World Health Organization

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Prequalification Team Inspection services
WHO INSPECTION REPORT
of the Quality Control Laboratory

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<tr><td>Corporate address of Laboratory</td><td colspan="3">1 Science Park Drive
Singapore 118221</td></tr>
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<tr><td>Physical / Chemical analysis</td><td>pH, density, refractometry, viscosity, loss on drying, water content, disintegration, dissolution, uniformity of dosage units (mass, content), friability, tablet hardness, particulate matter test</td><td>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</td></tr>
<tr><td>Identification</td><td>HPLC (UV-Vis), GC (FID), GC/MS, TLC, HPTLC, UV-VIS spectrophotometry, IR, AAS</td><td>HPLC (UV-Vis), GC (FID), GC/MS, TLC, HPTLC, UV-VIS spectrophotometry, IR, FTIR, AAS, chemical reaction, UHPLC</td></tr>
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	Assay, impurities and related substances	HPLC (UV-Vis, DAD, fluorescence, light scattering detection), GC (FID), TLC, HPTLC, UV-VIS spectrophotometry, AAS, volumetric titrations, potentiometry, nitrogen assay, UHPLC	HPLC (UV-Vis, DAD, fluorescence, light scattering detection), GC (FID), TLC, HPTLC, UV-VIS spectrophotometry, AAS, volumetric titrations, potentiometry, nitrogen assay, UHPLC	
	Microbiological analysis	Sterility test, microbial purity, test for pyrogens, bacterial endotoxins test (LAL), microbial assay	Microbial assay, Sterility test, bacterial endotoxins test (LAL), Microbial Limit Test	

Inspection details	
Dates of inspection	24-26 October 2016
Type of inspection	Routine inspection
Introduction	
History	The laboratory has been regularly inspected by WHO-PQT. The last WHO-PQT inspecti place in December 2014.
Scope and limitations	
Areas inspected	The scope of this inspection covered the laboratory activities relating to the pharmaceutical product testing i.e. the pharmaceutical testing activities performed by the Food, Pharmaceutical & Biological Testing Section including chemical, microbiological and biological testing for Finished Pharmaceutical Products (FPP) and Active Pharmaceutical Ingredients (APIs).
Restrictions	None
Out of scope	NA
Key persons met	Goh Wee Hong, Senior Vice President Lin Jianhua, Vice President Lim Hwee Jen, Product Manager Lim Yee Teng, Assistant Vice President Shirley Tjoa, Chemist Leong Yin Pheng, Senior Consultant Li Sihai, Assistant Vice President, Quality Management Representative (Chemical) Chew Wan Yu, Executive Microbiologist, Deputy Quality Management Representative (Chemical) Randy Chin Kok Fei, Product Manager
Abbreviations	AHU – air handling unit ALCOA – attributable, legible, contemporaneous, original and accurate

	API	active pharmaceutical ingredient		
	BDL	below detection limit		
	CAPA	corrective actions and preventive actions		
	CC	change control		
	CFU	colony-forming unit		
	CoA	certificate of analysis		
	DQ	design qualification		
	EM	environmental monitoring		
	FAT	factory acceptance test		
	FMEA	failure modes and effects analysis		
	FPP	finished pharmaceutical product		
	FTA	fault tree analysis		
	FTIR	Fourier transform infrared spectrometer		
	GC	gas chromatograph		
	GMP	good manufacturing practice		
	HACCP	hazard analysis and critical control points		
	HPLC	high-performance liquid chromatograph		
	HVAC	heating, ventilation and air conditioning		
	IR	infrared spectrophotometer		
	IQ	installation qualification		
	KF	Karl Fisher		
	LAF	laminar air flow		
	LIMS	laboratory information management system		
	LoD	limit of detection		
	LOD	loss on drying		
	MB	microbiology		
	MBL	microbiology laboratory		
	MR	management review		
	NMR	nuclear magnetic resonance spectroscopy		
	NRA	national regulatory agency		
	OQ	operational qualification		
	PHA	process hazard analysis		
	PM	preventive maintenance		
	PQ	performance qualification		
	QA	quality assurance		
	QC	quality control		
	QCL	quality control laboratory		
	QRM	quality risk management		
	RA	risk assessment		
	RCA	root cause analysis		
	SOP	standard operating procedure		

	TAMC	total aerobic microbial count		
	TFC	total fungi count		
	TLC	thin layer chromatography		
	URS	user requirements specifications		
	UV	ultraviolet-visible spectrophotometer		

Part 2	Brief summary of the findings and recommendations (where applicable)

TUV SUD PSB was previously known as Singapore Productivity and Standard Board (PSB) which in April 2006 merged with TUV SUD and became TUV SUD PSB Corporate Pte (TUV SUD PSB) Ltd. It changed its name to the current name a year later (April 2007). The test laboratories of TUV SUD PSB provided services include product testing, certification, inspection and auditing, across the Association of Southeast Asian Nations (ASEAN) regions including Singapore, Indonesia, Malaysia, Philippines, Thailand and Viet Nam with Singapore as the headquarter.

The following listed the summary of the testing activities carried out by the TUV:

1. Chemical & Materials test
2. Electrical & Electronics tests
3. Mechanical tests

Brief summary of the findings and comments

1. Organization and management

The laboratory had managerial and technical personnel to carry out their duties. Organizational charts, the organization and management structure of the laboratory and its place in corporate organization was presented to the inspectors. Responsibilities were specified.

The laboratory maintained a registry for receiving, distributing and supervising the consignment of the samples to the specific units; and keeping records on all incoming samples and accompanying documents.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

2. Quality management system

The Quality Management Manual clearly defined the quality policy, objectives, organization charts, responsibilities, authorities, references and more.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

3. Control of documentation

Documented procedures were in place to control the documents. Authorized SOP Master List identifying the current version, status and distribution of documents was available and presented to the inspectors. Documents had a unique identifier, version number and date of implementation. A system of change control was in place to inform staff of new and revised procedures.

All procedures were prepared and reviewed by authorized personnel. Each document was given a unique number and version number and was found to review periodically every 5 years.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

4. Records

Original observations, calculations and derived data, calibration, validation and verification records and final results, were retained. The records included the data recorded in analytical worksheets. The records included the identity of the personnel involved in the sampling, preparation and testing of the samples.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

5. Data processing equipment

The company employed Empower for managing the data generated for chromatographic analysis.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

6. Personnel

Generally the laboratory had sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions. Staff members undergoing training were supervised and were assessed on completion of the training. Personnel performing specific tasks were appropriately qualified in terms of their education, training and experience, as required. Current job descriptions were maintained.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

7. Premises

Generally, the chemical and microbiological laboratories were adequate in size and well maintain with proper cleaning regime and pest control. In addition, there were procedures in place for the disposal of chemical/reagents/microbiological waste. Microbiological testing was performed in a separate laboratory.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

8. Equipment, instrument and other devices

Generally the laboratory had test equipment, instruments and other devices for the performance of the tests and/or calibrations, validations and verifications. Calibration status labels were attached to instruments.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

9. Contracts

Laboratory had a procedure for the selection and purchasing of services and supplies. Contract agreement between UN agency and TUV SUD PSB was reviewed and found the responsibilities of the contract acceptor and contract giver were defined.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

10. Reagents

Generally reagents and chemicals were purchased from approved suppliers and were accompanied by the certificate of analysis, and the material safety data sheets as appropriate. Reagents in the chemical laboratory namely HPLC mobile phase were found to be properly labelled.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

11. Reference substances and reference materials

Due to time limitation, this area was not inspected.

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

A system was in place for the maintenance and calibration of equipment and instrument used in the laboratory.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

13. Traceability

The results of an analysis were traceable to reference substances, equipment and instruments used for analysis.

14. Incoming samples

A system was in place for receiving of incoming samples to the laboratory. Incoming samples were properly labelled with product identity. Once samples were received and checked, the samples were recorded and a unique laboratory number were given. A list of all incoming samples was maintained for tracking of the test status.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

15. Analytical worksheet

The analytical worksheets were used by analysts for recording information about the sample, the test procedure, calculations and the results of testing. It was complemented by the raw data obtained in the analysis. Analytical work sheets contained sample registration ID No, the date on which the analysis was started and completed, the name and signature of the analyst and other relevant information. Analytical worksheets were signed by the responsible analysts, verified and approved and signed by the supervisor/reviewer.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

16. Validation of analytical procedures

The laboratory used both pharmacopeia method and customer in-house methods. The analytical methods were not verified by the laboratory prior to their uses.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

17. Testing

Samples were tested in accordance with the work plan of the laboratory and agreements with customers. Test results were reviewed and evaluated. OOS results were investigated.

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

18. Evaluation of test results

Test results were reviewed and evaluated. The OOS procedure was in place. A number of OOS investigation reports were discussed**.**

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

19. Certificate of analysis

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

The issues related to this section have been adequately addressed by the laboratory, and the same shall be verified during future inspections.

20. Retained samples

Procedure was in place for retention of samples. The samples were retained by the laboratory on request from the customers for a period of 3 months.

21. Safety

Safety showers were installed and laboratory personnel were provided with protective clothing and equipment. No observation was recorded for this section.

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 the, TUV SUD PSB Pvt Ltd, located at 1 Science Park Drive, Singapore 118221 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 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.

PART 4

List of GMP guidelines referenced in the inspection

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 TRS No. 961, 957), Annex 1
   http://www.who.int/medicines/publications/44threport/en/

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

3. 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

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six 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/

5. 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

6. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   Short name: WHO TRS No. 961, Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

7. 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

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert 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/

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. 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/

14. 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

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