



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Quality Control Laboratory**

Part 1: General information

Name of QC Laboratory	TÜV SÜD PSB Pte Ltd		
Physical address	1 Science Park Drive, Singapore 118221		
Contact person and email address.	Dr Li Sihai sihai.li@tuv-sud-psb.sg		
Date of inspection	1-2 December 2014		
Type of inspection	Routine inspection		
Type(s) of testing included in the inspection	Physical, chemical, and microbiological testing, including instrumentation		
Summary of the testing activities performed by the QC Laboratory	<i>Type of analysis</i>	<i>Finished products</i>	<i>Active pharmaceutical ingredients</i>
	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), , UV-VIS spectrophotometry, FTIR	HPLC (UV-Vis, fluorescence), GC (FID, MS), TLC, UV-VIS spectrophotometry, AAS,

			UHPLC
	Assay, impurities and related substances	HPLC (UV-Vis, fluorescence,), GC (FID, MS), TLC, HPTLC, UV-VIS spectrophotometry, AAS, UHPLC	HPLC (UV-Vis, fluorescence,), GC (FID, MS), TLC, UV-VIS spectrophotometry, AAS, UHPLC
	Microbiological tests	Sterility test, microbial purity, test for pyrogens, bacterial endotoxins test (LAL), microbial assay	Microbial purity, test for pyrogens, bacterial endotoxins test (LAL), microbial assay
	Stability studies	RH chamber	RH chamber

Part 2: Summary

General information about the company and site

TÜV SÜD PSB, headquartered in Singapore, provides services in product testing, certification, inspection and auditing, which together represent a comprehensive and integrated suite of services aimed at helping companies achieve business excellence.

The company employs more than 820 employees in the Association of Southeast Asian Nations (ASEAN) region: Singapore, Indonesia, Malaysia, Philippines, Thailand and Vietnam. Of these, more than 488 staffs work at the headquarter in Singapore. With a global network of partners and international recognition arrangements, TÜV SÜD PSB serves customers from all over the world.

TÜV SÜD PSB has more than 30 years' experience in testing and certification. Its capabilities in pharmaceutical testing include chemical, microbiological and biological testing. Chemical tests performed by its laboratories include assay, uniformity of content, dissolution test, disintegration test, etc. The microbiology laboratory conducts microbial limit tests for both oral and topical applications as well as sterility testing. TÜV SÜD PSB also provides biological testing including both *In-vitro* and *In-vivo* testing.

Products tested include various types of drugs e.g. contraceptive pills and injectables, Paracetamol tablets, Amoxicillin tablets, Ciprofloxacin tablets, Doxycycline tablets, Co-trimoxazole tablets, Oral Rehydration Salts and raw materials to BP, EU and USP standards as well as medical devices such as surgical gloves, gowns, IUDs, implants and gloves. Other products tested include cough syrups, health supplements, and Chinese Proprietary medicines.

Its clients include multinational companies (MNC), local companies, government and international buying houses in Singapore and overseas.

TÜV SÜB PSB offers a wide range of testing services in 3 major fields: Chemical and Materials, Electrical and Electronics, and Mechanical.

Chemical & Materials

- Food and pharmaceutical testing
- Microbiological and DNA based testing
- In vivo and In vitro testing
- Micro-contamination analysis and surface analysis
- Coatings evaluation and construction materials testing
- Environmental monitoring and analysis

Electrical & Electronics

- Environmental and reliability tests
- Electrical safety tests
- Electromagnetic compatibility tests

Mechanical

- Building and industrial materials tests
- Consumer product mechanical safety tests
- Fire safety and security tests

History of WHO and/or regulatory agency inspections

A WHO routine inspection of TÜV SÜD PSB Pte Ltd Singapore was conducted on the above-mentioned dates. The last inspection of this laboratory was performed by WHO in March 2012.

The inspection focussed on the quality management system and its analytical activities, in particular the areas of quality control testing prequalified by the WHO.

Inspected Areas

The inspection focused on the quality management system of the laboratory and its analytical activities for physical/chemical (identification, assay, impurities, related substances using UV-VIS, HPLC, GC, IR) and microbiological tests (sterility and microbial limit test). The requirements of the WHO Good Practices for Pharmaceutical Quality Control Laboratories (Annex 1 of TRS 957) and WHO Technical Report Series No 961 (Annex 2, WHO Good Practices for Pharmaceutical Microbiology Laboratories) covered in the inspection were as follows:

- Organization and personnel
- Quality management
- Premises and Equipment
- Documentation
- Sample flow and sample storage
- Reagents and reference substances
- Traceability
- Safety

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

- Dr LIN Jianhua, Vice President, Chemical Centre
- Dr LI Sihai, Assistant Vice President, Chemical Centre
- Ms LIM Hwee Jen, Product Manager, Chemical & Materials– Food & Pharmaceutical
- Ms LEONG Yin Pheng (Mrs Kam), Product Manager, Chemical Centre
- Mr Randy Chin Kok Fei, Microbiologist, Chemical Centre
- Ms CHEW Wan Yu, Microbiologist, Chemical Centre
- Mr LOO Jia Jian (JJ), Engineer, Sales, Chemical Centre

2.1 Organization and management

There was an organization structure in place comprising managerial and technical personnel with the authority and resources needed to operate a laboratory. The management and personnel working in the organization were independent without any conflict of interest. There was an organization chart available showing clearly the roles and responsibilities of various key personnel.

2.2 Quality management system

The laboratory has a quality management manual in place which provided administration of quality policy, objectives, organization charts, responsibilities and authorities and references, among others.

Some of the key procedures e.g. Out of Specification (OOS), Proficiency Testing (PT), and laboratory staff training procedures) were found to be lacking or inadequate in order to meet current requirements.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.3 Control of documents

The documentation system was based on ISO 9001:2008 and ISO 17025:2005 QMS which provided direction on the management of documents. Basically, all quality procedure documents were prepared after the review and approval by authorised personnel. Each document was given a unique number with version number included. The Quality Manual and SOPs are reviewed periodically, at least once every 5 years.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.4 Records

In general, this area was not found to be satisfactory as several examples of poor records both electronically and paper-based were noted. While reviewing some of the executed records, it was noted that analysts were not provided with laboratory notebooks to record actual results of testing. Similarly, inadequate controls were noted for electronic records in various computer based systems.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.5 Data-processing equipment

This area was found to be inadequate as the current computer-based systems for management of analytical data did not assure adequate confidence of the test data. Several issues were noted in a number of aspects which included but not limited to access control, audit trail, back-up, date/time and zones. During the inspection of HPLC computer systems, it appeared that back-ups were not done as chromatograms

were still available in the system since 2012. Similarly, documents (various data files) were still available since 2005; these cast doubt on timely back-up of data.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.6 Personnel

In general, the personnel met during the inspection appeared to be confident, knowledgeable and cooperative throughout the inspection. Training could be further improved as weaknesses were noted on the training assessments, and including objectivity in reviewing understanding from training of various subjects / topics / tests, and the need for re-training.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.7 Premises

Overall, the laboratory had adequate space with the exception of the microbiology laboratory, which was found to be congested. Space appeared to be insufficient for the storage of various autoclaves, washing and equipment (balances).

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.8 Equipment, instruments and other devices

In general, the laboratory was equipped with modern equipment (HPLC, GC, IR, balances, autoclaves, isolator, etc) and instruments.

2.9 Contracts

Contract between TUV SUD PSB and UN Population Fund (UNFPA), Denmark dated 8/10/2012 for Petogen injection, National Malaria Elimination Programme (NMEP) dated 6 November 2014, Society for Family Health (SFH), Nigeria dated 12/9/2012 and Marie Stopes International (MSI) dated 30/6/2014 were reviewed. It was noted that no procedure was available on renewal of contracts as all the service agreements were based on client requirements and tender periods.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.10 Reagents

Not inspected.

2.11 Reference substances and reference materials

It was noted that the laboratory uses primary reference standards for the routine testing of various pharmaceutical products. The primary reference standards were procured from USPRS, EPCRS and Int. Pharmacopoeia and stored in refrigerator under 5°C. There was however no considerations given on proper storage of these reference standards once they were opened for initial use or retained for another use. It is to be noted that pharmacopoeias do not guarantee multiple use of their reference standards and make it clear that they are for single use if reference standards were meant for quantitative analysis.

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

Master calibration schedule was available; however several weaknesses were noted. For example, autoclaves were qualified once every three months using chemical indicators (CI) but biological indicators (BI) were not used when load was autoclaved. The laboratory should review the current requirement and perform the test accordingly.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.13 Traceability

The analysis was done using primary reference standards procured from pharmacopoeial commissions and ATCC. The standard weights were calibrated against National Standards. Although, the primary reference standards (USPRS, EPCRS, and Int. Pharm. CRS) used for routine testing were stored in a refrigerator (below 5°C), the storage conditions could be further improved to protect the quality and stability of opened reference standards which were retained for further use.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.14 Incoming samples

There was a system for receiving sample and a TRAK IT computer system for tracking samples from clients. However, there were several weaknesses in the handling of incoming samples.

It was also noted that the laboratory did not maintain a list of products / samples specifically for pharmaceuticals as the list provided included food products as well.

This made it difficult to assess how many pharmaceutical products were received by the laboratory in certain period of time.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.15 Analytical sheet

In general, analysts were not issued with laboratory notebooks or analytical worksheets to record down test results.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.16 Validation of analytical procedures

Most analytical procedures follow pharmacopoeial monographs. However major changes in compendial test methods used for routine testing were made without validation or re-validation of the analytical procedures.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.17 Testing

In general, modern test methods and equipment were available in the laboratory and samples were tested in accordance with the work plan of the laboratory. During inspection, it was noted that sterility testing was done by both the direct inoculation and membrane filtration method.

2.18 Evaluation of results

Test results were evaluated by the laboratory manager to ensure that they meet the specifications used. Out of specifications (OOS) and doubtful (atypical) results were investigated. A SOP on OOS was available but criteria on retesting and hypothesis testing did not meet the international norms, therefore it was advised to refer to the UKMHRA guideline on OOS for completeness and better clarity. However, some weaknesses were observed in this area.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

2.19 Certificate of analysis

A certificate of analysis was prepared for each batch of a substance or finished product tested.

2.20 Retained samples

Samples were retained by the laboratory based on request from clients. These samples were retained for 3 months after testing before they were discarded. The retention sample room was not inspected due to lack of time.

2.21 Safety

Safety showers and personnel protective equipment were provided for laboratory personnel. However, at the Bacteriology Room where MLT were conducted, hairnets were not worn by the operators.

The observations raised from this section have been satisfactorily addressed, and it will be verified during future inspections.

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, *TUV SUD PSB, Singapore* 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.