

WHO PUBLIC INSPECTION REPORT Finished Product Manufacturer

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Hetero Labs Ltd., Unit V
Production Block	Module 3, 4 & 5
Physical address	Survey No. 439, 440, 441 & 458, APIIC Formulation SEZ, Polepally Village, Jadcherla Mandal, Mahaboob Nagar Dist-509 301, Andhra Pradesh, India.
Contact address	As above
Date of inspection	6 to 9 February 2012
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Oral solid dosage forms
	HA
Summary of the activities performed by the manufacturer	Production and quality control

Part 2: Summary

General information about the company and site

The site inspected was Hetero Labs Ltd., Unit V, Survey No. 439, 440, 441 & 458, APIIC Formulation SEZ, Polepally Village, Jadcherla Mandal, Mahaboob Nagar Dist-509 301, Andhra Pradesh, India, here after referred to as Hetero Labs Unit V. The site is located about 80km from Hyderabad city and about 60km from the international airport.

According to the company presentation, the site employed 421 personnel.

History of WHO and/or regulatory agency inspections

Hetero Labs Unit V is licensed by the Drug Controller of Andhra Pradesh. The site was previously inspected by WHO Prequalification of Medicines Programme in November 2010 for FPPs. The site has also been inspected by US FDA, Infarmed and other national drug regulatory authorities.

Focus of the inspection

The inspection focused on general principles of GMP and the production and control of three PQ FPP tablet products. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Warehouses including sampling and dispensing areas
- Module III production facilities
- Module IV production facilities
- Module V production facilities
- QC facilities (physico-chemical) including storage of retention samples
- QC facilities (microbiology laboratory in Hetero Lab Unit VI)
- Water system and HVAC facilities
- Document review
 - o Facility layouts
 - o Organogram
 - o Job descriptions
 - o Training
 - o Product Quality Reviews
 - o Change control
 - o Deviation control
 - o Complaints
 - o Recall

- o Supplier's Approval
- o Release, rejection control
- o Document control
- o Self-inspection

Document review (production) including

- o VMP
- o BMR/BMR masters
- o BMR's of the inspected products
- o Manufacturing process validation
- o Cleaning validation
- o Software (LIMS) validation
- o Manufacturing equipment calibration, qualification (validation) and maintenance
- o Water system
- o HVAC system

Document review (QC, physico-chemical), including

- o LIMS system
- o Personnel and qualification
- o Sample handling
- o Handling of reference standards
- o Analytical instrument calibration, qualification, maintenance
- o Recording of analytical tests, handling of raw data, reporting
- o OOS handling
- o Stability testing

2.1 QUALITY ASSURANCE

A quality assurance system was implemented and maintained.

The QA department was lead by the Head QA, reporting directly to the Corporate QA. The QA and QC units were independent from production. Managerial responsibilities were specified in job descriptions.

There was an SOP describing the requirements for product quality reviews. The 2011 PQR's for the inspected products were reviewed:

A number of SOP's were reviewed during the inspection, including:

- SOP on annual product review
- SOP on approval / rejection of starting materials
- SOP on procedure for code to code transfer of raw materials
- SOP on training programme
- SOP on allotment of batch numbers
- SOP on handling of market complaints
- SOP on product recall
- SOP on change control programme
- SOP on vendor qualification

SOP on document control
SOP on deviations
SOP on self-inspection

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Production was performed in a multi-product facility and production equipment was not dedicated. Validations, qualifications were performed according to the corporate/site policy and documented procedures.

Adequate premises and equipment were available for production, in-process controls quality control and storage.

Manufacturing processes and quality control test requirements were generally well defined in approved documents.

2.3 SANITATION AND HYGIENE

The facilities and procedures for sanitation and hygiene established on the site were found to be adequate to ensure that premises and equipment were properly cleaned so as to avoid contamination and cross-contamination.

2.4 QUALIFICATION AND VALIDATION

The Validation Master Plan was a general document that stated the company's validation policy. The manufacturing procedures are re-validated every 5 years or in case of significant change in raw materials, equipment or procedures.

Cleaning validation was based on the physico-chemical attributes of the products and APIs (strength, potency, solubility).

The manufacturing process and cleaning validation protocols also serve as validation report master record forms.

Process validation had been performed when the batch size increased. Separate "validation reports" were issued for the 3 consecutive validation batches and the results were summarized in a "Summary report".

Qualification of the LIMS system, introduced in October 2011, was reviewed. The system had been installed and validated at the company's Unit III site and it is managed from here. At Unit V, qualification consisted of verifying it's functionality at this site. The operation of the system was supported by a number of SOPs issued by Unit-III.

Four new walk-in stability chambers had been installed and the qualification record for the 30°C/75%RH unit was reviewed.

There was a list of major equipment and their unique identification numbers. Calibration/qualification and maintenance programs were in place for critical manufacturing and quality control equipment, HVAC and water systems.

The following SOP's were reviewed:

Validation Master Plan
SOP on process validation
Process validation protocol
SOP on cleaning validation programme

Validation batches of selected products were reviewed.

2.5 COMPLAINTS

SOP on handling of market complaints was available and found to be acceptable. The company claimed that there had been no complaints for the PQ products manufactured at this site.

2.6 PRODUCT RECALLS

SOP on handling product recalls was available and found to be acceptable. It provided for a classification of recalls into class I, II, and III with corresponding times for implementing a recall specified. The effectiveness of the recall procedure had not been evaluated at this site as recalls are managed by Hetero Labs Unit III.

2.7 CONTRACT PRODUCTION AND ANALYSIS

There was no manufacturing activity contracted out for the inspected products. Sipra Lab, Hyderabad had been qualified to perform quality control testing, if needed. A new agreement was available and the report of an audit conducted by Hetero in January 2010 was also reviewed. This laboratory had also been audited by the USFDA, was ISO 170025-2005 accredited and ISO 9001-2008 certified.

Microbiology testing was temporarily being done by Hetero Labs Unit VI (a different building on the same site as Unit V).

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were conducted according to SOP which required that each department be inspected at least twice per year. A schedule was available and detailed checklists were used for the inspections. Details of findings were not reviewed but records for 2011 indicated that all self-inspections had been completed on time.

Vendors were qualified according to SOP. QA was responsible for assessing the need and coordinating audits of vendors. All APIs for prequalified products were manufactured and supplied by other Hetero facilities. These had been audited by Unit V.

2.9 PERSONNEL

Personnel in GMP areas (production, warehousing, quality assurance, quality control) were full-time employees. The employment of temporary workers was confined to other activities.

Organization charts and job descriptions were in place. Individual responsibilities were defined and recorded as written job descriptions. Delegated duties were clearly defined. The people met during inspection appeared competent and had a good understanding of GMP requirements.

The job descriptions of QA and production managers were reviewed during the inspection:

2.10 TRAINING

Training was conducted according to SOP and training records were kept. The effectiveness of training was assessed and recorded in the training files. A schedule for on-going training was available. The suitability of trainers was assessed and a list of suitable trainers approved by QA. Selected training file's including a dispensing operator and casual workers were checked.

2.11 PERSONAL HYGIENE

Personnel hygiene was included in the training received by all personal during induction and basic GMP training.

Photos describing the gowning procedures were appended to the changing procedures and provided on the walls of changing rooms.

The level of hygiene observed and the measures taken to maintain this were considered acceptable.

2.12 PREMISES

There premises for manufacturing, storage and quality control of the inspected products were generally of a satisfactory standard. Layouts of the facilities were available and up-to-date.

The production facilities of Unit V were multi-products facilities and situated in one building.

Warehouses were situated in the same building. The environmental conditions (temperature, humidity) at the different storage facilities were maintained and recorded.

The premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. The company claimed that there are no other highly active products or non-pharmaceutical products are manufactured in the same facility.

Processing areas where products are exposed were supplied with filtered air through filters. Pressure differentials between zones were specified and monitored by Magnehelic gauges.

The utilities including the HVAC system and Purified Water (PW) were visited and were considered to be well designed and maintained. AHU were operated according to SOP which included detailed instructions for start-up and shut-down.

2.13 EQUIPMENT

Process equipment was installed and maintained in a way that minimizes risk of contamination and cross contamination.

A qualification/calibration and preventive maintenance program was in place and was followed.

Production equipment was identified as to its content or purpose and cleanliness status by label. Maximum hold times had been determined.

Cleaning procedures for critical manufacturing equipment were available and had been validated.

2.14 MATERIALS

Materials were controlled by a SAP computerized system. Written procedures for the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available and followed.

The storage conditions (temperature and humidity) of the inspected products were controlled between 15 to 30⁰C. Temperature and RH was monitored daily.

All containers of raw materials were sampled individually and tested for identity while full testing was done on composite samples (with rules for compositing).

Materials were tested according to the material code of the initial order. A request from warehouse could be submitted to QC for additional testing for the purpose of the material code transfer for other specifications.

It was observed that reduced testing for APIs and excipients was permitted by SOP. All APIs used in PQ products were sourced from other Hetero facilities and these had been audited.

The water system had been qualified and maintained. Purified water was continuously monitored (on-line and off-line for chemical, including TOC, and microbiology parameters) and found to be satisfactory.

2.15 DOCUMENTATION

A SOP for document control was available and acceptable. Documentation was maintained and reviewed according to the written procedure. Documentation included: batch master formula, specifications for raw materials, packaging materials and packaging components, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and various standard operating procedures and protocols. There were corresponding records in the form of reports, forms, checklists, logbooks, registers maintained as evidence of compliance with the procedures and specifications.

The QA department was responsible for the control of the preparation, review, approval, distribution of documents. QA was responsible for the final release of finished products and this was documented.

2.16 GOOD PRACTICES IN PRODUCTION

The inspected finished dosage form facilities were multi-product facilities.

The temperature, relative humidity and air pressure differentials were monitored according to written procedures. The site inspection of the production areas covered following areas:

- Granulation
- Blending
- Compression
- In-process controls
- Punches and dies storage and maintenance room
- Coating
- Visual inspection
- Packing lines
- HVAC technical area
- PW production plant

Production usually runs in two or three shifts.

Validated manufacturing procedures were followed. The master batch manufacturing record and selected BMRs were reviewed.

2.17 GOOD PRACTICES IN QUALITY CONTROL

The physico-chemical QC laboratory was situated in the Unit V building. A microbiology laboratory in Unit V is in the process of being established. Microbiology testing was done in the micro lab of Unit VI (a separate building adjacent to Unit V). The site inspection of QC activities covered the following areas:

- Analyst qualification
- Specifications, test methods and records
- Operation of the LIMS system, including data integrity
- Wet laboratory
- Instrumental laboratory (spectroscopy, KF, dissolution, etc.)
- Chromatography (HPLC) laboratory
- Chromatography (GC) laboratory
- Sample preparation
- Reference Standards
- Stability chambers
- Microbiology laboratory of Unit VI

A LIMS system (“Caliber”) was introduced in 2011. The system was not connected to any laboratory instruments and data was manually entered. In addition to the LIMS record, hard copies of worksheets and associated records were kept. The system included an audit trail function which was checked during the inspection.

The QC laboratory was responsible for approving raw materials, primary and secondary packaging materials and finished products against approved quality specifications.

The quality specifications contained the requirements and the test methods to be followed. The samples taken by QC staff for testing were registered in the LIMS.

ID testing was done in the laboratory.

The operation and calibration of the GC with headspace analyser and auto sampler was reviewed. Requirements were specified in SOP. The machine had been re-qualified in December 2011 with appropriate records kept.

Working reference standards were stored in a cold chamber and a register was available

The microbiology laboratory at Unit VI appeared suitably designed and was staffed by 11 people. Media was prepared according to SOP. Every batch prepared was QC tested, including for fertility. Microbiological sampling and testing of process water was performed according to SOP. Records of purified water testing during January 2011 were reviewed and no observation made.

OOSs were handled according to a documented SOP. Investigations had been done and recorded.

Samples of starting materials and finished products were retained for future analysis. Stability studies were performed according to ICH requirement 25°C/60%, 30°C/75%, 30°C/65% and 40°C/75%. The qualification of walk in Stability chamber for 30°C/75% was reviewed.

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 Labs Ltd., Unit V, Survey No. 439, 440, 441 & 458, APIIC Formulation SEZ, Polepally Village, Jadcherla Mandal, Mahaboob Nagar Dist-509 301, Andhra Pradesh, India, was considered to be operating at an acceptable level of compliance with WHO GMP.

All the non-compliances observed during the inspection that were listed in the full report 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.