

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

API manufacturer

Part 1: General information

Name of Manufacturer	Hetero Drugs Limited, (HDL) Hetero Labs Limited, (HLL)
Unit number	Unit-IX
Production Block	N/A
Physical address	Plot No 2, Hetero Infrastructure LTD, SEZ, N.Narasapuram (Vill) Nakkapally (Mandal) Vishakhapatnam (Dist) Andhra Pradesh. INDIA
Contact person and email address.	Mr.C.Raghunath Vice President – QA & RA Hetero Labs Ltd.
Date of inspection	20 to 23 June 2011
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Active Pharmaceutical Ingredients against HIV/AIDS
Summary of the activities performed by the manufacturer	Production and quality control

Part 2: Summary

General information about the company and site

Hetero Drugs Limited (Unit-IX) and Hetero Labs Limited (Unit-IX), are both located at N.Narasapuram (V), Nakkapally (M), Visakhapatnam District, Andhra Pradesh, India – 531 081. Both are owned by Hetero Corporate based in Hyderabad. The location is about 84 km away from the Vishakhapatnam Air port. There are 272 employees in HDL and 443 in HLL.

History of WHO and/or regulatory agency inspections

This report is of the first inspection by WHO Prequalification Programme. The site was inspected by the Indian authority in October, 2010, licensed, but the certificate had not yet been issued by the time of the WHO PQP Inspection.

Focus of the inspection

The inspection focused on the production and control of HIV/AIDS APIs. The inspection covered all the sections of WHO GMP for Active Pharmaceutical Ingredients including quality management, personnel, building 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 and change control etc.

Inspected Areas

Introductory Meeting

- Introductions
- Scope of inspection

Overview of activities at site

Organization Chart

Job Descriptions

Staff training programme and records

Inspection of Quality Management System

- Product Quality Reviews
- Deviations
- Complaints
- Recalls
- Change Controls
- Out of Specification investigations

Inspection of warehouse

Raw materials warehousing – solids and liquids

Finished APIs

Receipt of materials

Sampling

Dispensing of materials to production

Inspection of production site

- APIs manufacturing
- Materials handling
- Recovery of solvents
- Cleaning
- SOPs and records
- packaging

Quality Control

SOPs, registers and records including:

- Sampling and sample handling
- Work allocation
- Raw data of IR, HPLC

Documentation:

- Specifications and test methods
- SOPs, logbooks, records
- Worksheets and test reports
- Stability program
- OOS results
- Analytical method validation
- Evaluation of results, release and rejection procedures
- Trending of results
- Labelling of finished APIs

Materials

- Chemicals and reagents
- Reference standards
- Retention samples
- Equipment, instruments and devices

Utility

- Water System
- HVAC

Documents and records review:

Document management system

- Batch document preparation
- Packaging
- Cleaning
- API testing and release

Validation and qualification:

- Validation Master Plan
- Validation protocol and report
- Validation and qualification status and schedule
- Equipment qualification
- Process validation
- Cleaning validation

Post inspection closing meeting

2.1 QUALITY MANAGEMENT

A system for quality assurance was established and covered all the basic elements of GMP. An organization chart was reviewed and found to be acceptable. Production and control operations had been specified in written procedures for deviation and investigation management, complaint and change control management.

The QA department and QC laboratory were independent from production and both reported to the management of the company.

2.1 PERSONNEL

- In general, the personnel met and interviewed during the inspection were confident in what they were doing. Job descriptions of selected key persons e.g. Manager of QA and Manager of Production were reviewed by the inspectors:

Training:

The Training SOP was reviewed. All departments were included. Corporate and Plant QA Departments were responsible for preparing the GMP training schedule. Corporate and Plant QA departments conducted GMP training. In addition, there were department-specific training schedules.

The training of new employees was assessed by the review of the individual daily logbooks that they were required to maintain for the initial training period. Other training was assessed by the trainee answering a written test that was department-specific. Individual training records were kept.

Casual workers were trained in the relevant documents in the local language and were supervised.

2.2 BUILDINGS AND FACILITIES

Overall, buildings were constructed of materials compatible with the activity being conducted. All were of reinforced concrete with the outsides of the walls rendered and painted. In general, internal finishes were of rendered painted walls, but some walls were partly tiled, such as in warehouse sampling and dispensing rooms. Also, polished stone slabs were used to part-tile some classified areas. The same type of polished stone slabs was used for flooring. The flooring in the raw materials warehouses was of Khota stone. Process reactor floors were of concrete with tiled finish. Ground floors were of brick.

Finishes in Pharma areas were of appropriate design with surfaces easy to clean and with coved joints between walls and floors.

SOP on Operation of demineralised water generation system and SOP on Water and DM water sampling and testing schedule were reviewed.

2.3 PROCESS EQUIPMENT

Generally, process equipment was designed, and installed satisfactorily. Also, materials used were satisfactory. Reactors were equipped with overheads and utilities to allow the normal range of organic reactions to be conducted.

Specific plant, designed for solvent recovery, was installed in a separate building located some distance from the production areas.

Production equipment was cleaned on a scheduled basis as per written SOPs. Cleaning status was shown by a cleaning label. Equipment calibration schedule and planned preventive maintenance program (PM) of equipment and systems was in place. Spot checks showed that the schedules had been followed and records were maintained. SOP on Preventive maintenance programme and records were reviewed.

Calibration requirements were described in corporate SOP. This covered QC instruments and production plant gauges but not balances. Balance calibration was covered in a separate SOP. This SOP was a general policy document. All Department Heads were responsible for compiling their department's calibration programme. Each schedule was approved by QA. Each class of instrument had its own specific SOP.

Computerized systems: Data capture of QC chromatography data was done electronically. Electronically operated QC instruments were linked to a network.

2.4 DOCUMENTATION AND RECORDS

In general, the documentation system was established and maintained in compliance with GMP requirements. Documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Specifications and testing procedures were available. Documents related to the batch release were stored one year after the expiry date of the batch.

2.5 MATERIALS MANAGEMENT

In general, material management was found acceptable. Materials were received and handled according to written procedure specified in the documents. Materials were procured from the approved suppliers. Sampling and dispensing booths were installed in the Raw Materials Warehouses. The key starting material and critical starting materials were specified in the document.

2.6 PRODUCTION AND IN-PROCESS CONTROLS

There was no production performed during the inspection. The selected BMRs had been reviewed. Production operations followed defined procedures. Production and in-process controls were conducted at an acceptable level.

2.7 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Written procedure for receiving and testing and releasing packaging and labelling materials, Log books were maintained detailing labels issued and a numerical tally recorded for reconciliation. Labels were stored in locked QC cupboards with keys held by the Heads of the Laboratories.

2.8 STORAGE AND DISTRIBUTION

Facilities were available for the storage of materials and operated at acceptable level.

API and intermediates were released as per procedures in the SOP.

2.9 LABORATORY CONTROLS

There was adequate facilities, personnel, approved procedures for sampling, testing, approval or rejecting materials.

Documents, log books and data were inspected and found satisfactory in general. These included:

- SOP on Resolving out of specification results and OOS flowchart
- The impurity trend analysis.
- The microbiology lab: SOP for media preparation and the log book and records, the validation of autoclave.
- The raw data of IR and HPLC for assay and impurity for selected batch.
- Reference standard working standard and retention sample
- PH meter, melting point apparatus.
- Stability
- Retention Samples

2.10 VALIDATION

The Validation Master Plan was available and covered all areas. Revalidation schedule was subject to change controls listed. Process was done and critical process parameters were established. Cleaning validation was in line with the GMP requirement.

The Process Validation SOP and the Prospective Validation Protocol were available. Details in the protocol included the equipment used, batches identified, batch numbers of material used and critical process parameters recovery of solvents. Following satisfactory validation, the process details were used to write the process master Formulas.

2.11 CHANGE CONTROL

The Change Control SOP covered all products and quality systems in all departments. Reference to informing customers and regulatory authorities was stated in clauses. Changes were investigated by means of Change Request Form with details entered into the annual logbook. Planned change controls in the 2010 were inspected.

2.12 REJECTION AND RE-USE OF MATERIALS

There were no rejections in 2010 and 2011 fund. SOP Resolving out of specification results and OOS investigation flow chart were reviewed.

The SOP on recovery solvents/ recovered materials and flow chart as well as the solvents recovery plant were inspected.

2.13 COMPLAINTS AND RECALLS

There were no complaints and recalls in 2010 and 2011.

Complaints were handled according to written procedure. It was required that the receipt of all complaints was confirmed to the customer within specified time of receipt and the PQA (Plant Quality Assurance) Department notified. Details were entered into a log following the format and the PQA had to raise a Complaint Investigation following the format and conduct a detailed investigation. Based on the findings of the investigation, complaints were classified as “established” (valid) or “not established” (not valid). A preliminary summary had to be submitted to the complainant within specified days. On receipt of a satisfactory response, or after specified days, complaints were closed.

Product Recalls were handled according to written procedure. This procedure was very thorough. The QA department was in control of the procedure. The Company has never had to instigate a recall.

2.14 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Contractors, including Laboratories, were included in the same SOP as that used for materials. It covered the supply of raw materials, packing, services and outside testing laboratories. The HDL and HLL both had contracts for the provision of testing such as GCMS, LC-MS-MS, NMR, powder XRD and HPLC. Other providers were subject to contracts as defined in the relevant SOPs. The contact was approved by the PQA Head as per SOP.

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, Hetero Drugs Limited (Unit-IX), Hetero Infrastructure LTD - SEZ, N.Narasapuram (V), Nakkapally (M), Visakhapatnam District, Andhra Pradesh, India – 531 081 and Hetero Labs Limited (Unit-IX), Hetero Infrastructure LTD - SEZ, N.Narasapuram (V), Nakkapally (M), Visakhapatnam District, Andhra Pradesh, India – 531 08 was considered to be operating at an acceptable level of compliance with WHO GMP guidelines 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 three years, provided that the outcome of any inspection conducted during this period is positive.