

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

Name of Manufacturer	Laurus Labs Private Limited -Visakhapatnam
Unit number	VSP1
Production Block	GCB-1A, GCB-1B, GCB-1C and GCB-2
Physical address	Laurus Labs Private Limited, Plot No. 21 Jawaharlal Nehru Pharma City, Parawada Mandal, Visakhapatnam - 531021, Andhra Pradesh, India DUNS: 915075687
Contact person and email address.	Dr Vaidyanathan N. Iyer VP-Quality & Regulatory Affairs Laurus Labs Private Ltd Hyderabad-500078 India • E-mail : vaidyanathan.iyer@lauruslabs.com
Date of inspection	09 - 12 April 2013
Type of inspection	Routine inspection.
Active Pharmaceutical Ingredient(s) included in the inspection	1. APIMF090: Efavirenz (Ph. Int.), anhydrous, polymorph I (ELT-301/AEFZ) 2. APIMF139: Emtricitabine (AECB) 3. APIMF141: Nevirapine (ANVP) 4. APIMF152: Lamivudine (ALMD) 5. APIMF157: Tenofovir disoproxilfumarate (ATDF) 6. APIMF195: Tenofovir disoproxil fumarate (BTDF) 7. APIMF193: Abacavir sulphate (AABS)
Summary of the activities performed by the manufacturer	Manufacturing, quality control, packaging, distribution of non-sterile APIs and intermediates

Part 2: Summary

General information about the company and site

Laurus Labs Private Limited is a pharmaceutical services organization (PSO). The head-quarters is located at Serene Chambers, 2nd Floor, Road No: 7, Banjara Hills, Hyderabad-500 034 and the Research and Development center (including Quality Assurance-QA/Quality Control-QC-Stability) is located at Plot No: DS1, IKP Knowledge Park, Shameerpet, Turkapally, Hyderabad-500 078, Andhra Pradesh, India.

The drug substance manufacturing facility is situated at Jawaharlal Nehru Pharma City, Visakhapatnam; in south east coastal area of India. The site manufactures about 40 various active pharmaceutical ingredients (APIs) for domestic and export (including EU and US) markets.

The site's manufacturing blocks and workshops:

- General Chemistry Building (GCB) - multipurpose:
 - o Ground floor with intermediate blocks (GCB1A, GCB1B, GCB1C) and centrifuge rooms.
 - o First floor with intermediate blocks A, B, C, intermediate storage rooms, charcoalization rooms and crystallizers.
 - o “Pharma area” (classified as “Class 100,000”) for final processing, including 5 crystallization/centrifuge and 7 drying modules.
 - o Purified Water (PW) plant.
- General Chemistry Building 2 (GCB2) - multipurpose:
 - o Intermediate area with reactors, dryer and centrifuge rooms and 2 crystallizer modules.
 - o The controlled (classified as “Class 100,000”) “Pharma area” includes crystallization, drying and packing areas.
 - o Purified Water (PW) plant.
- General Chemistry Building 3 (GCB3), out of the inspection scope.
- Hazardous Block 1 (HAZ-1).
- Hazardous Block 2 (HAZ-2).
- Powder processing area at the Finished Goods Warehouse (FGWH) with blending and micronization rooms (1-6).
- Oncology Block, out of the inspection scope.

History of WHO and/or regulatory agency inspections

This was the second inspection of this site by WHO Prequalification of Medicines Programme (WHO-PQ), the first was in July 2011. According to the company presentation, the site has been inspected and approved by the following agencies:

- USFDA-USA (October 2009)
- TGA-Australia (November 2009)
- MHRA-United Kingdom (January 2010)
- KFDA-South Korea (January 2011)
- WHO-PQ (July 2011)

– USFDA-USA (November 2012)

Focus of the inspection

The inspection focused on the following APIs and manufacturing workshops:

API	Internal code	Batch size (kg)	Manufacturing blocks	APIMF
Emtricitabine	AECB	56	GCB1-B	APIMF139
Nevirapine	ANVP	85	GCB1-B, HAZ-2	APIMF141
Lamivudine	ALMD	47.5	GCB1-B	APIMF152
Tenofovir disoproxil-fumarate	ATDF	195	GCB1-A/GCB1-B/FGWH	APIMF157
Tenofovir disoproxil fumarate	BTDF	185	GCB1-A/GCB1-B/FGWH	APIMF195
Abacavir sulphate	AABS	56.1	GCB1-B	APIMF193
Efavirenz	ELT-301/AEFZ	379	HAZ-1/HAZ-2/GCB1-A/GCB1-C/GCB2 FGWH Zone 5, 6	APIMF090

The inspection covered most of the sections of the WHO good manufacturing practices for active pharmaceutical ingredients (Reference No. 2), including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging, Identification and Labeling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls.

Inspected Areas

Day 1: 09 April 2013

The first day of inspection covered the following:

- Introductory Meeting
- Overview of activities at site
- Overview of the buildings and facilities
- Overview of the manufacturing processes
- Personnel and Organization chart
- Document control
- Vendor qualification
- Material management
- Tour of the Raw material (RM) warehouses (including warehousing and storage of raw materials)

Day 2: 10 April 2013

Feedback was given on the previous day's inspection and the company was given an opportunity to provide clarification.

The inspection of the following issues and areas followed:

- Gowning procedures
- Tour of the Finished product warehouse (including warehousing and storage of APIs)
- Tour of the Powder Processing Areas (Finished product warehouse)
- Tour of the GCB 2
- Tour of the GCB 1
- Review of the BMRs

Day 3: 11 April 2013

Feedback was given on the previous day's inspection and the company was given an opportunity to provide clarification.

The inspection of the following issues and areas followed:

- Manufacturing process validation
- Batch number generation and issuance of Batch Production and Control Records (BPCRs)
- Calibration, qualification and preventive maintenance
- Heat, Ventilation and Air-Conditioning (HVAC) system
- Purified Water (PW) system
- Contract manufacturing

Day 4: 12 April 2013

Feedback was given on the previous day's inspection and the company was given an opportunity to provide clarification.

The inspection of the following issues and areas followed:

- Job descriptions
- Training program
- Cleaning and cleaning validation
- Deviations/Change control/Out-Of- Specifications (OOS)
- Self-inspection
- Complaints and Product recalls
- Batch release and rejection
- Product Quality Review (PQR)
- Tour of the QC Laboratories (physico-chemical and microbiology)
- Sampling and testing of APIs, RMs and intermediates
- Out of Specification investigations
- Reference substances and working standards
- Stability program
- Analytical method validation

- Retention samples
- Post inspection summary meeting

At the closing meeting, the inspectors gave feedback on the inspection observations of the day and the entire inspection. The company was informed about the procedures and timelines for the report, Corrective and Preventive Actions (CAPAs) and WHO Public Inspection report (WHOPIR).

2.1 QUALITY MANAGEMENT

General

Quality management systems were established, documented and implemented in general.

The organizational structure, procedures and resources were provided. The QA/QC department was independent from production.

The production and quality control procedures were defined and were followed in general.

Product Quality Review

The Product Quality Reviews (PQRs) were prepared according to the SOP (QA/041, Preparation of Product Quality Review). The last PQRs of the inspected products were found to be acceptable in general.

Deviations

The standard operating procedure (SOP) QA/025, “Deviation handling procedure” was revised since the last inspection and the classification (as critical and non-critical) of the deviations implemented. The examples of deviations discussed during the inspection were recorded and formally investigated.

Batch release

The SOP on batch release was QA/031 (“Procedure for batch release”). There were 9 persons working for the QA Department with responsibility for batch release.

The batches were first released on the “Commercial Batch Approval/Rejection form” based on a checklist. Before distribution of the goods the final packaging and labelling was cleared on a “Dispatch clearance form”.

Change control

The SOP QA/008 (“Procedure for change control system”) was amended since the last WHO inspection included examples of the classification of changes.

The change control register and records were maintained. The examples of change control cases were discussed and found to have been handled adequately.

Self-inspection

The frequency of internal audits was 3 times/year (SOP QA/010, “Internal audits/Self inspections”). Amongst others the following areas were defined in the SOP for internal audit: Engineering, Production, QA, QC and Warehouse.

The audits were performed by 30 qualified auditors. The audit program for 2012 was accomplished; the first audit in 2013 was due in April.

2.2 PERSONNEL

There was adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

The number of personnel working for the site in different areas of the API manufacturing about 842 (522 employee and 320 contract workmen), amongst:

- production 273 (+240 contract workers)
- QA/QC 124 (+12 contract workers)
- warehousing 16 (+25 contract workers)
- engineering and maintenance 49 (+23 contract workers)

The training system did not change since the last WHO inspection and was conducted as per SOPs QA/005 (Employee training). Training programme and records were available for inspection.

Job descriptions of the following employee were reviewed.

- Senior chemist (FGWH-Powder processing)
- Senior officer (RMWH)
- Two helpers

Personnel hygiene

Personnel hygiene on the site was considered to be acceptable in general. The gowning and changing procedures (MFG-VSP1-045, “Personnel entry and exit procedure for Pharma area”; MFG-VSP1-065, “Personnel entry and exit procedure for Finished Goods Warehouse”; MFG-VSP1-045, “Personnel entry and exit procedure for Pharma area of GCB2”), of the controlled areas were inspected and some issues were noted.

2.3 BUILDINGS AND FACILITIES

Design and construction

In general buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate appropriate cleaning and maintenance.

For details of manufacturing workshops used for the inspected products and covered by the tours see section: “*Focus of the inspection*” above.

The risk of mix-up and cross contamination was mitigated by clean air supply, pressure differences between the critical areas, facility dedication and campaign based manufacturing.

Containment

There were oncology products produced and handled at the site in a dedicated block.

HVAC systems

The environmental conditions in the controlled areas (“Pharma” area of GCB1, GCB2, and Powder processing area in the FP warehouse) were maintained by means of HVAC (heat, ventilation and air conditioning) systems. The rooms were qualified according to the ISO 8 requirements, the re-qualification frequency was annual.

The monitoring program consisted of daily (pressure and temperature) and 6 monthly (non-viable particle count) tests. The test frequency of viable particles was 3 monthly based on the SOP: MB/VSP1/046.

The qualification and monitoring records of the AHU-17 system (supplying the FBD-RCVD room, GCB2) were available and discussed. They were generally found adequate.

Purified water (PW) system

The purified water was used in the final manufacturing steps mainly for crystallization and for cleaning. The water quality meets the specification of European Pharmacopoeia (Ph.Eur) and United States Pharmacopoeia (USP).

There are three PW generation systems:

- GCB1, supplying the loop of GCB1 facilities (the FPWH loop was removed since the last inspection)
- GCB2, supplying the loop of GCB2, GCB3 and the FPWH powder processing facilities (the old FPWH loop was replaced with a new one since the last inspection)
- OCB, supplying the loop of the Oncology building.

At the time of the inspection the GCB2 water system validation Phase III was ongoing, the Phase I and II completed.

2.4 PROCESS EQUIPMENT

The process equipment had unique identification code (SOP QA/VSP1-002, “Equipment coding”) and was of acceptable construction and design.

The annual maintenance program (SOP EM/VSP1-029, “Preventive maintenance schedule of equipment”) and the protocol for inspected equipment (SOP EM/VSP1-037, “Procedure for preventive maintenance of tray drier”) was available.

The equipment was qualified and calibrated regularly based on QA-019, “Equipment qualification”). The calibration, qualification and maintenance documents of the following equipment and measuring devices were discussed.

- Tray dryer TD-107, with the belonging temperature indicator (TI-307) and probe (TS-273),
- Balance EM/VSP1/024.

The qualification, calibration and maintenance were generally adequate, although some issues were noted.

2.5 DOCUMENTATION AND RECORDS

The paper based GMP documents were handled, prepared, reviewed, approved and distributed according to SOPs: QA-002 (Procedure for document numbering), QA-024 (Retention and destruction of documents) QA-037 (Preparation, issuance and retrieval of documents to various units and departments). There were two types of SOPs in place:

- “Common”, issued by the headquarter,
- “Local”, issued by the site.

The issued procedures (SOPs) and their IDs were recorded in a “Document master list” and a logbook.

The retention time for the different type of documents was defined.

2.6 MATERIALS MANAGEMENT

General controls

There were standard operating procedures in place for receipt, handling, storage and dispensing of materials. For example: WH/VSP1-001, “Receipt of raw materials”, WH/VSP1-002, Issuance of raw materials to manufacturing”. Every incoming material was recorded in the “Bin Card” given an internal ID and labelled.

There was “moving quarantine” system followed in the warehouses, meaning that in case of a status change not the material, only the status label changes.

The manufactured APIs and intermediates had unique item codes.

The suppliers/manufacturers of the raw materials were classified, then qualified, listed and their performance monitored according to the SOPs: PR-002 (Identification, qualification, re-qualification of vendors), PR-003 (Procedure for vendor performance rating).

Categories of the suppliers were:

- key starting material supplier,
- critical raw material supplier,

- general raw material supplier,
- primary packaging material supplier,
- secondary packaging material supplier.

The supplier status can be “provisionally approved” or “approved” based on the qualification status. The supplier list was regularly updated in the form of a paper based table.

The qualification and re-qualification records of selected suppliers/manufacturers were discussed with some issues noted which were adequately addressed through written CAPAs.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

Production processes were described and recorded by means of master production control records (MPCR). The BMRs of selected batches were discussed during the inspection as follows:

- Efavirenz: 4 batches
- Tenofovir disoproxil fumarate ATDF: 3 batches
- Tenofovir disoproxil-fumarate BTDF: 3 batches
- Abacavir sulphate: 5 batches

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The procedures for packaging and labelling have not been changed since the last inspection. The practice was inspected during the tour at the manufacturing workshops and the warehouses.

Packaging operations were conducted in designated areas following standard procedures and adequate records were maintained.

Packaging materials including labels were approved by QC/QA before use. Labelling and the records maintained could adequately facilitate traceability.

2.9 STORAGE AND DISTRIBUTION

The materials were stored in the Raw material warehouse, in the Finished Goods Warehouse and in the intermediate storage areas of the GCBs.

Raw materials were stored in ambient, controlled (below 25 °C) and cold (2-8 °C) areas.

The storage areas in the Finished Goods Warehouse were as follows:

- Controlled Room temperature (below 25 °C) for all of the inspected APIs apart from Tenofovir,

- Cold storage room, CS-102 (2-8 °C), for Tenofovir,
- Ambient storage area, mainly for marketed intermediates, out of the inspection scope.

The packaging material and solvent storage procedures and facilities did not change since the last inspection.

The dispensing of the raw materials is performed in the sampling and dispensing rooms of the RM warehouse.

2.10 LABORATORY CONTROLS

General

The Quality Control Department was responsible for the chemical, physical and microbiology testing of raw materials, intermediates, APIs and PW. The department consisted of a Wet laboratory and 3 Instrumentation laboratories. The main instrumentation was: HPLCs, HS-GCs, IR spectrometer, FTIR spectrometer, UV-VIS spectrometer, DSC, TOC testers, Polarimeter, particle size tester.

The analytical instruments were regularly qualified and maintained by external partners and internal staff. The qualification and maintenance records of the “HPLC 110” were discussed and available. No issue arose out of this review.

The specifications and analytical test methods for the raw materials, intermediates and APIs were available. The analytical test methods used at the site were developed and validated by the R&D laboratory in Hyderabad. The intermediate and API test methods were transferred from the R&D laboratory.

There were detailed sampling procedures available for raw materials, intermediates and APIs (SOP QC/VSP1/001, “Procedure for sampling of raw materials”; SOP QC/VSP1/003, “Procedure for sampling of intermediates”; SOP QC/VSP1/005, “Procedure for sampling of finished products”).

Samples were taken by the QC personnel and were recorded in Inward Registers. The sampling and sample distribution records, test records and COAs (certificate of analysis) for selected RM (4-chloro-4-fluoro-acetamide) and Efavirenz API were discussed and available. They were generally found adequate.

The working standards were qualified, stored in controlled place (refrigerator 83 and 30) and their usage recorded. The records of the working standard WS/VSP1/ELT/13/007 were available, discussed and found generally adequate.

Stability program

Stability program of the manufactured APIs was in place (QA/014, “General stability program”). The stability samples were stored in the R&D laboratory (headquarter, Hyderabad). The sampling and shipping records were available.

Retention, reference samples

The retention samples were stored in a dedicated, controlled room, in the same packaging as the commercial API batches.

Handling of OOS results

The procedure of handling OOS results (QA/004, “Procedure for handling out of specification”) did not change since the last WHO inspection. The OOS results were recorded in logbooks (issued annually) and investigated.

2.11 VALIDATION

Manufacturing process validation

The basic rules for manufacturing process validation and re-validation were described in the following procedures: QA/022, “Procedure for process validation”, QA/54 “Procedure on blending process validation, blending homogeneity”, QA/VSP1/015, “Procedure for drying validation”, QA/VSP1/018 “Procedure for micronizing process validation”.

The following manufacturing process validation documents were reviewed and compared to the existing MPCR (master production and batch control records):

- Efavirenz (ELT 301-1) synthesis: PVP/ELT301-1/06, PVP/ELT301-1/06,
- Abacavir drying: DVP/AABS-3/02, DVR/AABS-3/02

Cleaning validation

Cleaning validation was regulated per SOP QA/023 (Cleaning validation). The cleaning validation documents of the tray dryer TD-105 were discussed.

At the time of the inspection, only one cleaning run had been accomplished and documented (changeover after product: Valacyclovir hydrochloride).

2.12 CHANGE CONTROL

There was an established procedure for managing changes. Changes were documented, evaluated and approved before implementation. Selected examples were reviewed with no issues noted. *See details under section 2.1 above.*

2.13 REJECTION AND RE-USE OF MATERIALS

The policy and practice of batch reprocessing, reworking and recovery of materials and solvents did not change since the last inspection.

It was claimed, the recovered solvents were used only in the same process.

2.14 COMPLAINTS AND RECALLS

Complaints and recall were recorded and investigated according to a SOP QA/017, “Procedure for handling of customer complaints”.

There were 2 complaints recorded in 2013 regarding Efavirenz and 1 complaint for Abacavir. The complaints were investigated and negotiated with the customer.

There was a procedure for handling product recall SOP QA/050. Since the last WHO inspection, the SOP had been changed to provide for the closure of recalls within 30 days and frequency of mock recall once every 5 years. This frequency and an example reviewed did not ensure adequate verification of the effectiveness of the recall procedure. These issues were addressed adequately and verified through written CAPAs.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

There was no analytical testing contracted out concerning the inspected APIs. The contracted out manufacturing was the solvent regeneration (7 partners). The contract partners were regularly audited. An agreement with one of the contract manufacturers for solvent was reviewed and no major issues were noted.

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 following APIs manufactured at **Laurus Labs Private Limited, Plot No. 21 Jawharlal Nehru Pharma City, Parawada Mandal, Visakhapatnam - 531021, Andhra Pradesh, India (VSP1)** were considered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients (ICHQ7 guidelines):

- APIMF090: Efavirenz (Ph. Int.), anhydrous, polymorph I (ELT-301/AEFZ)
- APIMF139: Emtricitabine (AECB)
- APIMF141: Nevirapine (ANVP)
- APIMF152: Lamivudine (ALMD)
- APIMF157: Tenofovir disoproxil fumarate (ATDF)
- APIMF195: Tenofovir disoproxil fumarate (BTDF)
- APIMF193: Abacavir sulphate (AABS).

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.