

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

Name of Manufacturer	Hetero Labs Limited
Unit number	Unit-I, API
Production Block	NA
Physical address	I.D.A. Gaddapotharam (V), Jinnaram (M), Medak (Dt), Andhra Pradesh
Contact person and email address.	Mr C. Raghunath, Vice President, QA & RA Raghunath.c@heterodrugs.com
Date of inspection	4 to 7 March 2014
Type of inspection	Routine inspection
Active Pharmaceutical Ingredient(s) included in the inspection	1. Abacavir Sulfate 2. Didanosine 3. Efavirenz 4. Emtricitabine 5. Lamivudine 6. Lopinavir 7. Nevirapine 8. Stavudine 9. Tenofovir DF 10. Zidovudine
Summary of the activities performed by the manufacturer	Production and quality control of APIs

Part 2: Summary

General information about the company and site

The site inspected was **Hetero Labs Limited, Unit-I**, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District - 502319, Andhra Pradesh, India, hereafter called Hetero Labs Ltd, Unit-I. The company corporate office was located at 7-2-A2, Industrial Estates, Sanath Nagar, Hyderabad - 500 018, Andhra Pradesh, India.

According to the presentation given at the opening meeting, Hetero Labs Limited was established in April 1998. Unit I is located 50km on a 30 acres (70,721m³) plot with a built up area of 15 acres (30,000m³). The site had 10 manufacturing blocks: A, B, C, D, E, F, G, H, I, J and Pharma area. Block F and I were dedicated to synthesis of oncology APIs and were physically separated by a wall from other blocks. Most of the manufacturing blocks had two synthesis lines and two corresponding pharma areas for crystallization, drying, size reduction and packaging.

Hetero Laboratories Limited (HLL) Unit-I was started in 2002. At the time of inspection the Unit had 1134 employees as total.

Hetero Labs Limited Unit - I.	Gaddapotharam Village Hyderabad, India	APIs
Hetero Labs Limited Unit - II Baddi, India	Baddi, India	Finished dosages
Hetero Labs Limited Unit - III	Nakkapally, Visakhapatnam, India	Active Pharmaceutical Ingredients & Intermediates
Hetero Labs Limited Unit – III (EOU)	Jeedimetla, Hyderabad, India	Finished dosages
Hetero Labs Limited Unit – IV	Baddi, India	Finished dosages
Hetero Labs Limited Unit – V	Jadcherla, Hyderabad, India	Finished dosages
Hetero Labs Limited Unit – VI	Jadcherla, Hyderabad, India	Oncology Finished dosages
Hetero Labs Limited Unit – VII	Jeedimetla, Hyderabad, India	Finished dosages

Hetero Labs Limited Unit – VIII	Baddi, India	Finished dosages
Hetero Labs Limited Unit – IX (SEZ).	Nakkapally, Visakhapatnam, India	Active Pharmaceutical Ingredients
Invagen INC	Long Island, New York, USA	Finished dosages Manufacturing Unit

History of WHO and/or regulatory agency inspections

This was the third WHO inspection to this site. The site was previously inspected in 2005 and 2011. It was noted that the USFDA audited the site in 2013 (for one of the oncology products and found to be compliant).

Focus of the inspection

The inspection covered all the sections of the WHO good manufacturing practices for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities but focused on mainly (risk based) the manufacturing of Efavirenz.

Inspected Areas

Day 1: 4th March 2014

- Opening meeting
- Product Quality Review Reports
- Document system
- Change control
- Clarification on manufacturing process and particle size distribution (PSD) for Efavirenz
- Training records
- BMRs

Day 2: 5th March 2014

Feedback and discussion on the observations made in the previous day. Following documents were reviewed, including:

- Planned deviation (changes of the Efavirenz -EN, EV- manufacturing process)
- Internal audit program
- Deviation control
- OOS investigation
- Training program

- Clarification by the Hetero Labs Ltd, Formulation department on the particle size distribution comment raised by the WHO assessment team
- Tour at the warehouses

Day 3: 6th March 2014

Feedback and discussion on the observations made in the previous day. Following documents were reviewed, including:

- OOS investigation
- Site facility layouts

Tour at the manufacturing facilities covering

- Block A, Section II, powder processing areas
- Block A, Section II, wet chemistry areas
- Tour at the water plant

In addition Document review

- Qualification and maintenance of clean areas,
- Calibration and maintenance program of critical equipment

Day 4: 7th March 2014

Feedback and discussion on the observations made in the previous day. Following documents and areas were reviewed, including:

- Layout of the QC laboratories
- Review of policy and practice of chromatographic data integration, audit trails, backups, access rights etc.

Tour at the QC laboratories, including:

- Physico-chemical laboratories
- Microbiology laboratory
- Stability chamber room
- Retained sample storage

Closing meeting among inspectors

Exit meeting with site management

2.1 QUALITY MANAGEMENT

The quality management system was generally well established, documented and implemented. The site organizational structure was presented and was acceptable. Quality-related activities were defined and documented in general. The Quality Assurance department was independent from production. The persons authorized to release APIs were specified.

The quality management system at the time of the inspection was mainly paper based. It is to be noted that the company is planning to introduce some IT systems to support QA functions in due course (e.g. Trackwise software for handling investigations-deviations, change control, complaints- is also planned sometime July/August 2014).

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.2 PERSONNEL

There was an adequate number of personnel qualified, trained and experienced to perform and supervise the manufacture of intermediates and APIs.

There were training program in place for the permanent staff according to SOP including trainings of new recruits, fresher, experienced, job training, cGMP training, additional training. The training records of the Dy. General Manager QA, two executive QAs, a QA officer and an Analyst and an internal auditor were discussed. The training plan for year 2014 (covering different GMP topics), the training records and the competency matrix (supported with test records of the comparative tests) were available.

2.3 BUILDINGS AND FACILITIES

Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. There was adequate space for the orderly placement of equipment to prevent mix-ups and contamination.

The site has a separate block for the manufacturing of oncology products. In addition, there were no other highly sensitizing materials either produced or handled at this site as far as the inspectors were aware, nor were there any other APIs of high pharmacological activity, such as steroids or cytotoxic as claimed by the management. Areas for the final processing and packaging of APIs were provided with filtered air to achieve a Grade D standard (ISO 8 or Class 100,000).

Adequate lighting was provided in Grade D areas and in technical areas.

The purified water (PW) was used in the manufacturing process and for cleaning the equipment. The water system supplying PW was adequate in general. The source water was bore well water which was transferred through road tankers. The capacity of water system is 2250 litres per hour (2050-2450 litres). The system was equipped with double RO and EDI before purified water was stored in a primary storage tank (7500 litre). There were several secondary storage tanks before purified water was supplied to respective Blocks A/B, C/D, EGH, F, J and I tanks. The sanitization of the system was done once every month using purified water at 80-85°C for 90 minutes. Before sanitization, primary storage tank was checked for spray valve filter performance. The primary storage tank vent filter was replaced every 6 months once

integrity of vent filter was verified. The quality of the water was monitored on-line (conductivity, flow rate) and off-line (chemical tests, TOC, microbiology).

2.4 PROCESS EQUIPMENT

The design and construction of reactors and other equipment related to the process was adequate for the activities being conducted. The product contact surfaces of the equipment were suitable for the processes being conducted.

The equipment listed in the BMRs and the manufacturing process validation documents were in line. There was calibration and preventive maintenance program in place. The critical manufacturing equipment was listed in the Master Equipment/Instrument Record. The preventive maintenance program of the crystallizer and the connected measuring devices were discussed. The annual maintenance and calibration program with the protocols and the recent reports were available. No computer system was used in the production and control of the API except those used to particular analytical instruments.

2.5 DOCUMENTATION AND RECORDS

The procedures were prepared identified and handled according to SOPs. The manufacturing process and product quality related master documents were filed in “Master List BMR” and “Master List STP”. The folders and the Indices (containing the ID, version number and issue date of the documents in the folder) were up-to-date, and available (including the obsolete versions of the Indices) in the archive of the QA Department.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

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 warehouse layout and the procedure on material management were discussed. The key starting materials (KSM) were sampled & tested 100% for identification. A separate list of these KSM was maintained in the warehouse. The approved vendor list was used for verification before incoming supplies were accepted. A manual inventory system of materials was used whereby materials were recorded in incoming material inward register and assigned with unique number. The bin card for each incoming material was maintained.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Stainless steel (SS) and glass lined (GSL) reactors were used for production. The production process mainly was carried out in closed systems. IPC tests were carried out in the quality control laboratory. IPC samples were taken by production personnel.

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

Facilities were provided for storage of raw materials; packaging materials and intermediates. There were demarked areas for quarantine and released materials and a secure area for rejects. Materials were labelled with their status.

Raw materials and intermediates were stored in a warehouse under different conditions. During the inspection, warehouses for solid raw materials and the finished API warehouse were covered. A cold room existed for materials that required to be stored between 2^o - 8^oC. APIs and intermediates were released for distribution after they had been released by the Quality Unit according to the procedure.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.10 LABORATORY CONTROLS

The Quality Unit was independent from manufacturing. There were two QC Departments at the site separated physically and by organization (serving oncology and non-oncology, including WHO productions). The QC department (non-oncology), Chemical section was responsible for testing of incoming raw materials, in-process control samples, intermediates, finished products, stability samples. Procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Testing was performed according to approved specifications, test methods and related SOPs.

2.11 VALIDATION

The site had an overall validation policy document and procedures on manufacturing process, cleaning validation and analytical method validation. The Efavirenz manufacturing process was last validated in year 2008. Amongst the four Efavirenz batches manufactured in 2012 two batches were put into long-term stability study.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.12 CHANGE CONTROL

The changes in the manufacturing process were handled in a “Planned Deviation Report”. The system for management of changes was described in a procedure. The change control for particle size analyser was reviewed. A change request form for Sympatec particle size analyser was raised to discard the particle size analyser and shifted to Hetero Baddi site. The change control investigation did not cover the justification of the change and the replacement issues (purchase of a new Malvern PPS Analyser, installation, qualification, method verification) etc.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

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. According to the ARRs, there was no WHO pre-qualified product reprocessed or reworked since the last WHO inspection.

Materials and solvents were recovered in-house, tested and reused in the same manufacturing process.

2.14 COMPLAINTS AND RECALLS

A procedure on complaints and recall was in place.

The observations raised from this section have been addressed satisfactorily, and will be verified during future inspections.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Not inspected

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 **Hetero Labs Limited, Unit-I, 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.