



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

Part 1: General information

Name of Manufacturer	Hetero Labs
Unit number	Unit V
Production Block	Block-V, Block-VA
Physical address	Survey No 439, 440,441 & 458, TSIIC Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar - 509301, Telangana State, India
Date of inspection	15 – 18 June 2015
Type of inspection	Routine inspection
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing of solid dosage forms – Tablets (uncoated and coated) – Hard capsules Primary and secondary packaging Storage – Quality control
Dosage form(s) included in the inspection	Tablets (uncoated and coated)
WHO product numbers covered by the inspection	HIV-AIDS Tuberculosis
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, a division of the Hetero group was established in 1993. The corporate office and the manufacturing sites were as follows:

The Hetero Labs Unit V was located about 80 km from Hyderabad city.

There were three blocks (Block-V, Block-VA, Block-VB) on the site with different multi-product formulation and packaging modules. Block V and Block VA were in the inspection scope. Cytotoxic products were manufactured in Block VB.

Manufacturing authorization: 50/MN/AP/2009/F/G, Exp. 18/12/19

The inspection was part of a 2 weeks inspection campaign covering Hetero Labs Unit 3 and Unit 5. As some of the areas were similar or common (e.g. QA system and the corporate procedures), the corresponding deficiencies were indicated in both inspection reports and the CAPAs are expected to be addressed at Corporate level.

History of WHO and/or regulatory agency inspections

The site has been inspected by the following authorities within the last 5 years:

- November 2010 United States Food and Drug Administration (USFDA)
- November 2010 Pharmacy and Poisons Board PPB Kenya
- November 2010 WHO Geneva
- February 2011 INFARMED Portugal
- June 2011 National Drug Authority (NDA) Uganda
- September 2011 Medicines Control Authority (MCAZ) Zimbabwe
- January 2012 Pharmacy medicines and Poisons Board PMPB Malawi
- February 2012 WHO Geneva
- March 2012 Medicines Control Council (MCC) South Africa
- April 2012 National Health Surveillance Agency (ANVISA) Brazil
- October 2012 Tanzania Food and Drugs Authority (TFDA)
- December 2012 Taiwan Food and Drugs Authority (TFDA)
- February 2013 FMHACA Ethiopia
- March 2013 INFARMED Portugal
- May 2013 Mexican health authority (COFEPRIS)
- May 2013 USFDA
- June 2013 Ministry of Health (MOH) Belarus
- October 2013 Ministry of Health (MOH) Oman
- November 2013 National Drug Safety Organization (NDSO) Lesotho
- August 2014 Democratic Republic of Congo
- December 2014 ZaZiBoNa (Zambia, Zimbabwe, Botswana, Namibia)
- April 2015 Jordan Food and Drugs Administration (JFDA)
- April 2015 USFDA



Focus of the inspection

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

Batch release

The SOP “Batch release system” was checked. The Quality Assurance (QA) executive or designees were responsible for review of the Batch Manufacturing Records (BMR) and Batch Packaging Records (BPR). According with the SOP the QA reviewer was responsible for checking Quality Control (QC) analytical reports. Three separate QA check lists were used for review of the BMR, packaging instructions and batch release.

The SOP “Preparation, approval, issue and control of worksheets for record of analysis” was checked.

Quality risk management (QRM)

The Quality Risk Management policy was defined in the SOP “Quality risk management”. The SOP was revised after Unit III inspection and was approved on 14th June 2017; Annexure HACCP implementation procedure was modified.



The QRM principles were based on FMEA and HACCP. There were two risk management registers in place: one for production and one for equipment. It was said that the risk assessment (RA) were carried out for all products. Due to the time constrain performed RAs were not verified.

The RA protocol for the specific product was 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 to verify 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 PQR contained:

- 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;
- review of adequacy and effectiveness of any other previous product process or equipment corrective actions based review of previous PQR and trends;
- review of new marketing authorizations and variations to marketing authorizations, a review of post marketing commitments;
- a 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.

Use of statistical tools was explained in the SOP “Trend analysis and handling out of trend results”. The SOP was revised on June 13, 2015 after Unit III inspection and deficiencies stated. The SOP explained process capability (Cpk) calculation formula.

The PQRs for specific products were reviewed.



The SOP “Trend analysis and handling out of trend results” was checked. The SOP was revised after Unit III inspection and was effective from 15/06/2015. The Cpk calculation formula was added and process capability requirements were specified. The SOP was applicable for chemical tests as relative substances and assay. The training on the new SOP was provided on June 14, 2015.

Deviations and Incidents

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

An incident number was assigned by the QA and recorded in the 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 production department were checked. The deviations were classified as planned and unplanned. The deviation registers were department-wise such as: Production, QC, QA, Engineering, Warehouse, and Microbiology. The deviations were trended quarterly and impact assessment was carried out.

The specific investigation reports were discussed.

The CAPAs were recorded in a register according to the SOP.

Change control (CC)

The SOP “Change control programme” and CC register (production) for 2015 were checked. The 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 specific CC cases were discussed.



SAP system

The 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. Significant deviations were recorded and investigated. 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 validation master plan was discussed. 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 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 a specific product were discussed. The manufacturing process was validated by three batches.



3.3 COMPLAINTS

The SOP “Handling of market complaints and quality defects” was reviewed. The head 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

The 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 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

Need to consider a recall was specified.

The trending was done by:

- market wise
- complaint type

The specific complaint investigations were reviewed.



3.6 PRODUCT RECALLS

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

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 the mock recall, performed every year. The last mock recall was performed on 07/03/2015 for USA market.

3.7 CONTRACT PRODUCTION AND ANALYSIS

Contract manufacturing facilities or quality control (related to routine quality testing of finished products) laboratories were not used.

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.

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 cross functional team. The auditors should have minimum two years of industrial experience and knowledge on the GMP/GLP. Auditors were trained on site. Refreshment training was given to all auditors every year. Self-inspection was carried out twice in a year according with



department wise check lists. Inter department self-inspection schedule for 2015 was checked. It was seen that schedule was followed – till the date of inspection five self-inspections were carried out.

The 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.

Frequency of self-inspection

The self-inspection was carried out twice in a year according with department wise check lists. Inter department self-inspection schedule for 2015 was checked. It was seen that 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

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

3.9 PERSONNEL

The individual responsibilities were clearly defined and recorded as written descriptions. Personnel were aware of the GMP principles, received initial and continuing training, including hygiene instructions. The Organogram presented was approved and dated, the QA General Manager and 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.

The contract labour workers were used on site. The SOP “Procedure for recruitment and job allocation of contract workers was checked.



Job descriptions

The individual responsibilities were clearly defined and recorded in written job descriptions.

Training

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

The SOP “Training programme” was the same as in Unit III. In the Unit V the SOP was not checked. 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.

Each employee should undergo induction training in the few days of his/her joining the organization. There were the following training programmes/modules:

- induction training
- on the job training
- cGMP training
- refresh /requalification training (SOP)
- training requirements identification (specific training)
- technical training
- re-training
- external training
- practical training
- training to housekeeping personnel
- safety training
- ethics training

According with the SOP training to the contract labour workers were on the following topics:

- basics cGMP
- contamination and mix-ups
- personal hygiene & Cleanliness
- behaviour at work place
- cleaning procedures and relevant SOPs

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

The training records related to the revised SOP “Trend analysis and handling out of trend results” were checked. The training for fourteen QC staff members were carried out on



Sunday, 14th June 2015. The training effectiveness evaluation specific staff members were checked. As training was given on Sunday for fourteen QC staff members, the entry records for these staff members were required and checked. In according with attendance records all 14 staff members were presented.

Personnel hygiene

The SOP “Procedure for personnel medical check-up and hygiene practices” was checked. Prior to employment and during 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 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.

The health checks for contract labour worker involved in visual inspection were reviewed.

The following training modules were presented to all contract workers upon recruitment.

- behavioural aspects in factory premises – orally explained and presented by video showing “do`s” and “don`t”
- general safety – orally explained and written presentation in English language
- 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.

3.10 PREMISES

General

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 were restricted to authorized personnel.

The warehouse areas were supplied by filtered air but not classified. The production areas (directly connected to the warehouse areas) were classified as Class 8.

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 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 temperature mapping studies protocol/report for the API warehouse, summer season, was checked. The 15 sensors were used, sensors calibration certificates were presented. The warehouse schematic drawing indicating sensors locations was also presented. The temperature was recorded every minute. The room was divided in 3 levels (height 8650 cm).

- Level 1 – 1.2 m
- Level 2 – 4.8 m
- Level 3 – 8.5 m

Weighing areas

The dispensing of starting materials was carried out in separate weighing areas belonging to the warehouse areas into Polyethylene bags or directly to the stainless steel vessels of the blenders.

Production workshops

The production cubicles opened to corridors classified as Class 8.

Environmental monitoring

The environmental monitoring was done in the production rooms and change rooms once per months by surface monitoring, passive air and active air sampling methods. Trends were presented as tabulates and graphs. The action and alert limits were specified. In case atypical colonies were found – those were identified.

Quality control areas

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

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 equipment and quality control equipment was in place. The PM annual schedule with the PM protocol and records of a specific stability chamber were discussed.



Calibration and qualification

The qualification and calibration policy did not change since the last WHO inspection. The documentation requirements of the qualification were described.

The qualification documents of a specific stability chamber were discussed. The re-qualification was performed following to the relocation of the chamber to another location.

The periodic calibration of the chamber was done according to the qualification protocol. The PM was due quarterly, last time PM was carried out on 18/08/15.

HVAC

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

Purified Water

The PW system in Block 5A was installed in 28 January 2014. The water source was bore well water. The PW in loop was in continuous circulation, the water temperature was maintained ambient.

The conductivity and PW flow rate was controlled continuously at the return. The PW tank air filter was replaced every 12 months. The filter CoA was available, filter integrity checks were done by external agency; validation certificate was presented to the inspectors. The PW tank and loop sanitization was carried out weekly by using hot water (more than 75 °C - 85 °C) continuously for 60 minutes. The Ultra Violet (UV) lamps were replaced after 7000 hours or if intensity was below 32 W/m²; UV lamps intensity was monitored on line. The total organic carbon analysis was done off-line in the QC.

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 and sampling point zero dead leg valves
- 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 502 joints. Boroscopic welding photos were available for 10 % of the joints.
- OQ – not checked during the inspection
- PQ:
 - o 3 stage approach was used



- o 1st phase was for 4 consecutive weeks, samples were taken and analysed from all sampling points.
- o 2nd phase was for 4 consecutive weeks, samples were taken and analysed from all sampling points.
- o 3rd phase was for one year, reduced sampling, covering all sampling points in one week. Samples from PW storage tank, return loop (were collected and analysed daily. Phase 3 was delayed because 3 user points were added to the loop. PQ for additional user points was done for continuous 4 weeks.

The PW trends for total aerobic microbial count (TAMC) and total organic carbon (TOC) for all 3 phases were checked for specific sampling points. The alert and actions limits were established.

Cleaning procedures

The SOP “Cleaning validation programme” was checked. The cleaning procedures were validated as defined in the SOP. Two type of cleaning was defined:

- Type A
 - o cleaning procedure between product change over
 - o change from higher strength to lower strength of same product
 - o change in colour of same product
 - o change in lower to higher strength of the same product (except granulation)
 - o after any major breakdown ore PM
 - o equipment was idle for more than 7 days from date of cleaning
 - o after continuous production of 6 days of the same product
- Type B
 - o cleaning procedure between batch to batch change-over of same strength of the product
 - o between type A cleaning and after any major breakdown or PM
 - o at the end of the day/end of activity

The cleaning validation was based on a 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 is replaced which calls for re-validation/cleaning verification. Two types of sampling techniques were used to collect the samples: rinse and swab method. Three consecutive cleaning cycles were validated. The cleaning procedure effectiveness was evaluated annually.

The SOP “Procedure for cleaning of octagonal blender” was checked.

The cleaning procedure and the corresponding cleaning validation documents were discussed. HPLC method was used for sample analysis. Cleaning results were checked by chemical analysis and microbial analysis (TAMC and total combined yeast and mould (TCYMC)).



3.12 MATERIALS

General

In general materials used for operations such as cleaning, lubrication of equipment was of a food grade. 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 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 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 (ACG Associated Capsules with three sites) were discussed. The API manufacturers were approved based on site audit which was 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 materials had unique item codes reflecting the material specifications.

All APIs under the scope of inspection were manufactured by Hetero Labs or Hetero Drugs, except Linezolid (form II) what was manufactured by Symed Labs Unit I what is part of the Hetero group.

The SOP Sampling, testing and release of packaging materials” was approved on 13 June 2015 after Unit III inspection and incorporated classification of critical, major and minor deficiencies. Training on the revised SOP was carried out on 13 June 2015.

The SOP “Sampling, testing and release of raw materials” was approved on 14 June 2015 after Unit III inspection. Training on the revised SOP was carried out on 13 June 2015.

The dispensed raw materials were stored in separate dispensed materials hold room.



3.13 DOCUMENTATION

General

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. The recent version of the Master SOP Index was issued on 29/05/15.

Labels

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

Specifications and testing procedures

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

Master formulae, packaging instructions

Formally authorized master formulas and packaging instructions were available for each product and batch size, pack size and type to be manufactured.

Batch processing records

The batch processing records were available for each batch processed. Before any processing 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 process, and that the equipment is clean and suitable for use. The line clearance was recorded.

Batch packaging 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:

Reprocessing and reworking

The SOP “Allotment of batch numbers” stated: “Reprocessing/reworking activity of the batch will not be permitted in the premises”.



The SOP “Repackaging of the finished goods” was reviewed. According with the SOP repackaging / relabeling operations shall be documented in respective BPR and the in process checks shall be carried out and the initial batch number will remain the same.

3.15 GOOD PRACTICES IN QUALITY CONTROL

General

The QC Department was independent from the 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.

Two QC laboratories in the inspection scope were situated in Module V and Module VA. The laboratory in Module V was general QC laboratory, but the laboratory in Module VA was dedicated for the stability testing. The analytical equipment were connected into the Laboratory Information Management System (Gas Chromatographs - GC: Chromeleon and Open Labs, High Performance Liquid Chromatographs - HPLC: Chromeleon).

The QCL stability testing laboratory was inspected. The same procedures were applicable for both QCL laboratories.

The SOP “Chromatography data management system” and the SOP “Good chromatographic practice” were checked.

The SOP “Electronic data / projects back-up / restoration / retrieval and audit trail verification” was checked. The SOP was reviewed after the Unit III inspection and was approved on 13th June 2015. The back-up procedure for stand-alone systems was incorporated in the SOP. The back-ups were carried out daily, weekly and monthly. The daily and weekly back-ups were taken on tapes, monthly on DVDs. There were two sets of back-ups DVDs: one set was store in the QA and the second in the IT department.

Control of starting materials and intermediate, bulk and finished products

The samples of the 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).

Stability program

The SOP “Stability management” was checked. The SOP was revised on 17 June 2015 after Unit III inspection and specified the place where to store withdrawn samples before analysis during the window period. For on-going stability studies preferably the first production batch should be used. The window period for the accelerated stability studies was specified 15 days and 30 days for the long term stability studies.



The control of the temperature and relative humidity (RH) in the stability chambers was assured by the ICDAS software program. The T and RH were recorded on line every 15 minutes and checked daily. The stability chambers were equipped with the sound alarm system.

Out of specification results (OOS)

The SOP “Investigation of out of specification” was reviewed. Laboratory OOS investigation were carried out in 4 phases:

- Phase I (a): assignable cause (obvious error)
- Phase I (b): no assignable cause (non-obvious error)
- Phase II: re-analysis / hypothetical analysis
- Phase III: investigation

According to the SOP OOS should be closed within 30 working days. OOS were trended quarterly as per:

- laboratory errors:
 - o analyst error
 - o instrument error
 - o method error
- manufacturing errors:
 - o personnel error
 - o process error
- product / material errors:
 - o product error
 - o material error

The OOS registers for 2014 and 2015 were checked.

The specific OOS investigation reports were checked.

The specific manufacturing process investigation incident report was checked. The fish bone diagram was used for investigation.

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 5 Polepally (Module 3, 4 & 5), located at Survey No 439, 440, 441 & 458 TSIC Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar - 509301, Telangana State, 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.