

**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer**

Part 1	General information
Manufacturers details	
Company information	
Name of manufacturer	Laurus Labs Limited (Unit-2)
Corporate address of manufacturer	Laurus Labs Limited 2 nd Floor, Serene Chambers Road # 7, Banjara Hills Hyderabad – 500 034 India
Inspected site	
Address of inspected manufacturing site if different from that given above	Plot No:19, 20 & 21 Atchutapuram Mandal, Visakhapatnam-District Western Sector, APSEZ, Andhra Pradesh, 531011, India
Unit / block / workshop number	Unit-2 (Unit Code: VSP-2)
Manufacturing license number, (delete if not applicable)	16/VSP/AP/2015/F&B/CC (Form-25 dated 15/9/2015)
Inspection details	
Dates of inspection	13-17 March 2017
Type of inspection	Initial cGMP inspection
Introduction	
Brief summary of the manufacturing activities	At the time of inspection, there were two manufacturing blocks (MB) in the facility; MB01 for Drug Products manufacturing for oral solid dosage forms (tablets and capsules) and MB02 for drug substances manufacturing. The site is located at APSEZ, Atchutapuram, Visakhapatnam, Andhra Pradesh, India. The Drug Product Manufacturing block has a built up area of 14,068 Sq. Mts. Phase-I (6983 Sq. mts.) which was in operation. At the time of inspection Phase –II was under expansion and was targeted to be completed in July 2017. Drug Product Manufacturing block consisted of three floors.

	- Ground floor: Raw Material Warehouse, Manufacturing area, Primary & Secondary Packing area, Change rooms, Secondary, Packaging material warehouse and Finished Goods and warehouse. - First floor; Quality Control, Quality Assurance and technical area for housing AHU's. - Second floor: Stability chambers, Microbiology Lab (under construction. Target date August 2017)
General information about the company and site	Laurus Labs Private Limited was incorporated as Laurus Labs Limited in December-2016, when it got listed in stock exchanges in India. It is a pharmaceutical services organization head-quartered in Hyderabad, Telangana, India. Laurus Labs Limited (Laurus) offers medicinal chemistry services, drug product and drug substances development, analytical services, contract manufacturing, small and large scale manufacturing of generic drug substances/products with major focus on Anti-retrovirals and Oncology molecules.
History	This is the first WHO-PQT inspection of Laurus Labs Limited, Unit-2, a drug product site, located at Plot No:19, 20 & 21, Atchutapuram Mandal, Visakhapatnam-District, Western Sector, APSEZ, Andhra Pradesh, 531011, India. The drug product site of Laurus Labs Limited was inspected by the USFDA in November/December 2016. The company had sent response to FDA-483 observations to USFDA and awaiting establishment inspection report at the time of inspection. It was noted that the company had filed 2 Abbreviated New Drug Applications (ANDAs) with the USFDA. The drug product site was also inspected by Behörde für Gesundheit und Verbraucherschutz (BGV) Hamburg and was approved.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Pharmaceutical quality system Production Quality control Personnel Utilities Materials
Restrictions	None
Out of scope	Drug substance manufacturing block (MB-02) Drug product facility currently under expansion Microbiology laboratory under construction
WHO product numbers covered by the inspection	Tenofovir Disoproxil (fumarate) (TDF) Tablet, Film-coated 300mg (HA679)

Abbreviations	AHU	air handling unit	
	ALCOA	attributable, legible, contemporaneous, original and accurate	

API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
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
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system
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 comments (where applicable)

Brief summary of the findings and comments

1. Pharmaceutical quality system

In general PQS was implemented. Production and control operations were specified in written form and c GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release; regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

QMS system consisted of the following elements:

- Validation and qualification
- Procedures (SOP) / documentation
- Change management
- Self-inspection
- Vendor management
- PQR
- CAPA management
- In-process QA / batch release
- Training development

The SOP “Risk management” was discussed.

The SOP “Annual product quality review”, deviations and corrective and preventive action was discussed.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were defined and systematically reviewed. Qualifications and validations were performed. Necessary resources were provided and records were made during manufacture. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

3. Sanitation and hygiene

The company had an SOP as the basis for its approach to personal hygiene and sanitation in its production facilities. Areas were cleaned frequently in accordance with an approved written program and SOPs. Handling and storing of cleaning aids like mops and wipes was discussed, with focus at more practical arrangements for the cleaning personnel. Microbial monitoring was regularly performed.

4. Qualification and validation

The key elements of a qualification and validation programme were defined and documented in a validation master plan. The Validation Master Plan (VMP) outlined the policy and approaches to be followed in qualification of equipment and validation of systems and processes. The document was comprehensive and appeared satisfactory.

The VMP (general VMP or activity specific plans e.g. in case of cleaning) was applicable for:

- Area/room qualification
- Utilities qualification
- Environment Monitoring
- Process validation
- Packaging validation
- Cleaning validation
- Method validation
- Stability studies
- Computer system validation

A specific product process validation data was discussed.

Separate document was available for cleaning validation.

5. Complaints

Complaints were handled by SOP. Complaints divided into three categories: critical, major and minor categories.

6. Product recalls

Product recalls were handled by SOP. The SOP was purportedly based on the EMA and USFDA guidelines. The recalls were divided into a number of classes. The SOP also included classes of success rates.

7. Contract production, analysis and other activities

This section was not inspected due to time constraint.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections were carried out by using SOP. Site specific list of auditors was available. Staff with at least 5 years' experience were considered for entry on this list. Audits were conducted once every 4 months. Audit check lists were available for different areas.

9. Personnel

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. During on-site inspection correct garments was observed.

Organograms of QC, manufacturing and QA were reviewed. Packaging function was covered by manufacturing organogram..

10. Training

An SOP was available on staff training. Different types of training in this module included were: Induction, cGMP/GLP/general training programs, job specific training, training on changed system/procedures, unscheduled training including external training.

Training records of the staff members were reviewed and were found to be satisfactory.

11. Personal hygiene

Personnel suffering from illness such as skin rashes, colds, and open lesions to the body were required to report the department head and were excluded from working in the clean and critical areas. Smoking, eating, drinking, chewing and the storage of food and personal medicines and smoking was prohibited in the manufacturing areas. Regular medical examination was carried.

12. Premises

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Quality control laboratories were separated from production areas.

Raw material warehouse had 1,200 pallets capacity, mobile racking system, 5 micron filter air with epoxy flooring. Separate quarantine, approved and rejected areas, sampling & dispensing booths with RLAF were provided.

13. Equipment

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis.

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment. Equipment in production area were non-dedicated and were shared with other products.

14. Materials

Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under appropriate conditions. Food grade oil was used for punches and dies lubrications.

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active ingredients and excipients) and packaging materials were available.

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer.

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure locations. Each delivery of a batch of printed or primary packaging material was given a specific reference number.

Facility covering warehouse (receiving bay, de-dusting, sampling, quarantine, rejected and approved area) and production (dispensing, sifting, granulation, drying, blending, compression, coating and primary packaging area) were inspected. The warehouse was equipped with compactors for the storage of quarantine and approved starting materials.

15. Documentation

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

Testing procedures were validated and were appropriately authorized and dated. Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

Specifications for starting and packaging materials, finished products and intermediates were available and contained required information about the materials.

16. Good practices in production

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were carried out in three IPC laboratories.

The raw materials for manufacturing of tablet were dispensed, processed, packaged and distributed under appropriate conditions. Actual yields were compared with expected yields at designated steps in the production process. Processing status of operation room was labelled with product names and batch numbers. In-process controls were performed by production and in-process QC analysts. Manufacturing areas were accessed through secondary change rooms. In production, dispensed starting material and intermediate products were identified during the different production stages using proper labels that include the identity and status of each material or product.

All core manufacturing, sampling and dispensing areas were as per ISO 8 classification and with dedicated air handling units to maintain temperature, relative humidity, and pressure differential with plenum HEPA filter.

Precautions were taken to prevent the generation and dissemination of dust by airlocks, pressure differentials, and air supply and extraction systems. Production areas were subject to periodic environmental monitoring.

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. Line clearance was performed and recorded in the BPRs. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

At the time of the inspection, TDF 300mg tablet (under assessment) was not produced by the manufacturer. The manufacturing facility was a multi-product, non-dedicated facility which produced several products using the same equipment. Most of the production was performed in closed equipment and materials from different stages were transferred through vacuum transfer and pneumatic systems using hoses dedicated for the active substances.

17. Good practices in quality control

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigations as appropriate. Analyst certification matrix was presented to the inspectors. Instruments usage logs books were maintained.

At the time of inspection, there were 66 staff members working in QC. The functions of the laboratory were divided into:

- Wet Lab
- HPLC/GC
- Dissolution
- Stability

The laboratory was well designed, maintained and equipped to perform the routine testing.

Tests followed the instructions given in the relevant written test procedure. Tests results were checked independently before the material or product was released. Samples were representative of the batches of material from which they were taken.

Before releasing a starting or packaging material for use, the QC manager ensured that the materials have been tested for conformity with specifications.

The SOP “Batch release” was discussed.

The SOP “on General Stability Program” was discussed.

The SOP on Out of Specification and Out of Trend /atypical results in chemical-physical testing was discussed..

The SOP “Receipt, storage, maintenance of control samples” was discussed. The samples were stored according to the schedule.

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, ***Laurus Labs Limited, Unit-2 (VSP-2)***, located at ***Visakhapatnam, India*** was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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 manufacturer, 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 cGMP guidelines referenced in the inspection***

1. 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.
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
<http://www.who.int/medicines/publications/44threport/en/>
3. 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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. 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
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1
5. 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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
6. 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
http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1
7. 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
<http://www.who.int/medicines/publications/44threport/en/>
8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, 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
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
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
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
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
13. 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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
14. 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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
19. 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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf
22. 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
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf
24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf