



**WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
Finished Product Manufacturer**

**Part 1: General information**

Name of Manufacturer	<b>Hetero Labs Ltd</b>
Unit number	<b>Unit V</b>
Production Block	NA
Physical address	<b>Hetero Labs Ltd. Unit V, Survey No. 439, 440, 441 &amp; 458, APIIC Formulation SEZ, Polepally Village, Jadcherla Mandal, Mahaboob Nagar Dist-509 301, Andhra Pradesh, India.</b>
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Date of inspection	23, 24, 25 and 26 November 2010
Type of inspection	Routine Inspection (Application for variation: Additional manufacturing site)
Dosage forms(s) included in the inspection	Tablets
WHO product categories covered by the inspection	Finished Pharmaceutical Products (FPPs) used in the management of HIV/AIDS (HA)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of tablets

## Part 2: Summary

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

The facility 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 Ltd, Unit V**. According to the Site Master File No.: SMF-FV-01-02 effective 19.10.2010 and the company presentation, Hetero Labs Limited was part of Hetero group established in 1993. Hetero group has manufacturing facilities and research centers in the following locations:

	<b>Name</b>	<b>Location</b>	<b>Responsibility</b>
1.	Hetero Research Foundation	Balanagar	R&D plus technical support to manufacturing facilities
2.	Hetero Drugs Ltd (Unit I)	Banthapally Village, Jinnaram Mandal	API manufacturing, approved by USFDA
3.	Hetero Labs Ltd (Unit-II)	Baddi	FPP manufacturing for Indian market
4.	Hetero Drugs Ltd (Unit III)	Jeedimetla, Hyderabad	FPP manufacturing, approved USFDA, ANVISA, WHO and Europe
5.	Hetero Labs Ltd (Unit IV)	Goddapotharam	API manufacturing, approved by USFDA.
6.	Hetero Drugs Ltd (Unit V)	Baddi	FPP manufacturing for the Indian market
7.	Hetero Labs Ltd (Unit V)	Jadcheria	FPP manufacturing
8.	Hetero Labs Ltd (Unit VI)	Jadcheria	FPP manufacturing - Oncology
9.	Hetero Drugs Ltd (Unit VI)	Nakkalapally	API manufacturing

The site of Hetero Labs Ltd, Unit V is located about 80km from Hyderabad city and about 60km from the international airport. It was located on a 75 acres plot of land with a built up area of 23, 381m<sup>2</sup> (Unit V: 9504m<sup>2</sup>). The unit was designed to have 7 production lines and 7 packaging lines:

- **Production module 1:** for Development and Pilot batches. This was under commission with no equipment in place and sealed off from the operation areas.
- **Production module 2:** designed in a cubicle concept and with capacity of 80 to 200kg batch size. This was already commissioned and this is where the validation batches were produced.
- **Production module 3:** designed in a modular concept and with capacity 400kg to 1600kg batch size. This was under qualification.
- **Production module 4:** designed in a cubicle concept and with capacity of 250kg to 750kg batch size. This was already commissioned.
- **Production modules 5, 6 & 7:** designed in a modular concept and with capacity 600kg to 2400kg batch size. This was under qualification.
- **One bulk packaging line and one blister packaging line** were already commissioned.
- **Two bulk packaging lines** were under qualification.
- **Three blister packaging lines** were under construction.

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The landscaping of the site was going on to reduce dust. It was surrounded by Aurobindo Pharma to the east, an open place to the west, Glochem Pharma to the North and the main road to the South.

According to the company presentation, the site employed 160 personnel, distributed as follows:

○ Quality Assurance (QA)	19
○ Quality control (QC)	45
○ Production (PD)	50
○ Engineering (EN)	34
○ Warehouse (WH)	05
○ Human Resources (HR)	03
○ Information Technology (IT)	02
○ Environmental Health & Safety (EHS)	02
<b>Total</b>	<b>160</b>

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

This was the first inspection of this site by WHO Medicines Prequalification Programme (WHO-PQP). The site was licensed by the Drug Controller of Andhra Pradesh under License No. 50/MN/AP/2009/F/G to manufacture tablets and hard gelatin capsules for human consumption. According to the company presentation, the site was inspected by USFDA between 15<sup>th</sup> and 19<sup>th</sup> November 2010.

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

The inspection focused on general principles of GMP and the production and control of tablets. 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***

#### **Day 1**

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards with the key staff of Hetero Labs Ltd, Unit V. The inspectors explained the procedure for the WHO Prequalification Programme, the procedures and standards used for inspection and timelines for processing the report and company responses to the inspection observations. The procedures for closing the inspection including the WHO public inspection report (WHOPIR) and Notice of Concern (NOC) were explained. The tentative inspection plan was discussed and confirmed. It was agreed the inspection will focus on aspects related to or that would impact on the production and control of tablets. The company made a presentation about the company and the site to be inspected. The presentation highlighted the company profile, the description of the site, a summary of quality assurance policies and manufacturing capacities, major equipment, product range plus the site inspection history. A copy of the presentation was obtained and will be filed in the company file.

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The inspection of the following areas and aspects followed:

Quality Management System review:

- Personnel Policies:
  - Organization charts (Plant, QA, QC, Production, Engineering, Warehouse, Human Resources, and EHS).
  - Job descriptions (AGM-QA, Ass. Manager-validation, DGM-QC, Ass. Manager-IP/FP/RM/PM/Stability, Executive RM/PM, Senior Production Executive Module 2, Senior Production Executive Module 4, Operator Module 2, Trainee Operator Module 2), QA Ass. Manager, QC Operator. The initial job descriptions were first signed in August 2010 and updated in November 2010. The head of Quality Assurance at the site (AGM-QA) had three deputies and the hierarchy of how one of them would be selected to perform his duties in his absence was not defined.
  - Training SOP and training records of Operator Module 2, Trainee Operator Module 2.
  - Health and Hygiene SOP. This outlined the general policy on hygiene into the site and the different facilities but it was not translated in local language.
- List of SOPs/SOP Index for QA, QC, HR, Warehouse, Engineering, Production. It was noted that several SOPs were prepared in the two months prior to the inspection.
- SOP on preparation, review, approval, control and revision of SOPs.
- SOP on the preparation and handling of forms.
- SOP on Allotment of Batch numbers. The format of the batch number was JYYNNN where:
  - J = stands for Jadcherla Unit V,
  - YY = the last digits of the year of manufacture, e.g. 10 for 2010.
  - NNN = Serial number of the batch per product.
  - In case the batch is packed in several presentations, a letter starting with A for the second presentation is added to the batch number.
- Annual Product Review SOP. This SOP highlighted the different chapters to be part of the report. It did not require the inclusion of excipient trending. The PQR for one of the products under focus was presented and discussed. It included the three batches manufactured for validation purpose.
- SOP on handling of deviations. It provided that planned deviations should be closed within 30 days. The registers (separate for each department) and the selected examples of planned deviations were reviewed in detail.
- SOP on handling unplanned deviations and incidents. Unplanned deviations and incidents were logged separately in logbooks. The logbooks were organized by department. Any CAPA which was not implemented during the investigation timeframe (15-30 days) was logged in a log book in order to assess its implementation. Selected incidents were reviewed in detail.
- SOP on reporting, investigation and disposition of incidences (unplanned deviations). It provided that an incidence should be closed within 15 days. The registers and selected examples were reviewed in detail.
- SOP on Cleaning of RMG (250L).
- SOP on Change control programme. Registers for QA/2010 indicated 17 changes while that for PD/2010 indicated 28 changes. Many involved update of documents and SOPs.
- SOP on investigation of OOS. Registers and selected cases were reviewed in details.
- SOP on Handling Complaints. No complaint had been logged for this site as no product had been yet marketed from the site.

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- Product recall system SOP.
- Product Master Files, codes, specifications for APIs and FPPs, plus list of approved vendors for the products in focus.

Review of site plans and HVAC System:

- Site layout, floor plans with material and personnel flow, area classification and pressure differentials, AHU distribution.
- Orientation tour of the site

Inspection of Receiving and storage areas + procedures:

- Starting materials, packaging materials and components receiving, quarantine and storage areas +SOPs:
  - SOP on entrance and exit of the warehouse.
  - SOP on receipt and storage of raw materials.
  - Records of receiving of selected consignments of raw materials.
  - Stock records and reconciliation of the API batches used in validation studies.
- Vendor approval, qualification and maintenance system: SOP.

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

**Day 2**

The inspectors started by giving feed back on observations of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspection then proceeded with a review of the areas stated below:

Sampling and dispensing areas:

- Sampling rooms for active and inactive materials:
  - SOP on operating a laminar flow provided for checking the  $\Delta P$  across all the filters and waiting for 15 minutes after switching on the LAF before use of the booth.
  - SOP on sampling, testing and release of raw materials. It provided for sampling each container of APIs and excipients for identification while other tests were done on composites made from samples of up to 10 containers. Half of the composite of all samples was used for full analysis while the other half was used as a control sample. Before sampling, an analytical reference number (ARN) was assigned to the received batch and this was used as a reference in all subsequent transactions/operations involving this batch.
  - Records of daily verification of the balance WHE-005 and calibration of standard weights WH01.
  - SOP on sampling, testing and release of packaging material. The sampling plan for visual inspection was consistent with ISO2859-1-1999: level II inspection, normal sampling for sample size and acceptance criteria based on AQL of 2.5%.
- Dispensing rooms for active (G022/G023 & G032/G033) and inactive (G026/G027) materials and related washing area (G030).
  - Records of daily verification of balances.
  - SOP on dispensing of raw materials. The dispensing was performed by two operators.

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- SOP on cleaning of sampling and dispensing areas. It provided for Type A cleaning for change of active substance and Type B cleaning for batch or inactive substance change over.
- SOP on operating and cleaning of the vacuum cleaner.
- Walk-in Cold room  $5.0 \pm 3^{\circ}\text{C}$ .

#### Inspection of Production activities:

- Production and in process controls.
  - Module II: Granulation G042, compression room G051 (*27 station with online dedusters and metal detectors: compression was going on*), IPC, coating room, inspection room (G070), equipment washing area.
  - Module IV: similar design as module II but with higher capacity: Compression machine - 51/56 stations. One compression room not yet operational, currently used for storage for IBCs.
  - Storage of cleaned production tools/equipment, FBD bags, general washing areas, store for punches & dies. Reviewed procedures and logs in these areas, e.g.:
    - SOP on operating the punch and dies polishing kit.
    - SOP on tablet punches and dies tooling receipt, inspection, usage, storage, cleaning and disposal.
    - Lubricant used for lubricating punches & dies plus its CoA. It was approved by QC and was of food grade.
- It was stated that Module 2 was dedicated for validation batches which would be scaled up to production batches produced in Module 4 and later Modules 3, 5, 6 and 7 when completed.

#### Review of the Purified Water generation and distribution system

- PW system drawings and summary of specifications and capacities
- Inspection of Water Generation and Purification System installations
  - Water was supplied from a bore well. The water was treated by softening, ultrafiltration, reverse osmosis and electro-deionisation operation before being stored and circulated in a stainless steel tank and circulated in the loop. Purified water was kept and circulated at ambient temperature ( $27^{\circ} - 40^{\circ}\text{C}$ ).

#### Review of the Compressed Air system

- Compressed air system schematic drawing and summary of specifications for Compressed Air system. It was an oil free compressor followed with filtration of  $5\mu$ ,  $0.01\mu$ , activated alumina,  $1\mu$  and  $0.01\mu$  filtration near the point of use.
- Inspection of the Compressed Air system installations

#### Review of the HVAC System:

- HVAC system schematic drawing and summary of specifications for HVAC
- Inspection of the HVAC technical area with focus on AHUs serving the following areas of Module II: granulation (EN005), compression, FBD and Coating machine.
  - The different AHUs were installed in a clean and organized technical area on the first floor. Filters were monitored once every two weeks and cleaned or replaced if needed.



At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

### **Day 3**

The inspectors started by giving feed back on observations of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspectors then reviewed the SOP on assigning code numbers to raw materials, packaging materials, in-process and finished goods.

The inspectors then made a quick orientation tour of the following section of the laboratory: Sample receipt area, instrumentation area, room for storage of reference and working standards, balance room, wet chemistry room, and the hot room. The inspectors then proceeded to inspect the following aspects of the quality control laboratory:

- SOP on numbering system in quality control department.
- Sample receipt, storage and related registers for finished goods samples, in-process samples and stability samples. Records of sampling of selected materials were reviewed in detail.
- Wet chemistry laboratory and management of laboratory materials:
  - Standardization, labelling and validity of volumetric solutions: 1 month.
  - Labelling and validity of test solutions: 3 months.
  - Labelling and validity of chemical powders: 3 years from date of first opening with a maximum of 5 years.
- Instrument laboratory: Qualification, calibration and preventive maintenance:
  - SOPs and records of calibration and daily verification of selected analytical balances using standard weights.
  - Qualification of HPLC and related protocol. The manufacturer used different HPLCs run by LC solutions or Empower software. The handling of the HPLCs and the audit trail were inspected for compliance. The qualification of HPLCs was initially and regular requalification was performed each quarter.
  - Routine calibration and qualification of dissolution testers, e.g. 12 stations with an auto-sampler.
- Starting materials and finished products specifications, testing and release.
  - Reviewed raw data and archived electronic data. All containers were sampled and tested for ID by IR (located in the adjacent Unit VI). Composite samples were prepared by pooling portions of samples from up to 10 containers and each was independently tested for assay and LOD. The remaining samples were divided into 2 portions (1:2) the portions pooled into two composite samples one for full analysis and the other kept as control samples.
- Preparation, storage and usage of Reference and Working Standards.
  - SOP on preparation, standardization, storage and usage of reference and working standards.
  - Records of analysis and preparation of selected batches of working standards.
- Qualification and monitoring the Purified Water system: Qualification protocol and report, sampling and testing SOPs, sampling schedules, results of chemical and microbial analysis and trends over phase I (*released on 18.11.2009*), II and III (*started on 15.12.2009 and not yet complete*) were reviewed. No major issues arose out of this review.

The inspection of the primary and secondary automatic bottle packing and blister packaging modules plus related IPC room (leak test apparatus) followed. There was no activity taking place.

**Qualification, validation and preventive maintenance:**

The inspection of the following aspects of qualification and validation system followed:

- Validation Master Plan: VMP-00 effective 10.04.2009 which outlined qualification, validation and calibration policies.
- The qualification report of the FBD in module 2 and related AHUs (completed in October 2009) were inspected.
- SOP on environmental monitoring which provided for passive and active air and surface sampling every month in related locations. Results for module 2 (Nov. 2009 - Oct. 2010), WH (Nov. 2009 - Oct. 2010) and Module 4 (Aug - Oct. 2010) were reviewed and noted to be very low.
- SOP on cleaning validation programme with related protocols and matrix for APIs (*based on dose criteria*). It was noted, that in addition, the cleaning of each product was validated.

At the end of the day, the team reviewed progress of the activities of the day and agreed on the tentative programme for the next day. Feedback was deferred to the following day.

**Day 4**

The inspectors started by giving feed back on observations of the previous day and obtained preliminary clarifications from management where deemed necessary. The inspection then proceeded with the review of the following areas:

- Process validation protocol and report for the product under focus. The validation had been done based on specifications for the USA market and the data were only evaluated and a report compiled according to the "Rest of the World" specifications. The BMRs and corresponding raw data for the three batches used in validation were reviewed in detail. The BMR did not record details of the extra sampling prescribed by the protocol and the sampling SOP.
- Records of sampling and testing of a consignment of HDPE containers 75cc, 5000 packed in 7 boxes. The sampling was not consistent with the SOP and ISO2859 guidelines.
- Stability testing programme:
  - SOP on stability management.
  - Protocol for the product under focus. The storage conditions used were 25<sup>0</sup>C/60%, 30<sup>0</sup>C/75%, 30<sup>0</sup>C/65% and 40<sup>0</sup>C/75% for packs of 30s and 250s in HDPE containers. The protocol allowed a picking window of 3 days and analysis had to be completed within 10 days during accelerated studies and 15 days during real time studies. The stability programme, records and data for three batches were reviewed.
- Self inspection SOP, schedule for 2010 and reports for audits carried out in May 2010. The policy was to audit all areas thrice a year and reports showed that the programme was followed and CAPAs reviewed and closed in a timely manner.
- Technology transfer protocol and report for the product under focus from Hetero Drugs Ltd Unit III to Hetero Labs Ltd Unit V.
- Analytical methods were transferred from unit III to Unit V according to SOP on analytical method transfer for site transfer products.

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- Analytical method transfer protocol and report for Assay by HPLC of the product under focus was assessed and no issues were noted.
- Area qualification report for granulation area in Module II (Room G043). It was supplied by AHU No. ENE-005. Qualification was performed in accordance to ISO14644 and WHO guidelines.
- SOP on batch release was assessed. No batch release for the market had yet been performed.
- The approval process of material codes was performed between the R&D, the QC, the IT and the QA in the corporate system. A material code was assigned to materials from different suppliers. This could not ensure that during the formulation of an authorized product, the authorized supplier was considered.

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feed back and a closing meeting for the inspection with reactions from the management of the company.

## **2.1 QUALITY ASSURANCE**

The company had an organization chart and job descriptions specifying the responsibilities and reporting relationships of the various staff. The quality assurance systems were supported by documented and approved procedures to guide routine operations and activities. There were systems for control and approval by QC/QA of starting materials, intermediate products, finished goods for use or distribution, but as commercial production commences, there may be need for installation of a computerized system (e.g. SAP) to strengthen these controls.

Policies and procedures were in place for qualification and validation of equipment and systems, change control and deviation management, self inspection and product quality review. These systems had not been fully tested or fully deployed since only submission batches had been produced. The vigilance, openness and strong motivation of the Quality Assurance staff and management demonstrated during the inspection were an assurance that continuous improvement was inevitable.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

The company had established adequate facilities and procedures for the production and quality control of the products applied for. The level of execution and/or maintenance so far in place was adequate to ensure products of consistent quality.

Never-the-less, the minor observations noted during the required attention to ensure continuous improvement. Indeed satisfactory CAPAs have been received.

## **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, equipment and apparatus were cleaned adequately and regularly to avoid chances of contamination and cross-contamination. A "wash hands" sign in the first level



change room would further strengthen the personnel hygiene procedures as they enter into production areas. This has been addressed.

## **2.4 QUALIFICATION AND VALIDATION**

Qualification of equipment and validation of systems and processes was guided by a Validation Master Plan, VMP-00 (effective 10.04.2009) which outlined policies and approaches to qualification, validation and calibration. Validation and qualification activities were guided by approved protocols. Equipment underwent initial qualification and requalification was planned every after 5 years while calibration and preventive maintenance was planned at least once a year. The principles for cleaning validation were established plus the policies on number of cleaning cycles, discussion of worst case, setting of limits, justification of the limits and analytical methods used and general documentation

There was a summary of qualification status and due date for routine requalification for major production, packaging and QC equipment and utilities. The qualification and validation status and the need for requalification or revalidation were also evaluated during PQR and change control procedures.

## **2.5 COMPLAINTS**

There was a system (SOP) for handling customer complaints. No complaint had been logged for this site as no product had been yet marketed from the site.

## **2.6 PRODUCT RECALLS**

There was a system to handle product recalls (SOP). It provided for a classification of recalls into class I, II, and III with timelines of 2, 7 and 15 days respectively for initiation of the recall. It provided for a dummy recall with one batch once a year to evaluate the effectiveness of the procedure. Since no product from this site had been marketed, the effectiveness of the recall procedure had not been evaluated either through a real or dummy recall.

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

There was a system to handle contracts which provided for evaluating contractors before being awarded a contract. No production on contract was envisaged at the time. Contracts existed with vendors of in-puts and services including selected complex analytical procedures like DSC, XRD, AA and microbiology testing, but these were not evaluated.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

The procedures for self inspection were outlined in an SOP. The policy was to audit all areas thrice a year and reports showed that the programme was followed and CAPAs reviewed and closed in a timely manner.

There was a procedure for vendor qualification (SOP) which provided for vendor audit. QA was responsible for assessing the need and coordinating the audit of vendors.

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## **2.9 PERSONNEL**

There was an organization chart and job description to guide personnel. The responsibilities of staff including key personnel like head of production, head of quality control and head of quality assurance were defined and there were personnel designated to deputise the key personnel in their absence. The responsibility for batch review and release was assigned to head of QA assisted by other QA officers.

There were adequate numbers of personnel to carry out the site responsibilities and the staff were found to be well motivated and committed to perform their work. A system had been put in place to ensure selection and maintenance of personnel with adequate knowledge and skills to perform assigned duties.

## **2.10 TRAINING**

The company had policies and programme for initial and regular training of personnel. The system was designed to ensure that newly recruited staff members received orientation plus training in basic GMP, hygiene & safety, written procedures, technical skills and SOP training as well as continuous training for continuous improvements and new procedures. Training records were maintained.

Records of training of selected personnel were reviewed and indicated that training was generally regularly conducted and records maintained. However, a need for more practical training for new staff and further strengthening of evaluation of the effectiveness of such training was observed.

## **2.11 PERSONAL HYGIENE**

Personnel hygiene was part of the basic training received by all personal during induction and basic GMP training. Production staff were required to undergo health checks on recruitment and regularly thereafter.

Procedures for entrance into production areas required staff members to change into clean factory garments and there were change rooms of adequate size but a clear sign to remind staff to wash their hands before entrance into production areas was lacking. This has now been addressed.

## **2.12 PREMISES**

Buildings and facilities used for manufacture and quality control were generally located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Two production lines (Module 2 and 4) and two packaging lines (one bulk and one blister) were complete and operational out of the planned 7 production lines and 7 packaging lines. The rest were either under various stages of construction, commissioning or qualification. Production module 2 was designed in a cubicle concept and with capacity of 80kg to 200kg batch size. This was already commissioned and this is where the validation batches of the product under focus were produced. Production module 4 was designed in also a cubicle concept and with capacity of



250kg to 750kg batch size. This was already commissioned and was ready for production of commercial batches.

The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. There was also sufficient space for the movement of materials and personnel. There were separate personnel and material entrances. Temperature, relative humidity and pressure differentials were regularly monitored and recorded.

The utilities including the HVAC system, compressed air, the water treatment plant, steam production and Purified Water (PW) were generally well designed, monitored and maintained. All critical processing areas were supplied with filtered air through EU4, EU7 and H13 filters (especially where air was re-circulated).

### **2.13 EQUIPMENT**

The site had adequate numbers of processing and testing equipment which were installed, cleaned and maintained in a way that minimized the risk of error and contamination. There were SOPs and logbooks to support the operation, use, cleaning and maintenance of equipment. Appropriate status and calibration labels were attached to the equipment. The calibration schedule and the related documentation were available. Some observations were made in relations to sieves, FBD bags, punches and dies, but these have been subsequently adequately addressed.

### **2.14 MATERIALS**

#### *Starting materials*

All materials were sourced from approved suppliers. They were quarantined, sampled and tested before approval for use. A list of approved vendors was available at the receiving area and was always followed in procurement and receiving of materials reviewed. All containers of active pharmaceutical ingredients were sampled individually and tested for identity while full testing was done on a composite sample. Materials were identified by a unique number, but the system in place for control of materials was not robust enough to ensure that the manufacture complies with registration commitments with respect to specifications and source of APIs. Some incidences were observed where APIs from different vendors were controlled under one code. This concern has been satisfactorily addressed.

Purchase of a computerized system (SAP) had been initiated. The conditions of storage were all controlled and monitored and were generally found to be appropriate for the materials held.

There were procedures and facilities for separation and disposal of rejected materials.

#### *Packaging materials*

Packaging materials were purchased from approved vendors. Each consignment was quarantined, sampled and tested before release for use and the sample size was in line with MIL-STD-105E, ANSI Z1.4, ISO2859 or BS6001, although a few exceptions (visual inspection of HDPE containers) were noted.

### *Intermediate and bulk products*

The hold times of various intermediates and bulk products had been validated and were systematically monitored.

### *Finished products*

Procedures had been put in place to ensure that products were not released from the site unless each batch was tested and its production, packaging and testing records were reviewed and found in compliance with GMP and regulatory requirements.

## **2.15 DOCUMENTATION**

A documentation system was in place to guide production and control of products. These included: batch master formula, specifications of starting, 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.

QA department was responsible for the control of preparation, review, approval, distribution and review of documents. Most documents and SOPs were new.

## **2.16 GOOD PRACTICES IN PRODUCTION**

Production took place in two newly commissioned modules. Each module was separate and was fitted with equipment and facilities for granulation, drying, compression and coating equipments.

The production process of the product under focus had been successfully transferred from Hetero Drugs Ltd Unit III to Hetero Labs Ltd Unit V and the protocol used plus the report compiled were available. Production procedures were well documented and had been validated. Production was guided by comprehensive batch manufacturing instructions and records.

The various manufacturing stages were performed in effectively segregated areas. The rooms, equipment and containers were generally appropriately labelled with status, content and stage of processing.

Line clearance checks were conducted before start of production and packaging, though some lapses were noted in this area. In-process, yield and reconciliation checks were conducted at the appropriate stages and any deviation was recorded and investigated. Readings for  $\Delta P$ , temperature and relative humidity were taken regularly and recorded either in the BMR, BPR or logbooks.

Review of log book for punches and dies showed that their issue, use and maintenance were well controlled.

## **2.17 GOOD PRACTICES IN QUALITY CONTROL**

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There was a quality control and assurance department whose functions were independent of production. The laboratories generally had adequate facilities in form of space, working environment, equipment, chemicals, reagents, personnel and approved procedures for sampling and testing starting materials, packaging materials and finished goods. The equipment evaluated had been qualified and/or calibrated and the procedures were validated. Methods were transferred from unit III to Unit V according to the SOP on analytical method transfer for site transfer products. Selected cases reviewed did not raise any issues.

Samples of starting materials and finished products were retained for future analysis. Finished products were put on initial and continuing stability studies (SOP on stability management) and the hold time for intermediates and bulk products had been scientifically established.

The protocol and report for stability testing of product under focus showed that stability studies were conducted at 25<sup>0</sup>C/60%, 30<sup>0</sup>C/75%, 30<sup>0</sup>C/65% and 40<sup>0</sup>C/75% for packs of 30s and 250s in HDPE containers.

### **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 guidelines.

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

The WHOPIR is valid for a maximum of 3 years, unless the site is found to be non-compliant in another inspection before the 3 years had lapsed.