



Annex B

**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
API Manufacturer**

**Part 1: General information**

Name of Manufacturer	Aptuit Laurus Private Limited,
Unit number	Plot No 21
Production Block	NA
Physical address	Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam - 531021 Andhra Pradesh, India
Contact person and email address.	Dr Vaidyanathan N Iyer - Corporate QA vaidyanathan.iyer@aptuitlaurus.com
Date of inspection	18 - 21 July 2011
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	1. Efavirenz (APIMF 090) 2. Emtricitabine (APIMF 139) 3. Nevirapine (APIMF 141) 4. Lamivudine (APIMF 152) 5. Tenofovir (APIMF157)
Summary of the activities performed by the manufacturer	Manufacturer of Active Pharmaceutical Ingredients (non-sterile anti-viral)



## **Part 2: Summary**

### ***General information about the company and site***

Aptuit Laurus' drug substance manufacturing facility is situated at Jawaharlal Nehru Pharma City, Visakhapatnam; a city is situated in south east coastal area of India. The site manufactures various active pharmaceutical ingredients (around 21 APIs) including Efavirenz, Emtricitabine, Tenofovir, Lamivudine and Nevirapine. The site has two main manufacturing blocks, namely the General Chemistry Block (GCB) and the Oncology Block.

The GCB was further divided into synthesis of intermediates and API in 3 phases:

1. Pharma area with crystallization and centrifugation
2. Drying Modules
3. Powder Processing area

The research and development centre of Aptuit Laurus is located at Plot No DS1, ICICI, Knowledge Park, Shameerpet, Turkapally, Hyderabad, Andhra Pradesh, India. This centre is responsible to carry out pilot scale study, analytical method validation and stability studies of the Intermediates and finished APIs.

### ***History of WHO and/or regulatory agency inspections***

The site had not been inspected by the WHO before this inspection.

The site had been inspected by the USFDA in October 2009 and covered the entire site but with special focus on Efavirenz.

The site had been inspected by the TGA in November 2009 and covered the entire site, but with special focus on Gemcitabine Hydrochloride.

The site had been inspected by the UK MHRA in January 2010 and covered the entire site including Efavirenz, Emtricitabine and Tenofovir.

The Korean FDA inspected the site in January 2011 and covered Gemcitabine Hydrochloride.

### ***Focus of the inspection***

The inspection focused on the production and control of Efavirenz (APIMF090), Emtricitabine (APIMF139), Nevirapine (APIMF141), Lamivudine (APIMF152) and Tenofovir (APIMF157) APIs. 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 and Identification Labelling 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**

After arrival, the inspectors introduced themselves and informed the company representatives about the WHO prequalification programme. The company introduced personnel present and then made a presentation about the activities carried out at their R&D Centre/Kilolab and corporate office based in Hyderabad followed by the site activities.

Inspectors then proceeded to the review of the following documents:

- Job descriptions of key personnel and other selected staff
- SOP on Training of personnel and records for selected staff.
- SOP on batch Release
- SOP on batch numbering system
- SOP on Document control
- SOP for product quality review
- Product quality review (PQR)

### **Product quality review (annual product review)**

The SOP on preparation of annual product review was reviewed and found satisfactory.

The PQR report of Nevirapine anhydrous and Emtricitabine was reviewed and found satisfactory in general.

The SOP on procedure for reprocessing and re-working was reviewed. It was noted under the responsibility section that approval responsibility for reprocessing was assigned to manufacturing head instead of QA.

An SOP on Change Control was reviewed and found that impact assessment was not the part of procedure following a change in the process or any system.

The company's program for internal audits (self-inspections) was not covered during the inspection.

The procedure for batch numbering material code stated in a separate document. Batch numbers are defined for stages and drug substances. However, month system was not expressed appropriately like for year (last 2 digits). The batch numbering system covered various activities included but not limited to:

- reprocessing,
- reworking
- purification batches,
- blending of batches,
- Recovered solvents
- column distillation,
- Reactor distillation, micronized, compaction, micronization cum compaction, recovered in stepwise processes,
- Detoxification for oncology products, starting materials (which didn't comply specification e.g. further purification at site).



The procedure for in-process sampling was reviewed and found adequate.

The in-process sampling and submission of samples to QC lab was done by manufacturing staff but testing was performed by QC staff in the main laboratory.

### **Day 2**

The observations from the previous day were presented to the company.

Inspectors then continued with the review of documents as follows:

- PQR of Emtricitabine
- PQR of Efavirenz and Tenofovir
- The PQR for Tenofovir for 2010 covered the following:
- SOP on change control. Selected changes were reviewed:

The inspectors proceeded to a detailed inspection of plant inspection following the material flow. The inspectors visited the tank farm and storage warehouses covering receiving bay, quarantine, approved and rejected areas. At the end of the day, inspectors visited GCB-1B of the synthetic area of the GCB. Inspectors were notified wherein synthesis of Tenofovir previously took place in GCB-1B. Validation was in-progress to increase batch size with input of 200kg Adenine in GCB-1A. It was noted that GCB-1C was closed for extensive renovation.

### **Day 3**

After giving the observations of the previous day, inspectors continued with inspection of GCB-1A and GCB-1B of GCB plus related pharma and powder processing areas. In the afternoon, inspectors proceeded to quality control laboratories covering physical and instrumentation laboratories. The QC staff competencies and allocation of samples was reviewed. Other area reviewed included:

- Qualification and handling of working standards.
- Testing of selected raw materials, intermediates, APIs, recovered solvents and materials, including verification of electronic raw data.
- Calibration and qualification of some QC instruments.

### **Day 4**

The observations from the previous day were presented to the company. After which, inspectors proceeded to the quality control laboratory and reviewed various laboratory related documents, equipment logbooks, test reports including raw data (manual and electronic), etc.

The process validation report of Lamivudine was reviewed and found satisfactory in general.

An inspector proceeded to technical area and covered air handling units and water system. This was followed by records of routine maintenance, monitoring, trend analysis, sanitisation and requalification.

The qualification report of the tray drier was reviewed.



At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feedback and wrap up for the inspection and received reactions from the management of the company. There was consensus on all the observations made.

## **2.1 QUALITY MANAGEMENT**

The GMP systems, stipulated in ICH Q7, were implemented in the quality system of Aptuit Laurus, Visakhapatnam. Procedures and records were available for most performed activities. The awareness for quality topics was clearly present.

## **2.2 PERSONNEL**

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. Some issues were noted in relation to control of copies and version numbering of the organizational charts, while job description revealed cases of dual reporting relationships, inconsistencies in format (name or title) and lack of clarity on deputization of key personnel.

## **2.3 BUILDINGS AND FACILITIES**

Building and facilities for production in GCB 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 rooms for dispensing and sampling of raw materials, including raw materials for the production of the five APIs, were located in the raw material warehouse. The rooms were found in general appropriate for handling of raw materials to manufacture finished products. Temperature and humidity were monitored; however there were some ambiguity in terms of store at room temperature, cool and cold conditions which led to storage of some materials at inappropriate conditions.

## **2.4 PROCESS EQUIPMENT**

The process equipment in the most sections of GCB was not dedicated and was used to manufacture various products including contract manufacturing, Nevirapine, Tenofovir and Lamivudine. Only GCB-1C synthetic area and related pharma and powder processing areas (*which were closed for extensive renovation during inspection*) were claimed to be dedicated to Efavirenz. Although GCB-1A synthetic area was claimed to be dedicated to Tenofovir DF (*later change to "only one bay being dedicated and another bay of GCB-1A is multipurpose"*), it was



noted that some potable equipment rotated between this area and Phase B. 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. However, some of the SOPs found inadequate and didn't cover required information.

Some of the batch records of the manufacture of the Nevirapine, Lamivudine and Tenofovir, were reviewed in detail during the inspection and were largely consistent with the procedures described in the respective APIMF.

## **2.6 MATERIALS MANAGEMENT**

Materials management was checked in detail. The flow of raw materials for the production of various APIs was sufficiently described. The handling of some of the key starting materials was found to be inadequate as some were not stored at an appropriate conditions. The control of materials that have passed their retest period needed to be strengthened.

## **2.7 PRODUCTION AND IN-PROCESS CONTROLS**

The GCB production area was covered during the inspection including areas for micronizing and packing of finished product. Raw materials were sampled and dispensed in day store area in the production department. The controlled environment in these areas was in general sufficient.

## **2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

The inspection covered procedures for packing and labelling of materials in detail. During the plant inspection in GCB some containers were noted with insufficient information on the labels.

## **2.9 STORAGE AND DISTRIBUTION**

Raw materials and intermediates were stored in a warehouse under different ambient conditions. During the inspection - warehouses for solid raw materials and the finished API warehouse were covered. Conditions in the warehouse for solid raw materials were not controlled, in particular some of the materials were stored in a controlled room temperature (NMT 25<sup>0</sup>C) against the required storage in a cool place. A cold room existed for materials that required to be stored between 2<sup>0</sup> - 8<sup>0</sup>C. APIs were stored in an environmentally controlled warehouse, however some of the key starting materials were not appropriately segregated.



## **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. However, some of the laboratory practices were found inappropriate, in particular handling of working standard, access to key computer functions like dates and use of integration methods.

## **2.11 VALIDATION**

### Cleaning Validation:

The SOP on cleaning validation was reviewed and noted that cleaning was categorised into batch to batch cleaning, periodical cleaning, stage changeover cleaning within the same product and product change over cleaning. The protocol covered various aspects of cleaning including but not limited to the level of cleaning (1 & 2), selection of cleaning agent, sampling technique (rinse and swab sampling), acceptance criteria, general limit (10ppm) and swab recovery etc. The SOP on procedure for swab sampling was reviewed and it was based on hard to access areas and inaccessible area.

### Process validation:

The process validation reports evaluated were either the initial plant batches or done to support change, e.g. increase in batch size, change of process parameters. Process validation was generally well executed except the evaluation of the need for revalidation as part of change control need to be strengthened.

## **2.12 CHANGE CONTROL**

The system for management of changes was described in a procedure. Requested changes were listed in a register, documents about approval and implementation of changes were achieved separately. The reviewed changes were in general sufficiently documented. Responsibilities were defined; decisions about further investigations and actions were recorded. Impact assessment and the need for revalidations or requalification needed to be improved.

## **2.13 REJECTION AND RE-USE OF MATERIALS**

Processes of approval and rejection of raw materials were covered in detail during the 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. Complaints were listed in a register; investigations were recorded in detailed files. The investigations reviewed during the inspection were complete except that key information such as batch number, date of manufacturing and expiry were not documented in the complaint register.

The recall procedure was briefly covered during the inspection. Traceability of dispatched batches was ensured with data included in the batch record.

The company claimed that there were no recalls received in 2010 and 2011.

## **2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

It was noted during the inspection that contract manufacturing for several APIs were carried out at site (as contract acceptor). However, the same information was not stated in their submitted Site Master File.

It was clarified that contract manufacturing was carried out and in those cases; further purification could be carried out. Recovery of solvents was carried out on-site. This area was not covered during the inspection in detail.



### **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 **Aptuit Laurus Private Limited Plot No 21 Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam – 531021 Andhra Pradesh, India** were considered to be manufactured in compliance with WHO GMP 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.