

WHO PUBLIC INSPECTION REPORT API Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**
Part 1: General information

Name of Manufacturer	Laurus Labs Limited
Unit number	VSP 1
Production Block	General Chemistry Blocks: GCB-3, GCB-4, GCB-6, GCB-7, GCB-8
Physical address	Plot No 21, JNPC, Parawada Mandal, Visakhapatnam – 531 021, Andhra Pradesh, India
Contact person and email address.	Dr Vaidyanathan N. Iyer vaidyanathan.iyer@lauruslabs.com
Date of inspection	25, 26, 27 and 28 August 2014
Type of inspection	Triggered inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Efavirenz (APIMF090) Tenofovir Disoproxil Fumarate, BTDF (APIMF195)
Summary of the activities performed by the manufacturer	Manufacturing of Active Pharmaceutical Ingredients (APIs) and intermediates

Part 2: Summary

General information about the company and site

Laurus Labs is a pharmaceutical services organization (PSO). The head-quarter and the Research & Development center (including QA/QC headquarter) is located at Plot No: DS1, IKP Knowledge Park, Shameerpet, Turkapally, Hyderabad, India. The drug substance manufacturing facility is situated at Jawaharlal Nehru Pharma City, Visakhapatnam, Andhra Pradesh, India; in south east coastal area of India.

- 33.40 acres (1,35,162 Sq. M) area
- 291 Reactors available with total volume of ~ 1046 KL
- Part of GCB-7 Expansion is in progress (For Efavirenz)

The site manufactures about 40 various active pharmaceutical ingredients for domestic and export (including EU and US) markets. The site is ISO 9001:2008 certified.

The inspection was focusing on the following new facilities and facilities changed since the last WHO inspection (April 2013): GCB-3, GCB-4, GCB-6, GCB-7, GCB-8, RM & FG warehouse, Quality control.

Amongst the manufacturing blocks (General Chemistry Building-GCB) of the site, the followings were operational but out of the inspection scope:

- **GCB-1:** ground floor with intermediate blocks (GCB-1A, GCB-1B, GCB-1C) and centrifuge rooms, first floor with intermediate blocks A, B, C, intermediate storage rooms, charcolization rooms and crystallizers, “Pharma area” for final processing, including 5 crystallization/centrifuge and 7 drying modules, PW plant. No major changes since last inspection.
- **GCB-2:** Intermediate area with reactors, dryer and centrifuge rooms and 2 crystallizer and dryer modules, “Pharma area” includes crystallization, drying and packing areas (classified as “Class 100000”), PW plant, Hazardous Block 1,2 and 3. No major changes since last inspection.
- **Oncology Block:** No major changes since last inspection
- **GCB-5:** new building manufacturing of intermediate for customer project

Laurus is in the process to further expand its manufacturing capacity with the introduction of new manufacturing sites (VSP 3) which was out of the scope of this inspection.

History of WHO and/or regulatory agency inspections

The site was inspected by WHO last in April 2013. The site has also been inspected by several regulatory authorities such as:

- USFDA (October 2009)
- TGA (November 2009)

- MHRA (January 2010)
- KFDA (January 2011)
- WHO (July 2011)
- USFDA (November 2012)
- WHO (April 2013)
- PMDA, Japan, Desktop audit (August-2013)

Focus of the inspection

The inspection focused on the production and control of APIs mentioned under Part 1. The inspection covered all the sections of WHO-cGMP guidelines for Active Pharmaceutical Ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1: 25th August 2014

- Opening meeting
 - o Introduction
 - o Site presentation by the Site Quality Head.
 - o Exposition of the WHO inspection procedure by the lead inspector (it has been made clear that this is a special inspection which is triggered due to submission of amendment application.
- Regulatory inspections
- Changes since the last inspection
- Organisational charts
- Manufacturing processes of Efavirenz.
- Tour to GCB-6

Day 2, 26th August 2014

- Feedback of the inspection of day 1
- Process water monitoring
- Tour to GCB-8
- Tour to GCB-7

Day 3, 27th August 2014

- Feedback of the inspection of day 2
- Process validation
- AHU qualification
- Product Quality Reviews
- Tour to RM and FG warehouses
- Returned goods
- Tour to Quality control

Day 4, 28th August 2014

- Feedback of the inspection of day 3
- Tour to GCB-4 (comprising of ground, first and second floor)
- Analytical test method validation
- Product Quality Reviews (continued)
- Meeting between inspectors
- Exit meeting with the site representatives

2.1 QUALITY MANAGEMENT

There were arrangements for evaluations and monitoring of the quality of the systems, procedures and products through self-inspection procedures and annual product reviews. There were procedures for equipment and systems qualification and validation of procedures and processes. The observations raised following the inspection were appropriately corrected.

2.2 PERSONNEL

The key personnel did not change since the last inspection. Generally the standards with regard to the number of qualified staff, organization and job descriptions were on an appropriate level. The organization charts were completed down to the level of the different production blocks. The linking between all organizational charts was found adequate. The observations raised following the inspection were adequately corrected.

2.3 BUILDINGS AND FACILITIES

Building and facilities for production were, as far as covered during the inspection, suitable for production of APIs. In production areas there was sufficient space for handling of equipment and materials. For handling of APIs from the last purification step a clean room area with classification 100 000 (ISO 8) was available. Material- and personnel flow were defined and allowed a logical order of goods processing. In the clean room area environmental conditions were controlled and suitable for APIs. The observations raised following the inspection were adequately corrected.

2.4 PROCESS EQUIPMENT

The process equipment in the most sections of production areas was not dedicated and was used to manufacture various products. Like in the other production areas, process parameters were controlled manually. Status of equipment was indicated on labels, usage of equipment was recorded in log books.

2.5 DOCUMENTATION AND RECORDS

Procedures, reviewed during the inspection were in general prepared, suitably detailed, authorized and represented the current status. The observations raised following the inspection were adequately corrected.

2.6 MATERIALS MANAGEMENT

The existing material management system of the site has been extended to the new facilities. The raw materials are received, sampled, released, stored and distributed in the Raw material warehouse. Raw material is received from Warehouse based on the indent. Before batch charging for wet chemistry, the required raw materials are taken to respective reactors and proceed as per Batch production and control record (BPCR). After sampling by QC, the material is shifted to Quarantine room in the Pharma area. The products are stored in the quarantine rooms of the manufacturing blocks only temporarily (1-3 days) before sending out to the finished goods warehouse. After approval, in case of immediate dispatch, the material is released from the GCB directly. In case of storage, the material is shifted to Finished Goods Warehouse ; material shall be stored based on the storage conditions and further dispatched from there. The material inventory (including the material name, batch number, amount, reception and distribution dates) was recorded on "BIN cards".

2.7 PRODUCTION AND IN-PROCESS CONTROLS

The production area was covered during the inspection including GCB-3, GCB-4, GCB-6, GCB-7 and GCB-8. Raw materials were sampled and dispensed in day store area in the production department. The controlled environment in these areas was in general sufficient. The observations raised following the inspection were adequately corrected.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The inspection covered procedures for packing and labelling of materials in detail. In general, packaging and labelling of APIs and intermediates was found acceptable.

2.9 STORAGE AND DISTRIBUTION

The warehousing procedures and practices did not change since the last inspection. Finished Goods Warehouse was improved with an additional raw material warehouse (together with sampling and dispensing rooms for liquid materials) next to the existing warehouse and with cold chambers (CS-102, CS-103, 2-8 °C). The observations raised following the inspection were adequately corrected.

2.10 LABORATORY CONTROLS

The quality control laboratories, including chemical, instrumental and microbial analyses as well as validation of analytical methods, were covered during the inspection and found adequate in general. The observations raised following the inspection were adequately corrected.

2.11 VALIDATION

There was an adequate validation program in place for cleaning and process validation. The manufacturing validation policy did not change since the last inspection. The validation master plan (VMP) was regularly updated, reflecting the changes in the processes, facilities, equipment according to the SOP.

2.12 CHANGE CONTROL

The system for management of changes was described in a procedure. The changes regarding the new developments were investigated and recorded. The change control records of GCB-8 and the VMP version 6-7 were discussed.

2.13 REJECTION AND RE-USE OF MATERIALS

Processes of approval and rejection of raw materials were covered in detail during the inspection. The material rejection and reuse procedure did not change since the last inspection. Approval or rejection of manufactured APIs was recorded in the batch production records. The materials were reprocessed and reworked as per company procedure. Material and solvents were recovered in-house, tested and reused. The recovery procedures were validated and specifications used were generally adequate. Batches produced with recovered material and solvents were included in validation and stability studies.

2.14 COMPLAINTS AND RECALLS

The procedure for the handling of complaints was described in the SOP for procedure for handling of complaints. The procedures for handling complaints and recalls did not change since the last inspection. The investigations reviewed during the inspection were complete.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The contract manufacturers did not change since the last inspection.

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, APIs manufactured at *Laurus Labs Limited, VSP 1, Visakhapatnam, India* were considered to be manufactured in compliance with WHO cGMP for Active Pharmaceutical Ingredients.

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.