



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Hetero Drugs Limited
Unit number	Unit III
Production Block	Block A and B
Physical address	Hetero Drugs Limited, Unit III Block A & B, Survey No.: 51, # 22-110, I.D.A., Jeedimetla, Qutubullapur, R.R. District, Hyderabad 500 055, Andhra Pradesh, India.
Contact person and email address.	1. Mr. G.P. Rao - Vice president Operations <ul style="list-style-type: none">• E-mail: gprao@heterodrugs.com• Tel.: +91-40-23096172
Date of inspection	25, 26, 27 and 28 August 2009
Type of inspection	Routine Inspection
Dosage forms(s) included in the inspection	Uncoated and coated tablets and hard gelatine capsules. Oral liquids.
WHO product categories covered by the inspection	Products against HIV/AIDS (HA)
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and batch release of coated and uncoated tablets, hard gelatine capsules and liquid syrups.



Part 2: Summary

General information about the company and site

The facility inspected was **M/S Hetero Drugs Limited, Unit III Block A & B, Survey No.: 51, # 22-110, I.D.A., Jeedimetla, Qutubullapur, R.R. District, Hyderabad 500 055, Andhra Pradesh, India, here after called Hetero Drugs Ltd, Unit III.** According to the Site Master File, Doc No.: SMF-FIIIA-01-00, effective 27 May 2009, Hetero Drugs Ltd had its registered office at Hetero House, H. No. 8-3-166/7/1, Erragadda, Hyderabad - 18, Andhra Pradesh, India, plus manufacturing facilities and research centers in the following locations:

	Name	Location	Responsibility
1.	Hetero Research Foundation	Sanath Nagar, Hyderabad	R&D plus technical support to manufacturing facilities
2.	Hetero Drugs Ltd (Unit I)	Banthapally Village, Jinnaram Mandal, Medak District	API manufacturing
3.	Hetero Drugs Ltd (Unit IV)	Banthapally Village, Jinnaram Mandal, Medak District	API manufacturing
4.	Hetero Labs Ltd (Unit I)	Goddapotharam Village, Jinnaram Mandal, Medak District	API manufacturing
5.	Hetero Drugs Ltd (Unit II)	Gandhinagar, Hyderabad	FPP manufacturing - for domestic market
6.	Hetero Drugs Ltd (Unit III)	Jeedimetla, Hyderabad	API manufacturing
7.	Hetero Drugs Ltd (Unit III, Block A)	Jeedimetla, Hyderabad	FPP manufacturing
8.	Hetero Drugs Ltd (Unit III, Block B)	Jeedimetla, Hyderabad	FPP manufacturing

The factory site of **Hetero Drugs Ltd (Unit III, Block A & B)** at Jeedimetla, Hyderabad, was about 45km away from Hyderabad airport. It was located on a plot of 6 acres (22,740m²) of which, according to the company presentation, 6,430m² was built up for block A and 16,310 m² for block B. The immediate environment of the site was:

1. East : Main road
2. West : Hetero Drugs Ltd (Unit III) API manufacturing facility
3. North : Residential area
4. South : Electrical and insulators industry

There were two production blocks on the site, namely: Production Block-A (*Tablets and Hard Gelatin capsules*), Production Block-B (*Tablets, Hard Gelatin Capsules and Liquid Syrups*). Each production block had warehouses, manufacturing, packaging areas and QC laboratory. Utilities like HVAC and Purified Water system were independent for each production block. Dining facilities were common for the two production blocks. To avoid dust generation landscaping was carried out on the site.



1. Block A:

This block had four separate modular manufacturing areas with an annual capacity of 918 million tablets and 187 million capsules: Module 1 (*Tablets*) and 2 (*Tablets*) situated on the ground floor; Module 3 (*Tablets*) and 4 (*Capsules*) situated on the 1st floor. Service area was on the 2nd floor. Warehouses: RM and FG on the ground floor while PM on the 1st floor. QC lab was located on the 1st floor. The floor in the production area was epoxy coated.

2. Block B

This block had 6 manufacturing modules with an annual production capacity of 1.8 billion tablets, 350 million capsules and 3.5 million units of oral liquids. Ground floor had two manufacturing modules (*Module I for Tablets and Module II for Tablets & Capsules*), RM stores, FG warehouse, primary and secondary packaging areas. The 1st floor had the QC lab, stability chambers, control samples area, water treatment plant, PM stores, segregated cafeteria and service area. The 2nd floor had liquid syrups module, 2 tablets manufacturing modules (*Module 3 of 100kg and Module 4 of 60kg*), 1 module for tablet & capsule manufacturing (*Module 5 of 250kg which was under installation qualification*), RM stores, FG warehouse, 3 packaging lines and a microbiology lab.

According to the SMF, the plant employed a total of 438 people distributed as follows:

Department	No. of employees	
	Block A	Block B
Production	37	54
Quality Control	39	49
Quality Assurance	28	48
Warehouse	14	8
Engineering	16	23
Human resource Development	03	4
Research and development		39
Analytical development		33
Regulatory Affairs		40
Information Technology		3
Block total	137	301
Unit Total	438	

History of WHO and/or regulatory agency inspections

Hetero Drug Ltd (Unit III) was previously inspected by WHO Prequalification team in September 2006 (*Block B, Tablets & capsules only, non-compliant*), May 2007 (*Block B, Tablets & capsules only, Compliant*), November 2007 (*Block A, Tablets & capsules, Compliant*) and August 2009 (*Special inspection, compliant*).

The above manufacturing facility had a valid manufacturing drug license number 22/RR/AP/2001/F/R issued by the Drug Control administration of Andhra Pradesh, India and is valid until 31st December 2012 for the manufacture of the solid oral dosage forms (*Tablets & capsules*) and liquid oral dosage forms (*Liquid Syrups*). The licence was the same for Block A and B.

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According to the SMF and company presentation, the site had also been approved by the following regulatory agencies:

- Agencia Nacional de Vigilancia Sanitaria (ANVISA) - Brazil
- National Drug Authority (NDA) - Uganda
- Medical Control Authority of Zimbabwe (MCAZ) - Zimbabwe
- Pharmacy, Medicines and Poisons Board (PMPB) - Malawi
- Pharmacy and Poisons Board (PPB) - Zambia
- Ministry of Health and Social Service (MHSS) – Namibia
- Tanzania Food and Drugs Authority (TFDA) – Tanzania
- Food and Drug Board (FDB) – Ghana
- Ministry of Health (MoH) – Ivory Coast
- Ministry of Health (MoH) - Ukraine
- Ministry of Health (MoH) - Kenya
- Central Drug Control Board (CDCB) – India
- ISO 9001 - 2000 (BIS)
- US FDA (Block B only)
- Spanish Agency for Medicines and Healthcare Products (Block B only)
- Agencia Nacional de Vigilancia Sanitaria (ANVISA) - Brazil (Block B only)

Focus of the inspection

The inspection generally focused on the activities related to the production and control of tablets and had gelatine capsules in **Blocks A and B** and with particular focus on products listed in Part 1 above. The inspection covered all the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities but also paid special focus on verification of raw data to support the data summarized in dossiers submitted to WHO or related to batches supplied to several procurement agencies.

Inspected Areas

Day I

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards. They explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection including the newly introduced Notice of Concern (NOC) and elaborated on the tentative inspection plan. After confirming the inspection

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plan, the company made a presentation about the company and the site to be inspected. The presentation highlighted the capacities, Quality Management System and inspection history of the site. A copy of the presentation was obtained and will be filled in the company file.

The presentation also highlighted the following changes since the previous WHO inspection:

1. New equipment added in Block B:
 - a. Compression machine 37 Station (Cadmach)
 - b. Compression machine 55 station (Cadmach)
 - c. Compression machine 45 station (Cadmach)
 - d. Rapid Mixer Granulator 600L (Saral)
 - e. Octagonal Blender 400L (STM)
 - f. Octagonal Blender 2500L (SAAN)
 - g. Octagonal Blender 4500L (SAAN)
 - h. Roll Compactor (Tainfu Machinery)
 - i. Auto Coater 48 inches 120kg (Kevin)
 - j. Auto Coater 60 inches (Solace)
 - k. Bulk Packaging Line (Hyengi Pharmaceutical Equipments Co. Ltd)
2. New facility added to Block B:
 - a. Liquid Oral Manufacturing line on second floor
 - b. 250kg capacity tablet manufacturing line on second floor (to be completed in December 2009)
 - c. 100kg capacity Manufacturing line on second floor
 - d. 60kg capacity Manufacturing line on second floor
 - e. Pellets manufacturing area (to be completed in December 2010)
 - f. Purified water loop 2 was added on second floor
 - g. Microbiology Lab on second floor
3. Modification done to Block A:
 - a. Material entry for sampling and dispensing rooms were separated
 - b. Personnel entry separated for sampling and dispensing rooms
 - c. Dispensed material hold area created
 - d. Additional storage area created for storage of approved raw materials
 - e. Separate HVAC systems were provided to provide clean area air to sampling and dispensing areas
 - f. Area for storing the bulk finished products was created on ground floor and first floor
 - g. Two compression machines were added
 - h. Microbiology facility shifted to Block B.
4. Central warehouse situated on a separate compound (Built up area is 2380m²)
5. Other proposed changes:
 - a. SAP (to be completed in April 2010)
 - b. LIMS (to be completed in January 2010)
 - c. TRIMS (to be completed in April 2010)

This was followed by document review for the following areas:

- ⇒ SOP on Allotment of Batch Numbers, where batch number has a format: EYXXX where E = Export oriented unit, Y = the last digit of the year of manufacture, XXX = serial number starting from 001.



- ⇒ SOP on Allotment of Batch Numbers, where batch number has a format: AYXXX where A = Block A, Y = the last digit of the year of manufacture, XXX = serial number starting from 001.
- ⇒ SOP index for Block A
- ⇒ SOP index for Block B
- ⇒ Organograms for the Unit III, Block A, Block B and the different departments in each block
- ⇒ Job descriptions of key staff and other staff
- ⇒ Training SOP, SOP on the training programme and training records of selected staff.
- ⇒ SOP on Personnel Health and Hygiene and health record of selected personnel.
- ⇒ SOP on Annual Product Review and APR reports for selected products for the year 2008.

Inspectors proceeded to inspect the following areas of Block B: Change rooms; RM/PM Receiving areas; Sampling areas; Warehouses for RM, PM, printed PM, roll labels, foils and loose labels; Dispensing areas; Manufacturing areas on ground floor (Modules I and II); Manufacturing areas on second floor (Module III and Liquid area); primary and secondary packaging areas on the ground and second floors; IPQC area in module I. The SOPs, use and cleaning log books, temperature and relative humidity records in the various areas were reviewed. Production and packaging activities in certain areas were observed and the corresponding BMRs and BPRs were reviewed.

The inspection ended late in the day so the review of the progress of the activities of the day, and giving the day's feed back was differed to the next day.

Day 2

The inspectors started by reviewing the areas inspected the previous day and gave feed back on the observations made. The company acknowledged the observations and indicated that they had initiated corrective action on some of the observations.

The programme of the day was agreed upon and the inspectors proceeded to inspect the Gents' change rooms for Block B and the following areas of Block A:

- ⇒ RM/PM Receiving areas on the ground floor following the logical flow: Offloading bay, dedusting area, change rooms to the warehouses, staging areas, weight checking areas, quarantine areas, approved RM warehouse, solvent storage and dispensing area.
- ⇒ The SOPs, Registers, Checklists and other documents related to receiving RM: SOP for receiving RM, receiving checklists for selected RMs, Raw Material In-ward Register, Approved Vendor List, SOP on transfer of material from one grade to another.
- ⇒ Packaging material quarantine, testing, storage and dispensing areas on the first floor. The SOP related to the operation of the dispensing booth were reviewed.
- ⇒ Selected batches of RM and PM were identified for detailed review of their material codes, approved vendors, sampling, testing and use.
- ⇒ The newly redesigned sampling and dispensing areas for RM plus related SOPs, use and cleaning log books.
- ⇒ Change rooms to the production areas, manufacturing modules I and II on the ground floor, manufacturing modules III and IV on the first floor and related IPQC areas, primary and secondary packaging lines. Relevant SOPs, use and cleaning log books, temperature, RH and ΔP monitoring records were reviewed.



After lunch, the following areas of the HVAC system were reviewed:

- ⇒ AHU distribution and pressure differentials drawings for both Block A and B, revalidation schedule for the AHUs, daily ΔP monitoring records. The SOP on operation of AHUs (including start up and switch off sequence) was reviewed.
- ⇒ The change control related to separation of the material and man entries to the sampling and dispensing areas in Block A, and installation of AHUs plus the related qualification (Protocol and Report) was reviewed. The facility qualification SOP, protocol and report related to the change was also reviewed.
- ⇒ The technical area housing AHUs for block B was inspected with detailed focus to selected AHUs (one for Bulk Packaging area 1 and another for secondary packaging area on ground floor).
- ⇒ Filter cleaning SOP and area.
- ⇒ Dust collecting system for capsule filling machine and related SOP for cleaning and another under installation for the sifter in the granulation for module I.

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company and agreed on the tentative programme for the next day.

Day 3

The day started with inspectors reviewing a number of SOPs on document control:

- ⇒ SOPs on preparation, review, approval, control and revision of standard operating procedures in block A and the entire Unit III respectively.
- ⇒ SOP on Document control.
- ⇒ SOP on Preparation, review and control of formats.

The vendor qualification system was reviewed. The questionnaires (one for RM and another for PM) used plus the reports of evaluation of selected vendors and the analytical reports for the first 3 batches analysed during evaluation of the vendor were reviewed.

The documents for AHU distribution in Block A and requalification schedules in the VMP were reviewed. Records for the last requalification of AHUs for Module I in block A were reviewed. Aspects qualified included non-viable particle counts, Air velocity, air changes per hour, air flow visualization test (DVDs for Smoke test), viable counts, settle plates exposed for 2 hours and active air sampling, recovery test, containment and leak test. The SOP was evaluated.

The BMRs and analysis records of selected batches and materials used were reviewed.

The process validation protocols and reports, including primary source data for the selected products were reviewed.

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company. Management outlined some of the corrective actions already initiated. They were advised to make a system-wide review of the observations so as to prepare comprehensive corrective actions.

Day 4

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The team started with the inspection of the new Central Warehouse for Raw Materials and Finished Goods located approximately 2km across the road and which was opened in July 2009. It had the RM storage area on the ground floor and the FG store in the basement. They were supplied with filtered air from AHU located in the mezzanine floor. The packaging materials were stored in a smaller separate block. There was an offloading/dispatch bay, change rooms, quarantine area, sampling room with a UDAF sampling booth, washing area for sampling utensils, the rejected materials area and returned goods area. The SOPs and log books related to the area were reviewed.

At the main site, the Purified Water (PW) systems for the two blocks were evaluated. The related drawings, operating SOPs and log books, sanitisation plus monitoring SOPs and records, sampling points, chemical and microbiological analysis and trend analyses were reviewed followed by inspection of the PW installations.

The following aspects were reviewed:

- ⇒ Complaints handling system related to Block A, SOP, complaints registers for 2007, 2008 and 2009 plus records related to selected examples of market complaints.
- ⇒ Complaints handling system related to Block B, SOP, complaints registers for 2008 and 2009 plus records related to selected examples of market complaints.
- ⇒ Product recall procedures, SOP, dummy recall protocol and related report for Block A and SOP for Block B.
- ⇒ Change control procedures, SOP, change control registers for 2009 (separate for warehouse, production, engineering, QA and QC) plus records of selected changes, especially those highlighted in the company presentation at the opening meeting.

This was followed by inspection of the quality control laboratory. The following areas and aspects of the QC laboratory were inspected:

- ⇒ Available space and equipment in the following sections: change room, room for documents review, instrumentation room, wet chemistry laboratory, hot room, controlled samples room and stability area.
- ⇒ Stability chambers of the following conditions were available:
 - 25⁰C/60%RH
 - 25⁰C/60%RH
 - 30⁰C/75%RH
 - 30⁰C/65%RH
 - 40⁰C/75%RH
- ⇒ Stability management programme, stability protocols, chamber charging registers, sample withdrawal registers and analysis records for selected products and related batches.
- ⇒ Preparation and standardization of the Working Standards (WS), related SOP, Reference standards and WS use records.
- ⇒ Routine maintenance and calibration of selected equipment (e.g. dissolution tester).
- ⇒ SOP on back up and retrieval of electronic data that provides for monthly back up of electronic data from each major analytical equipment to a DVD/CD.
- ⇒ SOP on sampling, testing and release of raw materials plus records of sampling and testing if selected consignment of raw materials.



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

2.1 QUALITY ASSURANCE

There was an organization chart and job descriptions specifying the responsibilities and reporting relationships of the various staff. A need to keep them consistent and up to date was noted.

All the routine procedures were guided by clear, written and approved procedures. Any changes were controlled and deviations were documented and their impact assessed according to approved SOPs. There were parallel procedures for Block A and Block B but steps to integrate them into one system had been initiated.

Systems were in place to control and ensure the quality of starting materials, intermediate products, finished goods and related data generated during production, quality testing, calibration and validation.

Equipment and systems had been qualified and procedures and processes validated. Consistency and continuous improvement in the quality of systems, procedures and products were ensured through change and deviation control and were regularly reviewed and monitored through self inspection, annual product review and evaluation of trends.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

The available facilities at the site, the manufacturing and quality control procedures were generally comprehensive and well executed and maintained by adequately qualified personnel to ensure products of consistent quality.

Nevertheless, there were some observations that required attention to further improve the degree of GMP compliance.

2.3 SANITATION AND HYGIENE

The production and quality control facilities were maintained at high level of cleanliness. Cleaning procedures for the equipment and the premises had been validated and were well executed. Good waste collection and management procedures ensured a high level of hygiene of premises.

Personnel changing procedures and related gowning were appropriate but the facilities and requirement for washing hands before entering production areas were inadequate as staff would have to enter toilet areas to wash their hands. There have been subsequently adequately addressed.

2.4 QUALIFICATION AND VALIDATION



There were separate Validation Master Plans for Block A and Block B, which outlined the policy and approaches to be followed in qualification of equipment and validation of systems and processes. Qualification included definition of user requirement and specifications (URS), Design Qualification (DQ), Installation Qualification (IQ), Operation Qualification (OQ) and Performance qualification (PQ). Validation and qualification were guided by approved protocols. The schedules and frequencies for planned requalification, validation and revalidation were outline in the the VMP. Reports reviewed showed that generally equipment was qualified and systems and process were validated.

2.5 COMPLAINTS

There was a system to record and investigate market complaints and feed back was promptly given and appropriate corrective and preventive action taken in most cases reviewed. It was noted that there only had been one complaint in 2008 and one complaint in 2009 related to products from Block B.

2.6 PRODUCT RECALLS

There was a recall procedure which had classified the deficiencies that would require a recall, the means of communication to be used, the timelines to conclude the recalls (*Class I within 2 days, Class II within 7 days and Class III within 15 days*), composition of the recall committee and the parties to be informed while conducting a recall.

There was a procedure to conduct dummy recalls at least once very year in order to evaluate the effectiveness of the recall procedures. One of the dummy recalls reviewed covered a batch supplied in Cameroon, Nigeria, Rwanda and Zambia.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The company did not carry out any contract production. Specialized analytical procedures like Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), NMR, MS were performed by Hetero Research Foundation. Some other tests were out to other labs and in such circumstances there was a contract that complied with the principles of GMP.

2.8 SELF INSPECTION AND QUALITY AUDIT

There were procedures to conduct self inspection at least twice a year for the purposes of monitoring the quality system and continuous improvement of the procedures. This procedure was comprehensive and covered all areas of production, quality control, quality assurance and engineering. There was a schedule with defined teams and the record showed that the schedule was complied with.

Vendor evaluation and approval included evaluations by R&D and QA, evaluation of a Drug Master File if it existed, a questionnaire filled by the vendor, analysis of at least 3 batches of the material, provision of TSE/BSE certificate if relevant and vendor audits. Vendor audits were conducted for all API sources and most of the APIs were supplied by sisters companies of Hetero and they had been audited. Selected suppliers of printed packaging materials had also been



audited. Suppliers of other materials were only audited if indicated by other evaluations of following negative trends is the quality of supplies.

Vendor requalification was done once every 3 years for APIs, once every 5 years for other raw materials and packaging materials. A supplier was disqualified following failure of 3 consignments or delivery of a contaminated consignment or failure to take adequate CAPAs.

2.9 PERSONNEL

The personnel met were well qualified to perform the duties assigned and generally had a high consciousness of GMP. There was an organization chart and job description to guide personnel. The responsibilities of the key personnel like head of production, head of quality control and head of quality assurance were well 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. Minor deficiencies which were noted in this area, mainly related to documentation, have subsequently been addressed.

2.10 TRAINING

The company had a comprehensive training program for all the employees. Training programs were divided into five categories: - Induction training, cGMP training, on the job training (SOPs Training), Training on specific skills, and continuing training. The concerned department head identified the training needs based on their assessment and job assigned to the employees.

Records maintained included Personnel Training Card and Training Log Book.

Effectiveness of Training was assessed by:

- ⇒ **Immediate evaluation** of the personnel which was conducted after each training session by questionnaire or by oral assessment.
- ⇒ **Long-term evaluation** which was carried out by the concerned supervisor and training coordinator. The concerned department head identified the retraining needs of the employees based on their consecutive assessment and audit deficiencies. Any change in system or procedures requires retraining.

2.11 PERSONAL HYGIENE

Personnel were trained in personal hygiene procedure and facilities were provided in form of change rooms, protective garments and disinfectants. The facilities were generally adequate and the procedures were well enforced, but a requirement to wash hands prior to disinfection of hands was not documented anywhere. The health of the staff was checked on recruitment and thereafter every year. Medical check records were maintained for each staff.

2.12 PREMISES

There were two production blocks on the site:

- ⇒ **Production Block A** with four separate modular manufacturing areas: Module 1 (*Tablets*) and 2 (*Tablets*) situated on the ground floor; Module 3 (*Tablets*) and 4 (*Capsules*) situated on the 1st floor. The packing facilities included one bulk packing line, three blister packing lines



and one strip packing lines. RM and FG warehouses were located on the ground floor while PM warehouse was on the 1st floor. QC lab was located on the 1st floor.

- ⇒ **Production Block B:** This block had 6 manufacturing modules built in a cubicle concept with a unidirectional flow. Ground floor had two manufacturing modules (*Module I for Tablets and Module II for Tablets & Capsules*), while the 2nd floor had a liquid syrups manufacturing module, 2 tablets manufacturing modules (*Module 3 of 100kg and Module 4 of 60kg*) and 1 module for tablet & capsule manufacturing (*Module 5 of 250kg which was under installation qualification*). The packing facilities included 3 bulk packing lines, 2 blister packing lines, 1 strip packing line and one liquid filling and packing line. Ground floor had RM stores, FG warehouse, primary and secondary packaging areas. The 1st floor had PM stores.

The location, design, construction and maintenance of the premises were suitable to support production and storage of quality products. The design supported unidirectional flow of the manufacturing processing and there was adequate space for placement and operation of the equipment. The storage facilities allowed for effective segregation and security of materials and products at different stages of processing and those rejected.

The construction of the premises plus the installation of equipment and utilities enabled effective cleaning and maintenance. The premises were generally in a good state of repair. Block A was designed in such a way that staff used the production areas (granulation, compression and capsule filling) to go to the final stages of production (coating and capsule polishing). This restricted the block to modular campaign manufacturing only.

There were goods receipt areas with facilities for dedusting and quarantining the RM and PM. Entry into warehouses, production and QC areas was restricted and was through changing rooms where appropriate gowning took place. Watches and other loose jewellery were not allowed beyond the change rooms. There was no requirement or facilities to wash hands unless one had used the toilet although hand sanitization was practiced. This has been addressed.

Pest control was managed by an outside contractor following an approved procedure and schedule. The location and frequency of the type of control used to be was defined. Measures used included Insecticutors, rodent baits and glue pads.

HVAC and Dust extraction systems

There was an HVAC system fitted with a series of filters in the plenum (20 μ , 10 μ , 5 μ , and 0.3 μ) and designed with 90% - 95% re-circulated air and 5% - 10 % fresh air. Pressure across the filter was monitored regularly through potable magnehelic gauges while pressure differentials between adjacent areas was monitored using fixed magnahelic gauges. The return grills were either located on risers or on the ceiling. Observations were made with respect to balancing and operation of certain AHUs and the cleaning of filters. These have been addressed.

There were dedicated dust extraction system attached to compression and capsule filling machines. Plans had been initiated to install dust extraction systems to the sifting and milling machines to provide an environment conducive for manufacturing and to avoid cross-contamination.



Water purification system

There were two water purification systems: One serving Production Block-A, with a Purified Water (PW) storage tank of 1000 litres capacity and the second one serving Production Block-B with a generation capacity of 1200L/hr and a PW storage tank of 3000 litres capacity. Both systems were supplied from municipal water supply.

In Block A, water was purified by passing through dual filter (sand/carbon filter); Cation-anion exchange; mixed bed; high intensity UV disinfection unit; pumped via RO unit; UV system; 10 μ and collected in the SS316L storage tank fitted with a 0.2 μ vent filter. There was an online conductivity meter. The PW was pumped through 5 μ and 0.8 μ filters into a continuous recirculation user loop made of electro-polished SS316L at 1600LPH. The tank and the loop were fitted with temperature sensors to monitor the sanitisation conditions. The system was regularly monitored, sanitised and maintained such that the trend results showed that the water quality was well under control.

In Block B, water was purified by passing through a quartz filter; softener; RO-EDI system; and collected in a 3KL SS316L storage tank fitted with a 0.2 μ vent filter. From here PW was distributed into two continuous recirculation user loops made of electro-polished SS316L at 4200LPH each through a high intensity UV disinfection unit: - one loop supplied ground floor manufacturing area and QC laboratory on the first floor while the second loop supplied second floor manufacturing area, microbiology laboratory and analytical development laboratory.

2.13 EQUIPMENT

There were adequate numbers of equipment for the production and testing products manufactured at the site. They were generally well designed, had been qualified and they were regularly calibrated and maintained. The contact parts for all equipment were made up of SS316 while the non-contact parts were made of SS304.

There were use, cleaning and maintenance logs for each piece of equipment.

There was a schedule and corresponding records for the preventive maintenance programme of each piece or group of equipment. In all cases reviewed, the schedule was complied with and the equipment were generally in a good state of repair.

2.14 MATERIALS

Starting materials

There was a system for development, qualification, disqualification and requalification of vendors of Raw Materials and Packaging Materials. This procedure was generally well implemented and a comprehensive list of approved vendors existed. This list was always followed in procurement and receiving of materials reviewed. The system of vendor approval included a comprehensive questionnaire filled by the manufacture, testing of a pre-shipment sample and, when found necessary, auditing of the facilities of the vendor and/or production of pilot batches.

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Receipt of RM and PM followed the standard routine according to approved SOPs. A purchase order (PO), goods received note (GRN) and Certificate of analysis (COA) had to be available before goods were unloaded.

All containers of active and inactive materials were sampled and tested for identification. A sample from each container was tested for identity and the other tests were done either on a pooled or composite sample. There was a procedure for making composites and the SOP had been recently revised to remove the maximum number of samples that could be pooled.

The storage conditions of all materials were defined and a list was available at the receiving area to guide the staff to place the material in the right area.

Packaging materials

Packaging materials were purchased from approved vendors. Each consignment was quarantined, sampled and tested before release for use.

Intermediate and bulk products

Granules, uncoated tablets, coated tablets and capsules were stored in sealed SS In-Process Containers (IPCs) and their holding time had been validated.

Finished products

Each batch of finished products was held in quarantine until it was tested and its production, packaging and testing records reviewed and found in compliance with GMP and regulatory requirements.

Rejected materials and products

There were separate storage facilities in which rejected material were securely stored until either they were disposed off by return to the supplier or destruction, or they were reviewed and approved by QA for further testing and repackaging.

Reagents and culture media

Adequate records for the receipt and preparation of reagents and culture media were present. Preparation is carried out in accordance with written procedures. Standard stock reference culture and subcultures were used. Both positive and negative growth test were performed on all media.

Reference Standards

There were dedicated facilities (*LAF, refrigerator and desiccators*) for the preparation and storage of reference and working standards. The procedures for preparation of working standards were comprehensive. Reference and working standards were well labelled and the records for standardization of working standards were well maintained.

2.15 DOCUMENTATION



There were procedures for preparation, review, approval, authorization and control of standard operation procedures and other documents. There was a dual system of documentation, one specific to Block A and another covering the entire Unit III (*but this one did in practice only cover Block B*). For products reviewed, there was a master formula, specification of starting and packaging materials, production and packaging instructions, batch processing and packaging records, finished product specifications, standard testing procedures and corresponding results. Most of the documents carried a unique number and their documentation, change and retrieval were well controlled by the quality assurance department.

There were some minor observation on the reference numbering, scope, clarity and cross-referencing of some SOPs and documents. These were subsequently addressed.

2.16 GOOD PRACTICES IN PRODUCTION

There were written procedures and records to manage the receipt, quarantine, sampling, labelling, storage and dispensing of materials; cleaning of equipment and premises; processing, packaging and distribution of products.

Any deviations from the approved procedures were documented and approved before taking appropriate action. The process of assessing the impact/risk of incidents, deviations and changes needed to be strengthened and better documented. Limits for yield had been set at different stages of production and packaging and any results beyond the limits were investigated and documented.

The procedures employed in production tablets and capsule included wet granulation using a Rapid Mixer Granulator, dry granulation using a Roll compactor and melt granulation using a Hot melt extruder. Pelletisation was either by extrusion and spherodisation using an Extruder and Spherodiser or by wurster technique using a Fluid Bed Processor. Drying was done in a Fluid Bed Dryer while blending was done using either an Octagonal or Bin blender.

Compression was either single or double layers using single or double rotary compression machines, while either film or sugar coating was done in Auto coaters. Punches and dies were cleaned and inspected for damage on return to the stores.

Capsulation was done by tamping and dosing using Automatic Capsule Filling Machines.

Packaging was done either in strips (Alu/Alu), blisters (Alu/Alu, Alu/PVC, Alu/PVdC) or bottle containers.

The equipment used in processing and packaging had been qualified and the processing and cleaning procedures had been validated.

Records were maintained to confirm that procedures were followed during production and to facilitate review before release.

2.17 GOOD PRACTICES IN QUALITY CONTROL



There were quality control and quality assurance departments whose functions were independent of other units including production. Quality assurance department was involved in approving new vendors for starting and packaging materials and equipment.

The quality control laboratory had adequate facilities in form of space, equipment, reagents and chemicals to test all starting material, packaging materials, intermediates and finished products before release for use or distribution.

Adequate sampling procedures and plans were used and the testing procedures were documented and appropriately validated.

Quality assurance staff reviewed all the production and testing records for each batch before it was released for distribution. Retention samples were kept from each batch of starting materials and finished products to facilitate any future investigation, if necessary.

There was an adequate stability testing programme supported by several stability chambers. Records of stability testing were maintained and could support the storage conditions and shelf life claimed for the products.

Sample Management

Sample receipt and distribution was managed following an approved SOP. Testing of a sample was allocated to an analyst who had completed the necessary training.

General and wet chemistry laboratory

The laboratory and its fittings and services were in a good state of repair and there was a fume cabinet for safe handling of volatile chemicals and reagents.

Balances and other QC equipment were regularly maintained and calibrated. Preparation of bench reagents was satisfactorily recorded. The dissolution equipment was adequately calibrated and the records were available: the temperature probe was calibrated; shaft eccentricity, RPM and paddle clearance had been regularly checked; performance checks were measured using the standard USP tablets (Salicylic Acid and Prednisone). No matters of concern were noted.

Instrumentation

UV visible and FTIR instruments were used. Both were regularly maintained and calibrated. HPLC column logs were well maintained. Records of issue, performance and maintenance were available.

Components and packaging material testing laboratory

The testing laboratory was housed adjacent to the PM warehouse on a separate floor from the chemistry and microbiology laboratories. It was equipped to perform the necessary routine tests on packing materials. The necessary apparatus for testing PM was available.



The sampling plans used were consistent with those prescribed under British Standard BS 6001-1 and AQL were appropriately applied.

Records of sampling and testing of selected examples of packaging materials were reviewed with no major deficiencies observed.

Microbiology Laboratory

A new Microbiology Laboratory had been installed in Block B, which now covered all microbiological testing for both Block A and Block B.

The laboratory was well designed with two separate Cleanrooms designed with airlocks and pass boxes. A LAF working area was placed in each room. The work area was classified as class A and the surrounding Cleanrooms is classified as a class C room.

The Microbiology Laboratory was well equipped with two separate autoclaves. Both were found qualified and validated. A sufficient number of incubators were present. The temperature in each incubator was recorded on a daily basis.

The separate wash area with an autoclave used for decontamination was found adequate.



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, **M/S Hetero Drugs Limited, Unit III Block A & B, Survey No.: 51, # 22-110, I.D.A., Jeedimetla, Qutubullapur, R.R. District, Hyderabad 500 055, 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

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.