



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

Part 1: General information

Name of Manufacturer	Cipla Ltd
Unit number	Bangalore
Production Block	<ol style="list-style-type: none">1. Synthetic-1 Block (S1) and Extension (S7): non-antineoplastic multiproduct blocks for API synthesis.2. API Block III (E3): a non-antineoplastic multiproduct block for synthesis of APIs and its intermediates.3. API Block 1 (E1): a multiproduct block dedicated to anti-neoplastic APIs.4. API and Formulation block (FP): a multiproduct facility for finishing a non-antineoplastic APIs (ground floor).
Physical address	Virgonagar, Old Madras Road, Bangalore, 560 049 India
Contact person and email address.	<ol style="list-style-type: none">1. Mr. Davinder Singh: dsingh@cipla.com2. Mr. Kuber Jagdale
Dates of inspection	27 - 30 June 2011
Type of inspection	Routine Announced Inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Antineoplastic and Antibacterial Active Pharmaceutical Ingredients.
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control and release of Antineoplastic, Antibacterial and other Active Pharmaceutical Ingredients.

Part 2: Summary

General information about the company and site

The site inspected was the **Cipla Limited, located at Virgonagar, Old Madras Road, Bangalore, 560 049 India**, hereafter called **Cipla Bangalore**. The company corporate office is located at Mumbai Central.

According to the Site Master File Document No. SMF/Cipla/BLR/A, version No. 10 effective 22.02.2011 and the presentation given at the opening meeting, Cipla Limited is a public Limited Company established in 1935. Cipla Bangalore was established in 1972 as an agricultural research division for scientific cultivation of Dioscorea. It is located 45km from Bangalore airport on a 671,259m² plot with a built up area of 39,073.61m².

The site had one facility for the manufacture of Pharmaceutical Formulations and nine facilities for Active Pharmaceutical Ingredients and intermediates. The APIs facilities included multiproduct blocks and blocks dedicated for antineoplastics (synthesis, purification and finishing). The finishing operations of non-antineoplastic APIs was conducted in a separate facility on the ground floor of the building for formulations. This inspection focused on the following blocks and areas:

1. The warehouse, sampling rooms and dispensing rooms for antineoplastic raw materials, intermediates and APIs.
2. The main warehouse for non-antineoplastic raw materials, intermediates and finished APIs.
3. Synthetic-1 Block (S1) and Extension (S7): multiproduct blocks where one of the APIs was synthesized (hydrolysis and condensation).
4. API Block III (E3): a multiproduct block where the API was purified by recrystallization and clarification. An alternative purification process was in place.
5. API Block 1 (E1): a multiproduct block dedicated to anti-neoplastic where the second API under focus was manufactured.
6. Finishing Block (FP): a multiproduct facility located on the ground floor of the API and Formulations building for the finishing (drying, size reduction, blending if applicable, sifting and packing) of non-antineoplastic APIs.
7. Quality control laboratory (Wet chemistry, instrumentation, stability and microbiology).

According to the company presentation and the SMF, the site employed a total of 610 people distributed as follows:

<u>Department</u>	<u>Staff</u>
○ Production	165
○ Quality (QC, Lab QA, QA)	148
○ Engineering/Projects	47
○ R&D and Technical support	38
○ Administration and others	176
○ Warehouse and logistics	36
Total	610

History of WHO and/or regulatory agency inspections

According to the SMF and company presentation, the site was licensed by the Food and Drugs Administration, Karnataka State under licence No. NB-110/78 and SP-72/80 and had been approved by Danish Medicines Agency (2008), ANVISA Brazil (2008), US FDA (2009), TGA/EDQM (2009), Korean FDA (2010), and UK MHRA (2010). This was the second inspection by WHO-PQP; the first inspection was in June 2005.

Focus of the inspection

The inspection focused on the production and control of two APIs (Neoplastic and non-neoplastic). The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients, including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging and Identification Labelling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls.

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Inspected Areas

Day One: 27 June 2011

The inspection started with an opening meeting at which introduction were made and the inspectors explained the procedure for the WHO Prequalification Programme, the procedures and standards used for inspection and timelines for processing the report and company responses to the inspection observations. The tentative inspection plan was discussed and confirmed. The company showed a DVD about Cipla and made a presentation about the site to be inspected. These presentations highlighted the company profile, the description of the site, a summary of manufacturing capacities, location of production of the various APIs, the site inspection history and changes since the last WHO inspection. A copy of the presentation was obtained and has been filed in the company file at WHO.

The major changes highlighted include the following:

1. Change in key personnel and increase in staff strength across all functions.
2. Demolition of old blocks and construction of new blocks (API blocks II & III).
3. Expansion of purified water system (block III).
4. Extension of QC instrumentation area and creation of retention sample store.
5. Renovation of sampling and dispensing area.
6. Refurbishing of powder processing area (synthetics I).
7. New block for manufacture of APIs and Intermediates (API Block IV)
8. Operation discontinuation for one block of Finished Products manufacturing (Formulations IV)

The company presented the process flow charts for the APIs in focus.

The inspection of the following areas followed:

1. Plant layout: CP/MP/MP/13
2. SOP on Organisation chart and Job descriptions.
3. Organisation charts:
 - Manufacturing
 - Quality Assurance (QA)
 - Laboratory QA:
 - Quality Control (QC):
 - Synthetics-I
 - Block III
 - Block I
 - Finished Products
4. Job descriptions:
 - Site QA Head: employee 27616
 - QA Reviewer/investigator: Employee 45206
 - Production Head, Synthetics-1 and Extn: Employee 42668
 - Analyst – Microbiology: Employee 34371
5. List of 4 staff allowed to perform batch release.
6. SOP on Personnel training.
7. Training records of selected personnel.

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8. SOP on conducting annual product quality review.
9. APQR 2010 for the non-neoplastic API Methanol (M) route
 - Master production documents:
 - In-house specifications for API starting material, intermediate and API.
 - Number of batches and quantity of intermediate and API produced.
 - Yield.
 - Process parameters generally consisted with the APIMF submitted to WHO-PQ.
10. SOP on Change Control.
11. Change Registers: selected changes were reviewed.
 - One to include in-house code for the intermediate.
 - Adding a source of API starting material
 - Reprocessing a batch of API
 - IPA route of the API
 - Use of potable water instead of purified water. Regulatory approval considered, not yet closed.
 - Change in intermediate input batch size. Already communicated to WHO-PQ.
12. SOP on deviations
13. Deviations Registers: Selected cases were reviewed
 - To use a higher purity API starting material in stage I for one batch of API. Resulted in higher impurities in the final API, though still in the acceptance range and was abandoned.
 - Unloaded powder from drier before results of LOD were obtained because the TGA had malfunctioned.
 - Unexpected increase of yields of final API probably due to a more effective removal of dichloromethane before final crystallization.
14. Procedure for "Out-of-Specifications" and relevant registers (years 2010 and 2011).
15. Procedure for batch failure investigation. Examined two OOS and subsequent batch failure investigation:
 - referring to small traces of an unexpected solvent in one batch of API due to an error in cleaning procedure of the tray (batch reprocessed).
 - limit of water exceeded in one intermediate lot (batch reprocessed)
16. SOP for handling Customer Complaints. No complaints had been received for WHO related products in 2010 and 2011.
17. SOP on Product Recall. Provided for classification of recalls, levels of recall, means of communication. No recall in 2010 and 2011. It provided for a dummy recall once a year to evaluate the effectiveness of the recall procedure in export markets.

Day Two: 28 June 2011

Inspectors provided feedback on the observations of the first day and company provided clarification on some of the observations. Documentary evidence was presented which confirmed that the validation batches submitted in the dossier were manufactured with in-

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house intermediate under a code which was used to represent both the intermediate produced in-house and on loan licence.

The list of the materials used in the synthesis of the two APIs and their in-house codes were extracted from the respective PDS.

The site layout for blocks S1, E1, E3 and FP showing locations of the various pieces of equipment was presented. The equipment used in the manufacture of the two APIs was all identified.

The inspection of the warehouse followed starting with procedures for receiving of materials, quarantine area, sampling rooms and procedures, storage areas, status labelling, temperature monitoring, approved vendors for selected materials and dispensing procedures and rooms.

Production facilities, activities and records for the non-neoplastic API starting in Synthetics- 1 block, S7, E3 and FP were inspected.

Day Three: 29 June 2011:

Inspectors provided feedback on the observations of the previous day. The programme of the day was discussed and agreed upon.

Inspection of the following areas and activities followed:

- Synthesis of the neoplastic in Block E1 and the deep freezers used for storage.
- Quality control: sampling and analysis of starting materials, intermediates and finished APIs including; review of raw and electronic data (IR, HPLC, GC), calibration procedures and equipment; preparation of samples and reagents; retention samples.
- HVAC and dust control systems for Blocks E1 and FP: inspection of physical installation; review or operation, cleaning and maintenance procedures and records for selected AHUs; review of requalification protocol and report for selected AHU and clean area.

- Microbiological lab:

Total Viable Counts (TVC) and Bacterial Endotoxin Tests (BET) were carried out for purified water and WFI. BET test was carried out for the API. The rooms of the lab were classified and access was controlled. Pressure differentials were maintained between areas.

The sampling of water was described by one of the authorised operators (two operators of micro lab) and the relevant SOP was examined. Incubators were examined and their calibration tags were checked. Two incubation plates for two samples (one PW and one WFI) which were in the sampling schedule were checked for their actual presence in the incubators. Preparation of a lot of R2A medium and the relevant management SOP, validations and controls were checked. Procedure for sub-culturing of bacterial and fungi strains and relevant registration were examined. BET analysis: Examples of lysate sensitivity confirmation and controls of micropipettes were examined.

- Stability chambers and controls of their temperature:

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Table summary of stability studies of the non-neoplastic API at 30°C/65% RH was reviewed: there was one batch per year from 2007.

Raw data (paper and electronic record) of one batch submitted to stability at 30°C/65%RH 48 months point (HPLC analysis for impurities) and another at 25°C/65%RH 60 months stability point (HPLC analysis for impurities) was examined with no issues noted.

- Reference standards:

The refrigerators for storage of reference standards were examined and the relevant SOP for qualification of working standards was reviewed. Selected working standards and their relevant qualification were examined.

- Water purification and distribution systems:

The following aspects were inspected:

- PW production plants and the registration of changing of filters and sanitization.
- WFI production plant and the registration of changing of filters and sanitization.
- Examinations of the layouts of the water plant and loops.
- Sampling plan of the use point for control of quality of water. The approach was that the most critical points (inlet, outlet of production plant; after UV1 and UV2 and the inlet of potable water are controlled every week). All the other points are controlled at least every four months and every month one point from each block was controlled. The limits of the specification comply with PW and WFI pharmacopoeial standards.
- Trend analysis of the PW and WFI for the period February-May 2011.

- Analytical data to support the storage of the intermediate wet crude for one month.

Day Four: 30 June 2011

Inspectors provided feedback on the observations of the previous day.

The following aspects were inspected or reviewed:

- Calibration of temperature sensor for one of the reactors plus the documentation for minimum detectable volume of 726 litres.
- DOP test for HEPA filter for FBD.
- Requalification of neoplastic powder area: particle counts and air changes per hour.
- Cleaning validation for FBD. Cleaning validation for individual products that use this FBD was performed. A clear assessment of the worst case was not identified and not all the possible product changeover scenarios were covered.
- Vendor qualification for API starting materials. This involved a supplier questionnaire, analysis of 3 batches, manufacture of trial lab scale batches and site audit.
- Validation master plan version 04, effective 24.03.2011.
- Procedures and control of labelling of APIs.
- Self-inspection schedule and status for 2011. It was up-to-date.

- Analytical data to support the storage of dried API intermediate for 6 months. Provided reanalysis data of one batch analysed after one year.

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- Process validation:
 1. Examined validation report of the process. Apart critical parameters and IPC control, the Company carried out further additional control for validation purpose. The PDS were reviewed against the process described in the assessment report from WHO and they reflected the process submitted to WHO. Furthermore the protocol for the validation of the increased batch size process was checked.
 2. For the neoplastic API, the Company presented to WHO a new submission of APIMF.

It was noted that in the APIMF the company did not present the process validation but declared that the process is an already consolidated process therefore the process validation was verified. Process validation was made in 2005 and the validation reports were available:

The PDS of the validation batches were compared with the process described in the APIMFs submitted in June 2011 and they reflected the process submitted to WHO.

- Validation of BET analysis carried out for the neoplastic API (matrix effect).
- Training records of selected QC operators and engineers were reviewed.

2.1 QUALITY MANAGEMENT

Generally QMS procedures were well executed. The documentation system at the site included procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. There was a Quality Unit consisting of Quality Assurance, Quality Control and Laboratory Quality Assurance. The responsibilities of the quality and production units were defined indication that the Quality Unit was independent from production. There was a system and records for self-inspection and annual product quality reviews.

2.2 PERSONNEL

The site had adequate number of qualified, experienced personnel to carry out the tasks in accordance to the applicable GMP. Individual responsibilities were generally defined in the organisation charts and individual job descriptions.

Personnel interviewed and records checked reflected that they were aware of the principles of GMP, although the training evaluation of some staff involved in the monitoring of the HVAC system and in manufacture of neoplastic APIs required further strengthening.

Entry to critical production, storage and quality control areas was restricted to authorized personnel who underwent appropriate gowning.

2.3 BUILDINGS AND FACILITIES

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The building and facilities were designed to facilitate logical flow of production activities and to avoid cross contamination. The building and facilities were in a good state of repair and were adequately cleaned. Lighting in some sections of the main store needed to be improved.

The clean areas for purification stage were separate from those for the synthesis stages. The surfaces were smooth and the areas were supplied with separate AHUs and purified water.

The HVAC system was well designed but its routine maintenance needed further strengthening. Water which was purchased from outside was delivered in tankers and treated to different levels appropriate to its use.

2.4 PROCESS EQUIPMENT

The process equipment were designed and installed to facilitate containment and logical flow of production. They were regularly cleaned and maintained according to approved procedures and records were maintained. There were approved procedures to perform batch to batch and product change cleaning, and appropriate status labelling.

Measuring instruments were calibrated regularly but more care was needed in completing, and reviewing calibration records to ensure traceability and avoid the lapses noted.

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 an established SOP. The documents reviewed were found to be comprehensive. Batch production records were consistent with Master Production Instructions and the dossier. Any changes were handled through change control.

Procedures were generally readily accessible apart from some in the neoplastic powder processing area which were kept outside the area.

Quality control records were well completed and assembled to provide adequate traceability of the samples tested, the reagents and equipment used, procedures used and conclusions reached.

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 labelling of some raw materials needed to be improved especially with respect to name and address of manufacturer. The storage of starting materials, intermediates and finished APIs was generally adequate and the storage conditions were regularly monitored.

Materials at different manufacturing stages were identified with a unique batch number and stage of processing. The hold times, retest dates and expiry dates of the different materials had been established and were being respected.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production processes were guided by documented procedures and detailed instructions. Production processes were either conducted on campaign basis in multipurpose workshops and equipment. There were in-process controls conducted at appropriate stages to monitor the processes plus the quality of the intermediates and APIs. The cleaning procedures, design of the buildings, equipment and the planning of production facilitated prevention of cross-contamination.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Materials at different stages processing were identified with a unique batch numbers and stage of processing. Intermediates and finished APIs were packed using packaging materials meeting the relevant specifications. The labelling of finished API's was adequately controlled.

2.9 STORAGE AND DISTRIBUTION

Cipla Ltd, Bangalore had appropriate and separate storage areas for starting materials, packaging materials, solvents, intermediates, and finished APIs. The packaging could support adequate storage and transportation and records maintained could support traceability.

2.10 LABORATORY CONTROLS

The main QC laboratory was situated in a separate block. The premises, facilities and utilities were separate from production and were in a good state of repair. There were dedicated rooms for wet chemistry, instrumentation, hot areas and balance room. There were adequate pieces of equipment with up to date calibration status.

The microbiology laboratory was separated from the chemical laboratory. There were stability chambers for the different storage. Retention samples were adequately maintained.

2.11 VALIDATION

The policies for validation and qualification were outlined in the Validation Master Plan. Randomly selected equipment indicated that the equipment validation was adequately implemented. Utility systems had been qualified and were regularly monitored and requalified.

Manufacturing process and cleaning procedures related to the APIs in focus had been validated and the validated status was maintained via robust change deviation control procedures.

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2.12 CHANGE CONTROL

Elaborate procedures for change control were in place. Changes were generally adequately documented, well evaluated and implemented. The regulatory implication of the changes was evaluated and where necessary, variations were submitted to the relevant authorities for approval. It was noted that recent changes in the batch size of the non-neoplastic API under focus were handled through change control and submitted to WHO-PQ for approval.

2.13 REJECTION AND RE-USE OF MATERIALS

There was no use of recovered solvents or materials in the manufacture of the APIs under focus, However the recent changes in the batch size of the non-neoplastic API, did have the provision for use of recovered solvent conforming with release specifications.

A number of reprocessing steps had been incorporated in the routine production procedures with appropriate in-process checks to determine their necessity.

2.14 COMPLAINTS AND RECALLS

Procedures were in place to handle customer complaints and any recalls. The effectiveness of the recall procedure had been established through a mock recall. No complaints had been received and no recall had been made in 2010 and 2011.

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The company used several contract laboratories for some analyses but none involved the APIs under focus. In the past, the site used a contractor to manufacture the intermediate for the non-neoplastic API on loan licence but this had since been discontinued. This area was therefore not inspected in detail.

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, **Cipla Ltd, Virgonagar, Old Madras Road, Bangalore, 560 049 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.

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