easy maintenance. Premises were kept clean and tidy to ensure safe work. Temperature was routinely controlled and recorded in the different areas.

Microbiology section:
The microbiological laboratory facilities were of a suitable size and construction and were designed to suit the functions and operations to be conducted in them. Surfaces and finishing were suitable. Premises were kept clean and tidy.

A single air handling unit (AHU) was installed to supply the air to the classified area including change rooms. AHU consisted of EU 4, EU5, EU9 2 filters and EU 13 HEPA filter. HEPA filter was installed in the plenum. Biosafety cabinet was used for culture handling and LAF for handling of sterile media and conducting microbial limit test.

Microbiological laboratory premises, LAF and biosafety cabinet environmental conditions were monitored microbiologically once in a month. Area classification had been carried out (outsourced, class 100'000), but not reviewed in detail during the inspection.

2.8 Equipment, instruments and other devices of physical/chemical and microbiological laboratories:

Each item of equipment and instrument used for testing, verification and calibration was uniquely identified. IQ, OQ and PQ were carried out for laboratory equipment and instruments after shifting to the new premises. Labels attached to the equipment and instruments showed calibration date, calibration due date and preventive maintenance due date.

Micropipettes were calibrated once in three months. Calibration report was spot checked.

2.9 Contracts

A contract had been signed with another company including sterility testing and endotoxin testing. Audit report of the contract acceptor was available.

2.10 Reagents

Purchases

Reagents were purchased from approved suppliers.

Evaluation of suppliers

Approved list of suppliers/vendors was discussed – the Quality unit should approve the list (in addition to procurement & finance personnel).

Solvents and reagents

Small amount of solvents used for analysis were stored in metal cupboards in the chemistry laboratory. Solvents were assigned expiry date for two years from the date of opening, if not specified earlier by the manufacturer. Large amount of solvents were stored in a chemical store room in flame proof cupboards.

Smaller amount of reagents used for analysis were stored in the chemistry laboratory on shelves. Dry reagents were assigned expiry date of three years from the date of opening, if not specified earlier by the manufacturer. SOP covered handling of reagents and indicators. A separate SOP covered handling of chemicals.

Updated inventory lists were available for reagents and solvents.

Water

Purified water (PW)

Water was sourced internally using a deionisation and RO unit. It was explained that the water system was sanitized/cleaned every two months. Sanitisation/cleaning records were presented to the inspectors.

HPLC grade water

MilliQ water purification unit with a storage container was used.

Reagent solutions prepared in the laboratory
SOP covered preparation and standardisations of volumetric solutions. Short-dated titration solutions had not been used.

Culture Media
Dehydrated culture media were used to prepare culture media ready to use. Dehydrated culture media were adequately stored under controlled conditions, according to the supplier information. The growth promotion tests were performed for every batch of dehydrated culture media and after preparation and sterilization of liquid culture media.

Culture media prepared by the laboratory were clearly labelled.

2.11 Reference substances and reference materials

Chemistry sector
In most cases standards were provided by customers. So far the Laboratory did not have experience in preparing working standards from primary/reference standards.

There were two SOPs on standard substances: for reference standards (pharmacopoeia or characterised by the customer) and for working standards.

Microbiology sector
All strains required for growth promotion and microbiological enumeration recovery tests were available. At the time of inspection, 13 strains were available and were adequately stored.

2.12 Calibration, validation and verification of equipment, instruments and other devices

All the equipment, instrument and other devices used for testing were verified and calibrated following the corresponding schedule and SOPs. There was a person responsible for each item of equipment, instrument or other device. On spot checks the calibration schedule was followed.

Preventive maintenance (PM) schedule was presented to the inspectors.

pH meters verification was adequately carried out before the work using six buffer solutions.

Analytical balance daily verification and monthly calibration was adequately carried out. Micro analytical balance (range 3 mg – 20 g) verification and calibration reports were reviewed and found to be adequate. Standard weights were available and were traceable to the calibration certificates.

Ultraviolet spectrophotometer calibration was adequately carried out every 6 months.

Dissolution equipment's were mechanically adequately calibrated every month and SS test was performed using Prednisolone standard every 6 months. Dissolution equipment

mechanical calibration set was available and was traceable to the individual calibration certificates.

HPLCs were adequately calibrated every six months.

On spot checks, the required reagents for calibrations were available and were traceable.

The Laboratory used Class A volumetric glassware for quantitative analysis. Upon receipt glassware was calibrated.

Excel datasheets
Excel data sheets were used for assay (HPLC and UV), uniformity of content (HPLC and UV), and dissolution profile (HPLC and UV, related substances (HPLC) calculations. Procedure "Validation & use of Excel sheets" along with Validation report of Excel sheet used for calculation of assay by HPLC was spot checked. Excel files were password protected, password was known only by QA Head. Sealed envelopes with all the passwords were available with management. File was "read only file". For every change to the Formula present in the cell, Excel sheet should be verified.

Autoclave cycles validation:
The microbiology laboratory had 2 autoclaves: one was used for media, clothing and instrument sterilization, and the other for media destruction.

Temperature & humidity mapping
Mapping studies lasted 24 h, readings were recorded every 10 min; the Laboratory used a computer software to receive and record temperatures in most temperature-controlled locations, both in mapping studies (with additional sensors) and in routine monitoring.

Walk-in stability chamber (30 °C / 75%) temperature mapping was presented to the inspectors. 8 T/RH sensors were used for the study. Microbiology laboratory incubator (30 °C – 35 °C) temperature mapping was also presented to the inspectors. 8 T sensors were used for the study.

2.13 Traceability
The reference material(s), equipment(s), reagent(s), culture media, analyst(s), calculation(s) were suitably recorded in the analytical report and therefore traceability was deemed suitable and sufficient.

2.14 Incoming samples
The Laboratory was not responsible for sampling; samples were received from the customers. SLS stated that they had Technical Agreements (TA) with all customers. TA with one of their customer was spot checked. Responsibilities, sample handling and testing and other activities were clearly specified.

SOP "Contract review and registration" was reviewed. The SOP was applicable for all types of samples received at SLS for testing, method development & validation, stability study programs and in-house samples testing.

Verification of the sample (by appearance) was carried out upon receipt, availability of standard substances, HPLC columns etc ("resources") was checked. The sample was registered by CSC in Job Order Register (JOR). In case several samples were received from the same customer within the same delivery, the JOR number was the same, but product samples were assigned individual traceable sample numbers.

Then the samples along with JOF for routine samples and respective filled TRF were sent to the QC Manager. Samples were cross verified at QC and entered to the Analytical reference register.

Sample registration was done manually. LIMS was used for stability sample management only.

Samples for analysis were stored in a separate sample staging room. T and RH were controlled and recorded (minimum and maximum) twice per day. T in the refrigerator and freezer was continuously monitored and recorded on line by the software every 30 minutes.

2.15 Analytical worksheet

Complete set of Analytical Report including Analytical worksheet (Amoxicillin 500 mg capsules) was reviewed. Calculations were checked by the Group leader or designee. Analytical worksheets were reviewed by QA Data reviewer and approved by QC Manager.

2.16 Validation of analytical procedures

SLS had done several method validations for manufacturers of medicinal products.
SLS stated that for routine testing they used customers' methods.
Analytical method transfer (AMT) had been conducted in several cases, when required by the customer. Simvastatin tablet AMT was reviewed.

2.17 Testing

Procedure "Testing of samples & Reporting results of analysis" was reviewed. This procedure was applicable for chemical and microbiological analysis. The following documents related to the tests were issued by the QA:

- Analytical work order
- Analytical data sheet
- Analytical report cover sheet for routine samples/stability samples

According to the procedure, samples should be tested preferably on FIFO basis and any sample not later than 30 days from the date of registration of sample. If the samples were not tested within 30 days, a deviation report should be raised.

Reporting of the results:
When all the tests were completed the results were entered in the form "Results of analysis" (ROA) which contained information about test parameter results and limits. Afterwards full Analytical Report (AR) was prepared which contained below listed documents:

- Duly filled completed Request for Analytical work record/analytical data sheet
- Completed ROA sheet
- Completed Analytical work record (AWR)
- Analytical data sheets including unused data sheets
- Duly filled request for additional AWR/analytical data sheets
- Analytical report cover sheet
- Microbiological report, if applicable
- External laboratory test reports, if any
- Photocopy of Deviation report/OOS or OOT report, if any
- Defective sheet, is any

Results obtained were compared with the relevant specifications.

Specifications
Customer specifications were registered in Customer Specification & Test methods entry register and kept in QC.

Approved list of Pharmacopoeias: USP, British Pharmacopoeia, European Pharmacopoeia and Indian Pharmacopoeia were available.

Microbial tests
Procedure "Microbial limit test" was reviewed. SOP was written according to the Harmonized method.

Investigation of out of specification (OOS) results
SOP OOS described a procedure which was generally acceptable. OOS registers were maintained. Specific OOS cases were reviewed.

2.18 Evaluation of test results

Review of Analytical reports (AR):
Compiled ARs were checked by concerned Section Head and afterwards ARs were submitted to the Head – QC for final verification. A review of raw data, weighing records, equipment printouts, spectra and chromatograms were done by the Data Reviewer in QA section.

2.19 Certificate of Analysis (CoA)

Procedure "Certificate of Analysis was reviewed.
CoA or Test report (TR) was prepared by the QA Executive or his designate. Unique number was allocated to the CoA/TR. This unique number was traceable to the sample unique number. CoA/TR was reviewed against the Results of Analysis and signed by QA Head/Manager.

2.20 Retained samples

Samples were retained for 1 year, if not otherwise specified by the customers. Retained samples were stored safely under controlled conditions. The Laboratory kept a register of retained samples. Currently there were no samples which should be stored at cool temperature. SLS stated that they are planning to purchase a fridge and freezer in the nearest future as well as perform T mapping.

2.21 Safety

Safety and eye showers were seen to be available. Procedure "Safety" SLS/QSP – 031, revision 00 was spot checked. Smoking, eating and drinking was not allowed in the laboratory. Staff was wearing laboratory protective clothing.

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 Stabicon Life Sciences Pvt. Ltd, located at Plot No. 28, Bommasandra Industrial Area (Sub-layout), 4th Phase, Jigani hobli, Anekal Taluk, Bangalore - 560 100, India was considered to be operating at an acceptable level of compliance with in compliance with WHO Good Practices for Pharmaceutical 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.