



**Prequalification Team Inspection services  
WHO PUBLIC INSPECTION REPORT  
(WHOPIR)**

**Finished Product Manufacturer**

**Part 1: General information**

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| Name of Manufacturer                                                 | M/s. Hetero Labs Limited                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Unit number                                                          | Unit-III                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Production Block                                                     | Block-A, Block-B                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Physical addresses                                                   | <u>Production Unit:</u><br>Survey No. 51, Plot 22-110, Industrial Development Area (I.D.A.), Jeedimetla, Hyderabad-500 055, Telangana State, India<br><u>Central Warehouse:</u><br>Plot-14 (Part), Survey No. 50, Phase-III, I.D.A. Jeedimetla, Hyderabad-500 055, Telangana State, India<br><u>Finished Goods Warehouse:</u><br>Plot-38, Survey No. 300 & 306, Sri Venkateswara Co-operative Industrial Estate (S.V.C.I.E. ), Ramireddy Nagar, Jeedimetla, Hyderabad-500 055, Telangana State, India |
| Date of inspection                                                   | 9 – 12 June 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Type of inspection                                                   | Routine inspection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Summary of activities of manufacturer (e.g. manufacturing, packing). | Manufacturing of solid dosage forms<br>– Tablets (uncoated and coated)<br>– Capsules<br>– Oral liquids<br>Primary and secondary packaging<br>Storage<br>Quality control                                                                                                                                                                                                                                                                                                                               |
| Dosage form(s) included in the inspection                            | Tablets (uncoated and coated), hard gelatine capsules and oral powders                                                                                                                                                                                                                                                                                                                                                                                                                                |



|                                                         |                                                              |
|---------------------------------------------------------|--------------------------------------------------------------|
| WHO product numbers covered by the inspection           | HIV-AIDS                                                     |
| Summary of the activities performed by the manufacturer | Manufacturing, packaging, quality control, stability testing |



## **Part 2: Summary**

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

The Hetero Labs Ltd, Unit III, a division of the Hetero group was established in 2001.

The Hetero Labs Limited Unit III was located about 45 km from Hyderabad international airport. There were two blocks (Block-A and Block-B) on the site with different multi-product formulation and packaging modules.

No hormones or cytotoxic products were manufactured in the unit.

Besides the site of the manufacturing workshops there were two outside warehouses belonging to the Unit III:

- The central warehouse for storage of excipients and packaging materials
- The finished goods warehouse.

The Hetero Labs Unit III was licensed by the Drug Controller of Andhra Pradesh. The manufacturing licences of the site:

Form 25 and Form 28, 22/RR/AP/01/F&B/CC, Dt. 07/06/2001 (30/03/2011-31/03/2016)

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

The site is regularly inspected by WHO Geneva and other foreign regulatory authorities:

- April 2002 WHO, Geneva
- August 2003 WHO, Geneva
- June 2006 WHO, Geneva
- September 2006 WHO, Geneva
- May 2007 WHO, Geneva
- November 2007 WHO, Geneva
- January 2009 ANVISA, Brazil
- August 2009 WHO, Geneva
- May 2010 Medicines Control Council (MCC) South Africa
- July 2011 AEMPS, Spain
- January 2012 Executive Board of Health Ministers Council for Cooperation  
Council States, Gulf
- February 2012 WHO, Geneva
- February 2013 National Drug Authority (NDA), Uganda
- July 2013 Pharmacy medicines and Poisons Board PMPB, Malawi
- October 2013 USFDA, USA
- April 2014 AEMPS, Spain
- February 2015 INVIMA, Columbia

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

The inspection focused on the general principles of GMP and the production and control of the prequalified products and products under assessment - tablets, capsules and oral solutions.

***Inspected Areas***

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

**3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)****Principle**

In general the PQS was implemented to ensure that pharmaceutical products fit for their intended use. The production and control operations were specified in written form and GMP requirements were generally followed. The managerial responsibilities were specified in the job-descriptions. Product and processes were monitored and the results taken into account in batch release and regular reviews of the quality of pharmaceutical products were conducted. The periodic management reviews were performed.

**Quality Risk Management (QRM)**

The Quality Risk Management policy was defined in the SOP.

The QRM principles were based on FMEA and HACCP. There were two risk management registers in place: one for the production and one for engineering. The Risk assessments (RA) were carried out for all products.

The RA registers for production (2014 and 2015) and the RAs for the specific products were checked.

As a tool the HACCP was used for the RA.

**Product Quality Review (PQR)**

The quality reviews of pharmaceutical products were conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements.

The SOP “Product Quality Review” was reviewed.

The PQRs were prepared annually consisting of 12 months manufacturing period and were based on a pre-defined quarterly schedule. The PQRs summarized the following data:



- review of starting materials and packaging materials;
- review of critical in-process controls, and finished product results;
- review of all batches that failed to meet established specification(s) and their investigation;
- review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant CAPAs taken;
- review of all changes made to the processes or analytical methods;
- review of marketing authorisation variations submitted, granted or refused, including those for third country (export only) dossiers
- review of the results of the stability monitoring programme and any adverse trends;
- review of all quality-related returns, complaints and recalls and the investigations performed;
- a review of adequacy and effectiveness of any other previous product process or equipment corrective actions based review of previous PQR and trends;
- a review of new marketing authorizations and variations to marketing authorizations, a review of post marketing commitments
- review of qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water or compressed gases and a review of the results of monitoring the output of such equipment and utilities;
- review of technical agreements to ensure that they are up to date;
- review of batches taken for reprocessing/reworking, if any,
- review of different pack sizes of the product offered in the market;
- review of the control samples of the product.

#### Deviations and Incidents

The SOP “Reporting, investigation and disposition of incidents” and incidents registers for 2014 and 2015 were checked. Incidents were defined as unplanned deviations and were classified as critical, major or minor.

The incident number was assigned by the Quality Assurance (QA) and recorded in batch manufacturing / batch packaging records (BMR/BPR). The copy of the incident report was attached to the BMR/BPR. According to the SOP incidents should be closed within 30 working days from the date of initiation, if not closed, proper justification should be approved by the QA/Corporate QA and logged in the corrective actions and preventive actions (CAPA) register. The incidents closed within 30 working days were not logged in the CAPA register.

The SOP “Handling of deviations” and deviation register for 2015 for the production department were checked. Deviations were classified as planned and unplanned. The deviation registers were department-wise such as: Production, Quality Control (QC), QA, Engineering, Warehouse, and Microbiology. Deviations were trended quarterly and impact assessment was carried out.

The specific deviations investigations were discussed.

The department-wise and category-wise quarterly deviation trends for review period: 1<sup>st</sup> January to 31<sup>st</sup> March 2015 were checked.



### Change control (CC)

The SOP “Change control programme” and the CC register (production) for 2015 were checked. Changes were classified as minor or major and trended quarterly. The SOP was applicable for:

- Approved drug products
- Manufacturing process
- GMP related equipment/facility/utility
- Computer system
- SOPs
- Master production records
- Specifications
- Standards test procedures
- Vendor and raw materials
- Packaging and labelling materials.

The separate CC registers were available for the different departments.

The change request note quarterly trend – 2015, period January 2015 to March 2015 was checked. The trending was done department wise.

The specific CC cases were discussed.

### SAP (enterprise resource planning) system

Materials were managed in the validated SAP system. Access to the system was controlled (independent user IDs and defined user rights). The material management records together with the audit trails were available.

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

In general good manufacturing practices were implemented. The necessary resources were generally provided. Qualification and validation were performed. The significant deviations were recorded and investigated. The records covering manufacture and distribution, which enable the complete history of a batch to be traced, were retained.

## **3.3 SANITATION AND HYGIENE**

The premises and equipment were maintained at acceptable level of cleanliness. The scope of sanitation and hygiene covered personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection.

## **3.4 QUALIFICATION AND VALIDATION**

### Validation Master Plan (VMP)

The key elements of a qualification and validation programme were defined and documented in the validation master plan. The commitment to maintain continued validation status was stated and responsibilities for performing validation were defined.



The VMP, effective date April 3, 2015 was reviewed. The VMP was applicable for:

- Facility / Area qualification
- Equipment qualification
- Process validation
- Cleaning validation
- Utilities & Services validation
- Analytical method validation
- Computer system validation
- Vendor / supplier qualification
- Personnel validation and Qualification

The VMP plan was approved by the plant Head and General Manager QA.

The responsibilities for QA, QC, engineering, production and research & development departments were described in the VMP. The re-validation requirements were stated.

The manufacturing process validation policy was defined in the SOP “Process Validation”. The process validation documents of specific products were discussed.

The manufacturing process was validated for three consecutive batches and also covered the packaging validation.

### **3.5 COMPLAINTS**

The SOP “Handling of market complaints and quality defects” was reviewed. The head of the QA or designee had overall responsibility for handling the complaints. The procedure was applicable for:

- Market complaints
- Quality defects
- Adverse drug reactions
- Adverse drug event

The complaints were classified as:

- Critical
- Major
- Minor

Classification was done by the Head QA/designee.

According with the SOP special attention should be given to establish whether a complaint or quality defect was related to falsified/counterfeit medicines. Investigations should include a review of previous quality defect reports, if relevant. The quality risk management (QRM) principles should be applied to the complaint investigation and to the decision making process in relation to the product recalls and other risk-reducing actions. If a product defect was discovered or suspected in a batch, consideration was be given to whether other batches should be checked in order to determine whether they are also affected. All decisions and measures taken should be recorded to the corresponding batch records.



The root cause analysis should be applied during investigation and appropriate CAPAs should be identified. The investigation should be completed within 30 calendar days from the date of receipt. The complaint should be kept open till all CAPAs are completed. The complaints records were quarterly trended and reviewed – trends were common, but complaint registers were market wise as:

- USA
- Europe
- Rest of the world

A need to consider a recall was specified.

The complaint registers for 2014 and 2015 were checked.

### **3.5.1 PRODUCT RECALLS**

The SOP “Product recall” was checked. Till the date of the inspection there was no product recalls. Overall responsibility for handling the recall was the Head of the QA responsibility.

The recalls were classified as:

- class I - should be initiated immediately but not later than 2 days after the receipt of complaint
- class II - should be initiated not later than 7 days after the receipt of complaint
- class III - should be initiated not later than 15 days after the receipt of complaint

According with the SOP, the competent authorities of all countries to which a given product had been distributed should be informed. The effectiveness of the arrangements for recalls were tested and evaluated by mock recall, performed every year.

### **3.7 CONTRACT PRODUCTION AND ANALYSIS**

Contract manufacturing facilities or quality control (related to routine quality testing of finished products) laboratories were not used. Services of one approved contract laboratory were utilised for few non-routine tests.

### **3.8 SELF INSPECTION AND QUALITY AUDIT**

The SOP “Self inspection programme” was reviewed. The QA in charge / designee was responsible for planning, organizing the intra department and inter department self-inspection, monitor and ensure the effectiveness of the CAPAs.

#### Items for self-inspection

The following items were included in the self-inspection:

- personnel;
- premises including personnel facilities;
- maintenance of buildings and equipment;
- storage of starting materials and finished products;
- equipment;
- production and in-process controls;
- QC;
- documentation;
- sanitation and hygiene;
- validation and revalidation programmes;

- calibration of instruments or measurement systems;
- recall procedures;
- complaints management;
- labels control;
- results of previous self-inspections and any corrective steps taken.

#### Self-inspection team

The self-inspection team was appointed by the QA Head and consisted of the cross functional team. The auditors should have minimum two years of industrial experience and knowledge of the GMP/GLP. The auditors were trained on site. The refreshment training was given to all auditors every year.

The QA Head / designee were responsible to evaluate both, the self-inspection report and the corrective actions as necessary.

A quality audit was conducted by outside or independent specialists or a team designated by the management.

#### Frequency of self-inspection

The self-inspection was carried out twice in a year according with the department wise check lists. The inter department self-inspection schedule for 2015 was checked. It was seen that the schedule was followed – till the date of inspection five self-inspections were carried out.

#### Self-inspection report

The self-inspection report was written at the completion of the self-inspection. The report included:

- Deficiency observed;
- Category of deficiency (critical, major and minor);
- Recommended CAPAs, target date and responsible person for CAPA;
- Status

#### Follow-up action

The QA Head / designee were responsible to evaluate both the self-inspection report and the corrective actions as necessary.

#### Quality audit

A quality audit was conducted by outside or independent specialists or a team designated by the management.

### **3.9 PERSONNEL**

#### General

The individual responsibilities were clearly defined and recorded as written job descriptions. Personnel were aware of the principles of GMP, received initial and continuing training, including hygiene instructions. The Organogram presented was approved and dated, The QA The General Manager and the QC General Manager reported to the Vice President. The separate Organograms were presented for the QC and the QA. In general, there were sufficient key and other qualified personnel to carry out the tasks for which the manufacturer was responsible.



The operations were usually carried out in two shifts, but in case of a need, operating three shifts were also possible.

Besides the full time staff, there were 144 contract/temporary workers (helpers) employed for the different kind of jobs.

The SOP “Procedure for recruitment and job allocation of contract workers” was reviewed.

#### Job descriptions

The individual responsibilities were defined and recorded as written job descriptions.

The job descriptions of the following personnel were discussed:

- CHAIRMAN & MANAGING DIRECTOR
- Head – CQA
- Vice President –QA
- General Managers QA (QP)
- General Manager –QC
- Director – formulation operations
- Associated Vice President – Operations Production Department
- Deputy General Manager- Warehouse
- Deputy General Manager –Engineering department
- General Manager -Projects
- Senior Manager-Human Resources
- General Manager – Environment Health Safety

#### Training

The training in accordance with the written programmes was provided for all personnel involved in the manufacturing areas and control laboratories as well as for the technical, maintenance and cleaning personnel. Besides the basic training on the theory and practice of the GMP, newly recruited personnel received training appropriate to the duties assigned to them. The continuing training was also given, and its practical effectiveness was periodically assessed. The approved training programmes were available and the training records were kept.

An analyst competency list and the signature specimen list of the QC laboratory and the training records of the selected personnel were presented to the inspectors.

The training programme was reviewed. The qualified trainers conducted on-the-job training, retraining, GMP training, refresher GMP training, specific training and identified training requirements of individual employees and were responsible for monitoring the qualification of their staff. The training schedule was reviewed; it was divided due to separate departments.

The training records and health checks for two contract labour workers were reviewed.



Upon recruitment the following training was given to the contract workers:

- behavioural aspects in factory premises – orally explained and presented by video showing “do`s” and “don’t”
- general safety – orally explained
- entry and exit procedures - SOP was available in local language, orally explained and presented by video showing “do`s” and “don’t”
- personal health and hygiene - SOP was available in local language, orally explained and presented by video showing “do`s” and “don’t”

The contract workers training effectiveness was examined orally.

Six QC analysts training records were reviewed.

#### Personnel hygiene

The SOP “Personnel Health and Hygiene” was checked. Prior to employment and during the employment (every year) personnel had to have undergone health examinations. Persons suffering from communicable diseases, respiratory diseases, and skin infections were given special attention and treatment and were not allowed to handle starting materials, packaging materials, in-process materials or medicines. Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines were not permitted in production, laboratory and storage areas

The direct contact was avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk product.

### **3.10 PREMISES**

#### General

In general the premises were located, designed, constructed, adapted and maintained to suit the operations to be carried out. The premises used for the manufacture of the finished products were suitably designed and constructed to facilitate good sanitation. The premises were designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. Access to the production premises was restricted to the authorized personnel.

#### Ancillary areas

The facilities for changing and storing clothes and for washing and toilet purposes were accessible. The rest and refreshment rooms were separate from the manufacturing and control areas.

#### Storage areas

The storage areas were of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation. The receiving and dispatch bays were separated and protected materials and products from the weather. The receiving areas were designed and equipped to allow containers of incoming materials to be cleaned. There was a separate sampling area for starting materials and packaging materials.



The storage and dispensing of APIs was performed in the warehouses belonging to the production buildings. The dispensing leftover materials (including excipients) were also stored here.

The excipient and packaging materials were stored in two warehouses located at Unit VII (having also manufacturing activity of pellets for domestic market) belonging to Unit III functionally (“Central warehouse”).

The products first enter the finished goods (FG) store belonging to the production workshops. The batches were transferred to the FG warehouse (shed 1 and 2). After release those were dispatched.

#### Production workshops

The premises were laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels and allowed logical positioning of equipment and materials. In general, where starting and primary packaging materials and intermediate or bulk products were exposed to the environment, interior surfaces were smooth and free from cracks and open joints, did not shed particulate matter, and permitted easy and effective cleaning.

The finger bags, screens and sieves integrity was checked before and after use. The punches and dies rotation was ensured and the food grade lubricant, released by the QC, was used. During the inspection, cleaning status of the Stainless Steel bins was visually checked using the lint free blue colour cotton. Checked bins were clean.

#### Quality control areas

The QC laboratories were separated from the production areas and designed to suit the operations to be carried out in them. There were suitable storage space for the stability and test samples, reference standards, solvents, reagents and records.

The in-process control (IPC) tests were carried out in the production cubicles by production operator and IPC personnel. The production cubicles were equipped with necessary instruments for the Loss on drying (LOD), weight checks, friability and disintegration tests.

### **3.11 EQUIPMENT**

#### General

The equipment were located, designed, constructed, adapted and maintained to suit the operations to be carried out. The balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. The calibration due-date labels were attached to the equipment.

#### Preventive maintenance (PM)

The preventive maintenance program of the critical process and quality control equipment was in place (SOP, “Maintenance procedure”). The PM annual schedule with the PM records of the following specific production equipment were cross checked:



- Fluid bed granulator: PM was carried out monthly, quarterly and yearly according to the SOP “PM procedure of Fluid Bed Dryer /Fluid Bed Processor”.
- Octagonal blender: PM was carried out monthly, quarterly and yearly.
- Tablet compression machine: PM was carried out monthly, quarterly and yearly.
- Coating pan: PM was carried out monthly, quarterly and yearly.

The SOP “Procedure for operation and preventive maintenance of air handling unit and dehumidifier/ventilation and exhaust units” was checked. The SOP was general and explained only general approach how to switch off and on AHUs.

#### Calibration and qualification

The qualification and calibration policy did not change since the last WHO inspection. The qualification documents of the fluid bed dryer and the calibration documents of the belonging measuring devices were available and checked.

#### HVAC

The environmental conditions in the production areas were controlled by the HVAC (heating, ventilation and air conditioning) system. The area classification was “Class 8”. Every manufacturing cubicle had its own AHUs (air handling unit). The AHUs were operated periodically and in the daily practice it was allowed to operate only certain AHUs during the production.

#### Compressed air

The compressed air was generated by eight air compressors. 0.01 µm filters were installed at the user points where it came in contact with product. The compressed air re-validation report was checked. During re-validation the following tests were done:

- Viable Particle counts (internally)
- Dew points, moisture content, oil mist, non-viable particle counts (done by external agency).

The test equipment names and serial numbers/IDs were not specified in the report of compressed air testing (Dew point, Moisture content, Oil mist) prepared by Hetero; therefore test equipment calibration certificates were not possible to connect/link with re-validation report, however it was noted that the sample location (production equipment) ID numbers were specified on the Test Certificates for determination of compressed air quality.

#### Purified Water

The PW system in Block A all modules was installed in March 2012 and started producing PW in June 2012. The water source was municipal water.

The PW in loop was in continuous circulation, the water temperature was maintained ambient. The Stainless Steel (SS) storage tank capacity was 3000 litres. The conductivity and PW flow rate was controlled continuously at the return. The PW tank air filter was replaced every 6 months. The filter CoA was available. PW tank and loop sanitization was carried out weekly by using hot water (more than 80 °C) continuously for 45 minutes. Ultra violet (UV) lamps were



replaced after 7000 hours or if intensity was below 32 W/m<sup>2</sup>; UV lamps intensity was monitored on line. Conductivity was monitored online and TOC off line.

The PW system installation documentation was presented to the inspectors and consisted of the following documents:

- DQ:
  - o Slope was 1: 100
  - o PW flow was NTL 1.2 m/s
  - o SS - 316L
  - o Point of use zero dead leg valves
  - o Dead legs up to 1.5D
- IQ: the following documents were spot checked
  - o Orbital welding was used; welder's certificate was presented to the inspector
  - o Calibration certificate for the welding machine was available
  - o In total there were 718 joints. Boroscopic welding videos were available for 10 % of the joints
  - o Test certificate for zero dead leg valve
- OQ – not checked during the inspection
- PQ:
  - o 3 stage approach was used
  - o 1<sup>st</sup> phase was for 4 consecutive weeks, samples were taken and analysed from all sampling points. Raw water, soft water and PW was tested in accordance with established specifications
  - o 2<sup>nd</sup> phase was for 4 consecutive weeks, samples were taken and analysed from all sampling points. Established specifications parameters were verified after completion of the stage. Routine sampling plan was established
  - o 3<sup>rd</sup> phase was for one year, reduced sampling, covering all sampling points in one month. Samples from PW storage tank, return loop, outlet of storage tank 2 and return line of storage tank 2 were collected and analysed daily.

PW trends for the total aerobic microbial count (TAMC) and total organic carbon (TOC) for all 3 phases were checked for the specific sampling points.

The alert and actions limits were established.

### **3.12 MATERIALS**

#### General

In general materials used for operations such as cleaning, lubrication of equipment was of a food grade. The incoming materials and finished products were quarantined after receipt or processing, until they were released for use or distribution. The materials and products were stored under the appropriate conditions and in orderly fashion to permit batch segregation and stock rotation. The water used in the manufacture of pharmaceutical products was suitable for its intended use.

#### Suppliers audit and approval

The vendors of the raw materials were qualified according to the SOP "Vendor Qualification". The approval of the vendors was the responsibility of the QA Head. The status of the vendors



was “approved” and “provisionally approved”. The “provisionally approved” vendors were used for stability and registration batches, and only raw materials from “approved” vendors can be used for commercial manufacturing. The suppliers approved by other Hetero labs sites were considered as approved. There were separate approved vendor lists available for the APIs, Excipients and Packaging Materials. The lists were updated and printed out every 6 months based on a master document (Excel sheet) handled by the QA. The vendor qualification records of a capsule supplier were discussed. The API manufacturers were approved based on site audit which is due at every 3 years.

#### Starting materials

The starting materials were purchased from approved suppliers. The starting materials were dispensed by designated persons, following a written procedure. The dispensed material and its weight or volume was independently checked and the check recorded.

The SOP “Sampling, testing and release of raw materials” was reviewed. ID tests were run in the warehouse using NIR/Raman Spectrometer, if applicable. If the ID test NIR/Raman Spectrometer was not available, the samples were analysed as per standard test procedure (STP).

The SOP “Sampling, testing and release of packaging materials” was reviewed. The Acceptance Quality Level (AQL) was applied for the packaging materials sampling (cases, packs, roll, container or boxes). The SOP was written following “Military standard”.

The SOP “Procedure for transferring of one grade materials to another grade” along with qualified vendor list for APIs and code transfer register were reviewed. The qualified vendor list was organized vendor wise and not API wised, so it was difficult to review.

The materials had unique item codes reflecting the material specifications.

The primary packaging material (HDP bottles) sampling procedure was evaluated on site: the AQL and military standard was followed.

The SOP “Inter block transfer of semi-finished goods” was checked.

#### Finished products

The finished products were held in quarantine until their final release. The status change and the material movements were recorded in the SAP system.

### **3.13 DOCUMENTATION**

SOPs, specifications, analytical test methods, batch processing and packaging instructions were designed, prepared, reviewed and distributed according to written procedure and stored in document archive in mobile racks for at least 5 years. BMR/BPR and batch numbers were issued and controlled by the Documentation group of the QA.

#### Labels

The labels applied to containers, equipment or premises were clear and unambiguous.



### Specifications and testing procedures

Approved, signed and dated specifications for the starting and packaging materials, intermediate and bulk products, finished products were maintained by QA department.

### Batch processing records

The batch packaging records were available for each batch or part batch processed. Before any packaging operation begins, the checks were made that the equipment and work station are clear of previous products (line clearance), documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. Line clearance was recorded.

## **3.14 GOOD PRACTICES IN PRODUCTION**

### General

The production operations followed processing and packaging instructions and were recorded in the batch processing and packaging instructions/records. The documents covered amongst: material receipt, dispensing, equipment cleaning, quarantine, sampling, storage, and labelling, dispensing, processing, packaging and yields (with reconciliation).

The specific BMRs/BPRs were discussed.

### Cleaning procedures

The equipment cleaning procedures were described in SOPs. Two type of cleaning was defined:

- Type A cleaning procedure between product change over
- Type B cleaning procedure between batch to batch change-over of same product.

The cleaning procedure of FBD and the corresponding cleaning validation documents were discussed.

The cleaning procedures were validated as defined in the SOP “Cleaning validation”. The cleaning validation was based on the cleaning validation matrix considering the solubility and the toxicity of the APIs. Whenever a new molecule (API) was entered into the production facilities, a cleaning validation assessment were performed investigating whether the worst case product was replaced which calls for re-validation/cleaning verification.

## **3.15 GOOD PRACTICES IN QUALITY CONTROL**

### General

The QC Department was independent from manufacturing departments.

The QC Department was responsible for sampling of raw materials and testing of raw material, packaging material, finished product (including stability), purified water and environmental samples.

The analytical equipment were connected into software (GCs: Chromeleon and Open Labs, HPLCs: Chromeleon).



### Control of starting materials and intermediate, bulk and finished products

The samples of starting materials, packaging materials, intermediate products, bulk products and finished products were taken by the approved methods.

### Specifications and analytical test methods

The materials had written quality specifications which contained the description of the belonging analytical test methods (STP). The analytical test methods were validated or verified (in case of compendia methods).

The quality specifications, analytical test methods and the test records of specific materials were discussed.

### Out of specification results

Not checked during this inspection.

### Microbiological laboratory (MB)

The MB laboratory was separated from the production and QC laboratory. Main activities performed in the microbiology laboratory were:

- Microbial Limit Tests of water and finished products
- Environmental monitoring
- Water analysis
- Preparation of media

The MB laboratory had two LAF booths, one was used for analysis and second one for culture preparations. The pH of media was checked before and after sterilisation. The site environmental microflora was isolated and known. Six autoclave cycles were validated. The autoclave loading patterns were presented to the inspectors. The autoclave validation protocols/reports were not checked during this inspection. For porous loads Bowie Dick test was performed.

The environmental monitoring samples were taken from production rooms and change rooms once per months by surface and volumetric methods. The trends were presented tabulated and in graphs. The action and alert limits were specified. In case the atypical colonies were found – those were identified.

The PW samples from storage tanks and return loops were analysed on daily basis. From the other sampling points samples were taken once in month on rotational basis. The trends were presented tabulates and in graphs. Action and alert limits were specified.

### Retention samples

The retention sample storage room situated close to the QA department and were controlled by the QA personnel. The retention samples from each batch of finished product were kept for at least one year after the expiry date at room temperature (NMT 25 °C). Finished products were be kept in their final packaging and stored under the recommended conditions. The samples of active starting materials were retained for 5 years or at least one year beyond the expiry date of the corresponding finished product whichever was longer.



### Reference materials

The official reference standards were used as described in the appropriate monograph. The working standards were qualified (tested), released and then stored in the same way as official standards: deep freezer, 5 °C desiccator at ambient temperature.

### Stability studies

A written programme for ongoing stability determination were developed and implemented. The SOP “Stability management” was checked. For on-going stability studies preferably first production batch should be used. Window period for the accelerated stability studies was specified 15 days and 30 days for long term stability studies.

The control of the stability program and the stability samples was assured in LIMS program.

### **Part 4: Conclusion**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned, Hetero Labs Unit III Jeedimetla (blocks A and B), located at Survey No 51, Plot No 22-110 IDA, Jeedimetla, Hyderabad, Qutubullapur, Rangareddy District, Telangana, 500 055, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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.