



**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**

Part 1: General information

Name of Manufacturer	Hetero Labs Ltd, Unit-I,
Unit number	Unit-I,
Production Block	Blocks C, D, E, G, H
Physical address	Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA
Contact person and email address.	Mr. C. Raghunath, Vice President – QA & RA Hetero Labs Ltd. Telephone: <ul style="list-style-type: none">○ Office : 0091 40 23704923/24/25, extn 2089○ Mobile : 0091 9849455560 Email : Raghunath@heterodrugs.com
Date of inspection	24 , 25, 26 and 27 January 2011
Type of inspection	Routine Inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Active Pharmaceutical Ingredients against HIV/AIDS (HA)
Summary of the activities performed by the manufacturer	Chemical synthesis, purification, packaging, quality control and batch release of Active Pharmaceutical Ingredients

Part 2: Summary

General information about the company and site

The site inspected was **Hetero Labs Limited, Unit-I**, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District - 502319, **Andhra Pradesh, India**, hereafter called **Hetero Labs Ltd, Unit-I**. The company corporate office was located at 7-2-A2, Industrial Estates, Sanath Nagar, Hyderabad - 500 018, Andhra Pradesh, India.

According to the Site Master File Version No. SMF-001.07 effective 29/06/2010 and the presentation given at the opening meeting, **Hetero Labs Limited** was established in April 1998. Unit I is located 50km on a 30 acres (70,721m³) plot with a built up area of 15 acres (30,000m³). The site had 10 manufacturing blocks: A, B, C, D, E, F, G, H, I, J and Pharma area. Block F and I were dedicated to synthesis of oncology APIs and were physically separated by a wall from other blocks. Most of the manufacturing blocks had two synthesis lines and two corresponding pharma areas for crystallization, drying, size reduction and packaging. The APIs within the WHO Medicines Prequalification Programme were produced in the following blocks:

1. **Block C.**
2. **Block D.**
3. **Block E.**
4. **Block H.**

It was stated that one of the WHO approved APIs used to be produced in Block J but this had stopped and the last batch was manufactured approximately 3 months before the date of inspection.

The site procured potable water delivered in tankers which was stored in an underground tank and pumped either directly to the manufacturing blocks or to the water treatment plant to produce purified water to be used during the various stages of synthesis. The site also generated its Nitrogen and compressed air.

According to the company presentation and the SMF, the site employed a total of 1008 people in 3 production shifts distributed as follows:

<u>Department</u>	<u>Staff</u>
○ Production	588
○ Quality Control	131
○ Quality Assurance	40
○ Engineering	114
○ EHS	25
○ Warehouse	58
○ R&D	24
○ TSD and Projects	08
○ HRM	20
Total	1008

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, **Andhra Pradesh, INDIA, 24 - 27 January 2011**

History of WHO and/or regulatory agency inspections

According to the SMF and company presentation, the site was licensed by the local authority and had been approved by USFDA (2004 and 2008), EDQM (2007), Denmark (2007), PMDA Japan (2008), KFDA Korea (2010). This was the second inspection by WHO-PQP; the first inspection was in May 2005.

Focus of the inspection

The inspection focused on the production and control of ARV APIs used in products under WHO-PQP assessment. The inspection focussed on blocks C, D, E and H. The inspection covered several the sections of the WHO GMP for Active Pharmaceutical Ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards with the key staff of the site. The inspectors explained the history and procedure for the WHO Prequalification Programme, the procedures and standards used for inspection and timelines for processing the report and company responses to the inspection observations. The procedures for closing the inspection including the WHO public inspection report (WHOPIR) and Notice of Concern (NOC) were explained. The tentative inspection plan was discussed and confirmed. The company made a presentation about the company and the site to be inspected. The presentation highlighted the company profile, the description of the site, a summary of manufacturing capacities, location of production of the various APIs and the site inspection history. A copy of the presentation was obtained and will be filed in the company file.

The inspection of aspects of the Quality Management System followed:

1. Organograms and Job descriptions:

- Solvent Recovery System.
- Production department.
- Quality Control department.1
- Engineering (Maintenance & Projects).
- Quality Assurance: QA-ORG-001-03 effective 30.12.2010.

It was noted that the job descriptions of key personnel did not specify the designated deputy to take on the responsibilities in the absence of the incumbent. It was also noted that the job descriptions of trainee chemists were similar to that of chemists and did not indicate that trainees had to perform the duties under supervision. These were subsequently adequately addressed.

2. Training:

The SOP on staff training was reviewed. It provided for induction training, job training and GMP training. A 60-days training plan was prepared for each new staff and evaluation of the induction training included a summary report, a test and certification. The training plan and records of selected staff were reviewed.

WHO Public Inspection report (WHOPIR):

**Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal,
Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011**

3. Change Control:

The SOP on change control was reviewed. The scope was comprehensive and classified changes as major, minor and temporary. Some of the examples listed as temporary changes included: to reduce cost, reduce impact on environment and to improve yield and quality which is not consistent with GMP and establishes industrial practice. These were subsequently adequately addressed. Although the SOP was specific about the authority to approve changes to manufacturing process, the responsibility to approve other changes was only clarified subsequent to this inspection. Regular review of SOPs was done through change control. There was no evidence that the Change control Register NO. 1 for 2010 had been formally issued by QA and although, it had page numbers, the total numbers of pages in the register were not recorded. Unused blank pages had not been formally closed. These issues have been subsequently addressed. Selected changes were reviewed.

- A change to remove a tray dryer and centrifuge from Block C. The documents listed as affected by the change did not include the BMR in which the equipment was listed. This has subsequently been addressed.
- A change to install AHU in Block C. The change control did not indicate that this was to be followed by area qualification. This has subsequently been addressed.
- A change to extend DM water distribution to Block I. This was followed by qualification.
- A change to remove specific Agitated Nutsche Filter Dryers from Block J. The BMR was amended accordingly.
- A change to reduce distillation time by replacing a normal vacuum pump with a dry vacuum pump. The BMR was amended accordingly but there was no justification given why requalification was not considered. This has subsequently been addressed.
- A change to amend the STP for one of the APIs to add test for impurities by HPLC. This was accompanied by validation and update of the DMF through a variation.
- A change to amend the STP for one of the API intermediates to introduce assay by HPLC.

4. Deviations:

The SOP handling deviations and incidents was reviewed. It provided for QA to approve all deviations and linking the deviations to the relevant BMR. Deviations had to be closed within 30 days and incidents within 48 hours.

5. Out-of-Specifications (OOS):

The SOP on handling OOS and the attached flow chart were reviewed. It provided for review of analytical records before retesting. The register for 2010 showed that 51 cases had been recorded. No OOS had so far been recorded in 2011. Selected cases out of those listed in 2010 were reviewed:

- OOS related to high levels of unknown impurity and total impurities by HPLC.

6. Complaints:

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011

The SOP on handling market complaints was reviewed. It did not provide for classification of complaints or consideration of the possibility of counterfeit. Selected examples were reviewed:

- A complaint related to high level of residual solvents in 2 batches of an API.

7. Product Quality Review (PQR):

The SOP on conduction product quality review was reviewed. The SOP provided for review of general systems separately from product review but did not provide for cross referencing where the systems had specific impact with the product, e.g. water. This has subsequently been addressed.

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

Day 2

After providing the company with a summary of the observations from the previous day, the inspectors proceeded to review documents related the following:

- Review of the reaction and synthesis flow charts for selected API were reviewed.

The inspection of the warehouse for solid starting materials followed. The receiving and sampling procedures were reviewed. There was a list of approved vendors to facilitate inspection of received materials. The quarantine area was not adequate to hold all received materials. Bulk materials were stored directly in the approved good store segregated with a yellow rope. The SOP on sampling provided for sampling all received containers of key raw materials and a reduced sampling plan for other materials. Records of receiving and sampling of selected API starting materials were reviewed. There were no API starting materials in stock for two of the APIs in focus.

The sampling and dispensing areas did not have systems to control dust and extract it from near the point of generation. This has subsequently been addressed.

The storage area for liquid raw materials and solvents stored in drums was well organized. The sampling and dispensing areas for liquids had three transfer pumps that were not dedicated. This has subsequently been addressed.

The tank yard for solvents was isolated in one corner of the site. There was a covered shed for sampling incoming tankers and a charging station with colour coded charging pipes and transfer pumps. Each tank had a level indicator and dispensing tank, although some of the level indicators had malfunctioned at the time of the inspection. This was subsequently addressed.

The inspection of the production blocks followed starting with Block E followed by Block C. There were no connections on site for charging ethanol from the day tank to one of the reactors. The inspectors witnessed sampling from one of the reactors. There was no extraction fan to control of fumes and the sampling staff used simple ordinary masks. These have subsequently been addressed.

WHO Public Inspection report (WHOPIR):

**Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal,
Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011**

The version of one of the APIs produced in Block C did not use any recovered solvents or materials. For example, distilled ethanol from one of the steps was collected and consequently collected by a waste management contractor. The TLC test to indicate completion of reaction in one of the synthetic steps evaluated had been removed via a change control based on historical data. Although it was noted from the BMR and filter log book that the leaf filter and candy filter were replaced after every batch and the micro filter was replaced after either every 10 batches or 6 months, whichever was shorter, there was no provision to check the integrity of the fitter before and after use. This has subsequently been addressed.

Tray dryers located in the Pharma area of block C were used to dry one of the APIs. Although, one of the tray dryers had a "cleaned" status label, powder residues were seen on the trays and inside wall of the tray drier. This was contrary to the SOP on cleaning of tray dryers. The drums dedicated for and containing one of the dried APIs were not labelled with the B. No. of the API there in or stage of processing. Although it was claimed that the pulveriser had never been used (there was no log book), white powder residue were seen stuck in its screens. These were subsequently addressed.

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

Day 3

After providing the company with a summary of the observations from the previous day, the inspectors proceeded to review documents related the following:

- Change control to remove TLC, water content and LOD tests for intermediates for one of the APIs which included evaluation of data from 192 batches of Intermediate-I and 120 batches of Intermediate-II produced in block C and few from Block H.

Inspection of block H followed. The design of the block and the process for one of the APIs provided for continuous recovery and re-use of recovered solvents in the same stage of processing. The recovered solvents and materials were identified by a unique batch number which was linked to the stage of recovery. They were tested against approved specifications before use. One of the recovered solvents was used in the last purification stage. Although no specific ratio of recovered to fresh solvents had been set for use, subsequent to this inspection, these have been set based on historical data. The practice was to use all the recovered solvents and top up with fresh solvent to meet the required volume. Subsequent to this inspection, a limit to the number of recoveries has been set, the profile of impurities in recovered solvents has been established and the limit of single unknown impurities in recovered solvents has been revised based on actual data. The applicant was advised to update the respective APIMFs and submit these changes for review by the assessment team.

The HVAC system serving the pharma area for Block H was inspected. The final purification (crystallization, centrifuge and ANFD) area was served with 100% fresh air filtered through 20 μ , 10 μ , 5 μ and terminal HEPA (H13) without recirculation and the exhaust was through a scrubber. Two AHUs served the powder areas (drying, blending, sifting, and packing) and each had a series of filters: 20 μ , 10 μ , 5 μ and terminal HEPA (H13) with recirculated air.

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011

There were two FBDs in the area for dying intermediates from Block C. Subsequent to this inspection, limits have been indicated on magnehelic gauges for the air supply and exhaust filters.

The QC laboratory was located on 3 floors: The ground floor hosted the testing of incoming raw material, intermediates, in-process testing and all GC testing. On the first floor, there was testing of finished APIs, stability testing, method validation, cleaning sample analysis, XRD and particle size testing. The stability chamber and retention sample stores were located on the second floor. Raw data on the GC, IR, HPLC and XRD was examined for selected samples. The SOP and records for calibration of the GC and HPLC were reviewed and no issues were noted. Specifications, raw data and records of testing of recovered solvents were reviewed. It was noted that the integrated spectra were not saved but the integration parameters were printed and filled with spectra. They were confirmed to be the same for all the samples and standards in the same run and we could reproduce the parameters as in the reported results. The raw data reviewed could not justify the specifications of recovered solvents with respect to potency and maximum single unknown impurity (MSUI). These have been revised following review of the impurity profiles and actual historical data. The applicant was advised to update the respective APIMFs and submit these changes for review by the assessment team.

Raw data for test before release of selected batches of API were reviewed. This included results of chromatographic purity and XRD (*2θ values determined daily*) to confirm the polymorphic form (only for batches supplied to one client).

Working standards were in place for the APIs in focus. Certain WS and Primary Reference standards were stored in the fridge: 2 - 8°C.

Each container of finished API was sampled for testing but the identity test by IR was conducted on a pooled sample. The comparison was only visual, as parameters like, wave number of main peaks, purity index, slope and intercept were not used.

There were several stability chambers for various study conditions: 2 - 8°C; 25°C/60%; 30°C/75%; 30°C/65%; 40°C/75% and one standby chamber for all conditions.

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

Day 4

After providing the company with a summary of the observations from the previous day, the inspectors proceeded to review documents related to the following:

The solvent recovery centre had 9 distillation columns each dedicated for the recovery of different solvents from different levels. The various components were adequately labelled, although there were no log books for the various lines. These have been put in place.

The inspection of the water treatment and distribution system followed. Portable water was delivered on site by tankers. The water is dosed with chlorine, passed through a clarification

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011

tank, filtered through a multi-grade filter (MGF), softener, ultrafiltration (UF), dosed with sodium metabisulfate to remove chlorine and dosed with NaOH to adjust pH. Water is then filters through two reverse osmosis columns in series (RO-I and RO-II) reducing conductivity, electro polished in the EDI to further reduce conductivity, then treated with UV light to reduce microbial load and TOC and the purified water is stored in the steam jacketed mother tank. Water is then circulated to 7 distribution tanks each supplying an independent loop: (1) Blocks A and B, (2) Blocks C and D, (3) Intermediate area for blocks C and D, (4) Blocks E, G and H, (5) Block F, (6) Block I, (7) Block J. Water is dumped into each of the distribution tanks with the help of PLC controlled level sensors and valves to ensure that there is flow back and recirculation between the mother tank and the distribution tanks which would pose a risk of cross contamination, especially with oncology products in blocks F and I.

The process validation of one of the APIs in block H was reviewed. It was conducted based on approved protocols for production process, for the drying process and for the pulverisation process. Validation was carried out in stages comparing batches produced using recovered solvents and materials with those prepared using fresh solvents and materials only, based on the same API specifications. This did not include XRD, although batches produced for one of the clients were always tested by XRD and the retention samples for the validation batches were tested during the inspection and confirmed that the API was form II.

- Stage-I: involved 6 batches where only fresh solvents were used and 2 batches which used recovered solvents and materials from the 6 batches. Three of these batches were used in validation of the drying process.
- Stage-II: involved 4 batches where only fresh solvents and materials were used and 2 batches where recovered solvents and materials were used.
- Stage-III: involved 3 batches which used only fresh solvents and materials and 1 batch in which recovered solvents were used.
- Final stage: involved 4 batches using fresh solvents and materials and 1 batch using a recovered solvent.
- The expected yield for the various stages was reviewed.

The same equipment as in current use was used in the validation and the amount of recovered solvents used depended on availability and not any specific ratio. All the available recovered solvents and materials were used first and topped up with fresh solvents and materials.

The ratios used in the validation batches had not been fixed for routine manufacturing. Subsequent to this inspection, these have been set based on historical data. The applicant was advised to update the respective APIMFs and submit these changes for review by the assessment team.

The receiving, sampling and testing records of the key API starting materials were reviewed. The review showed that the key API starting material was manufactured and supplied by Hetero Unit IV. Each container was sampled and tested for ID by melting point and a pooled sample was fully tested including ID by HPLC.

The results of analysis of the validation one of the API batches produced using recovered solvents and materials were reviewed. Each container was sampled and tested by IR. Its

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011

reserve sample was also tested by XRD during the inspection and confirmed to be form II. Results of specific impurities and related substances by HPLC and residual solvents showed that the API produced with recovered solvents and materials was equivalent with that produced with only fresh solvents and materials.

Review of cleaning validation revealed that it was done according to the blocks based on APIs produced and equipment chain used. The cleaning validation for one of the APIs in block C was done using an approved protocol. The same equipment chain was used to produce another API. Both rinse and swab methods were used with acceptance criteria based on the therapeutic dose and 10ppm (100ppm for intermediates). A UV analytical method with a LOD of 3ppm and recovery factor of 1.0 was used. The amount of solvent used was specified. The results of rinse and swab analysis from a glass-lined reactor and a centrifuge were reviewed and found acceptable.

The SOP on product quality review was evaluated. It provided for compiling the PQR of each API in January of every year to cover the period of January to December of the previous year. The review covered number and quantity of batches produced, trends (in-process, intermediates, finished API, yield, quality attributes: ± 3 sigma if No. >10), validation, stability, retention samples, changes, complaints, key starting materials, reprocessing, OOS, CAPAs, submitted DMFs and their variations and audits by DRAs. General systems like water, training, calibration, preventive maintenance, environment parameters (Temp, RH, ΔP , particle counts, microbial counts), and general changes/deviations/OOS per department were reviewed separately.

The PQR for one of the APIs for 2010 was reviewed. It did not indicate the reference number of the BMR/BPR used. It covered stage-I: 420 batches, stage-II: 424 batches, stage-III: 213 batches and final stage: 212 batches. A sudden rise (still below alert limits) in residual solvents by GC from below detection level was not discussed. The stability data supported a retest period of 24 months. Only 1 change and 5 deviations had been requested, reviewed and approved. Hetero Unit III (*original Hetero Unit IV*) was added as a new source of the API starting material through change control. It was noted that this was already included in section 3.2.S.2.3.2 of the updated DMF of November 2010 already submitted to WHO-PQP.

The PQR for another API for 2010 was reviewed in the afternoon of last day. Trend analysis of in-process, yield, analysis of quality attributes and OOT were included in the PQR. 121 batches of the API were produced and released in 2010. Total 12 changes were requested and approved. In 2010, there was no recall, no out of specifications, no deviation, and no reprocessed batch. There was one complaint regarding observed silica gel pellets while sifting through #25 mesh of one batch, the investigation had been done and reported and preventive action had been taken. In addition, there was one planned deviation and one general deviation in the year 2010.

The SOP on reprocessing and reworking was reviewed. The reprocessing allowed included: re-crystallization from the same solvent, re-filtration through the same size of filter and re-distillation using the same type of distillation column. Reworking was generally not allowed, but could include re-crystallization from a different solvent, re-filtration using a finer filter and re-milling using a different type of mill. In any case, any reprocessing or reworking

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, **Andhra Pradesh, INDIA, 24 - 27 January 2011**

proposed by production department had to be reviewed by R&D to recommend appropriateness of the method and approved by QA. The first batch had to be put on stability and approval by the respective DRA was a requirement. Reprocessing of reprocessed batch was not allowed.

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.

2.1 QUALITY MANAGEMENT

Generally QMS procedures are well executed. The site had an acceptable documentation system consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. The responsibilities of the Quality and production units were defined. There was a system and records for self inspection and Annual product quality review.

2.2 PERSONNEL

Generally, the site had adequate numbers of qualified and experienced personnel to carry out the tasks in accordance to the applicable GMP. Individual responsibilities were generally defined in the Organograms and individual job descriptions.

The heads of production and quality control were independent of each other.

Personnel interviewed reflected that they were aware of the principles of GMP. Entry to critical production, storage and quality control areas was restricted to only authorized personnel. Personnel were provided with appropriate protective clothing. The Personnel hygiene procedures were also adequate.

2.3 BUILDINGS AND FACILITIES

Buildings and facilities were generally well designed in a good state of repair and were adequately cleaned. The clean areas for purification stage were separate from those for the synthesis stages and floors, walls and ceilings were smooth to facilitate cleaning. These purification areas were supplied with adequately filtered air and segregated with airlocks and pressure differential to prevent cross contamination. The flow of activities in the pharma zone in H-block was not logical as there were to and fro movements between crystallization and powder area.

There were adequate facilities for treatment and distribution of purified water and this was regularly monitored and sanitised.

2.4 PROCESS EQUIPMENT

Process equipment was generally in a good state of maintenance and qualification. There was a system to indicate the status of the equipment. Cleaning procedures could be tightened. Cleaning status of some equipment like scoops should be strengthened.

2.5 DOCUMENTATION AND RECORDS

There was a system for documentation in form of SOPs, manufacturing procedures, log books, specifications, testing procedures. These were designed, approved and controlled according to established SOPs. Review of certain documents/reports could be improved.

2.6 MATERIALS MANAGEMENT

Materials were sourced from approved suppliers. On receipt they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. The storage of starting materials, intermediates and finished APIs was generally adequate and the storage conditions were regularly monitored. Materials under a different status and stage of processing were adequately segregated.

Containers with some materials at different stages processing were not identified with a unique batch number and stage of processing.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production procedures were generally well executed. Processes were guided by well documented procedures and detailed instructions. Different production stages were conducted in segregated facilities. There were in-process controls conducted at appropriate stages of synthesis to monitor the quality of the intermediates and APIs. The process used was generally similar to those outlined in the dossiers submitted to WHO. The cleaning procedures, design of the buildings and equipment, plus the planning of production facilitated prevention of possible contamination.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Final API packaging activities were not reviewed in detail due time factor. However, the pack size was not mentioned in the BPR.

2.9 STORAGE AND DISTRIBUTION

Hetero Unit I had appropriate and separate storage warehouses and areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. Conditions of storage were monitored and appropriate records for stock and distribution were maintained. API packaging and distribution activities were not reviewed in detail due time factor.

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011

2.10 LABORATORY CONTROLS

There was a separate block for QC department. The premises, facilities and utilities were separate from production and were in a good state of repair. Testing of incoming raw material, intermediates, in-process testing and all GC testing was located on the ground floor. On the first floor, there was testing of finished APIs, stability testing, method validation, cleaning sample analysis, XRD and particle size testing. The stability chambers and retention sample stores were located on the second floor. There were adequate pieces of equipment with up to date calibration status.

Records of sample receipt and allocation, analysis were maintained.

The microbiology laboratory was located in a separate block from the chemical laboratory but was not inspected.

There were stability chambers for the different storage conditions and records of charging and withdrawal of samples for testing were available and consistent with the protocols and regulatory requirements.

2.11 VALIDATION

Validation reviewed was generally adequate. Validation of manufacturing processes had been done and the relevant protocols and reports were available. Selected protocols and were reviewed. These protocols were well designed and executed. The critical process parameters, sampling plans and their acceptance limits had been well stated. Generally, the conclusions reached were supported by the results of validation.

2.12 CHANGE CONTROL

There was a procedure for change control which included evaluation of the validation status of the system and prescribed appropriate control measures to preserve the validated status. There was a change control register and appropriate records were maintained. Several changes were reviewed which proved that the change control in place was well designed and adequately implemented.

Certain procedures provided for in the change control procedures, i.e. Temporary changes were not consistent with GMP.

2.13 REJECTION AND RE-USE OF MATERIALS

Recovery of solvents and materials at different stages of synthesis was done according to documented instructions and were tested to meet predefined specifications. Some of the specifications allowed low potency and high unknown impurities, although these were not supported by actual results. These were revised subsequent to this inspection. Solvent recovery was done either on-line or off-line at the solvent Recovery System area located on the same site near the ETP. Recovered solvents were used at the same stage of synthesis. The use of recovered solvents and material had been included in the process validation of

WHO Public Inspection report (WHOPIR):

Hetero Labs Ltd, Unit-I, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, Andhra Pradesh, INDIA, 24 - 27 January 2011

synthesis of one of the APIs in block H. The resultant API had equivalent purity to the one produced with fresh solvents and materials only.

The specifications of recovered solvents and control use off recovered solvents and materials were changed subsequent to this inspection. The applicant was advised to update the respective APIMFs and submit these changes for review by the assessment team.

2.14 COMPLAINTS AND RECALLS

There were procedures for handling customer and market complaints and product recall. Generally the procedures were adequate.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The site used contract laboratories to conduct certain specialized tests but the agreements with the vendors were not reviewed due to time constraints.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, as well as the corrective actions taken and planned, **Hetero Labs Ltd, Unit-I**, Survey No. 10. I.D.A, Gaddapatharam Village, Jinnaram Mandal, Medak District, **Andhra Pradesh, INDIA**, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines and in particular, WHO Good Manufacturing Practice for Active Pharmaceutical Ingredients.

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.