

WHO PUBLIC INSPECTION REPORT API Manufacturer
**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
API Manufacturer**
Part 1: General information

Name of Manufacturer	Cipla Ltd.
Unit number	Unit I, II & III
Production Block	Unit I, – Bulk Drug-1 (finishing area), – Bulk Drug-II (finishing area), – Bulk Drug-V Unit II, – API Manufacturing-I, – API Manufacturing-II Unit III, – Bulk Drug-I, – Bulk Drug-III, – Bulk Drug-IV
Physical address	Plot No D-7 Unit (I), D-22 (Unit III), D-27 (Unit II) MIDC, Kurkumbh, 413 802 District: Pune (Maharashtra) INDIA
Contact person and email address.	Mr Davinder Singh (dsingh@cipla.com) Mr Kuber Jagdale (kuber@cipla.com)
Date of inspection	19, 20, 21 and 22 August 2014
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	<u>Prequalified APIMFs</u> Abacavir Sulfate, APIMF199 Emtricitabine, APIMF061 Lamivudine, APIMF001 Lumefantrine, APIMF075 Nevirapine, APIMF007 Nevirapine Hemihydrate, APIMF154 Oseltamivir Phosphate, APIMF173 Stavudine, APIMF003 Tenofovir Disoproxil Fumarate, APIMF025 <u>APIMFs Under assessment</u> Atazanavir Sulphate, APIMF189

	Darunavir Ethanolate, APIMF251 Efavirenz, APIMF253 <u>APIMF accepted under CEP</u> Fluconazole (CEP)
Summary of the activities performed by the manufacturer	Production and control of active pharmaceutical ingredients and intermediates

Part 2: Summary

General information about the company and site

The site inspected was Cipla Ltd, Kurkumbh, Unit I, II & III, Plot No D-7, D-22 and D-27, MIDC, Kurkumbh, 413 802, District Pune, Maharashtra, India. The company corporate office is located at Mumbai. Cipla Ltd is a public limited company established in 1935 and managed by a professional board of directors. It manufactures and markets wide range of pharmaceutical formulations and active pharmaceutical ingredients (APIs). The corporate headquarter (including corporate QA and R&D) is located in Mumbai. Cipla has manufacturing facilities (formulation and APIs) all over India, whereas four API manufacturing facilities are located at:

- Bangalore
- Patalganga
- Kurkumbh
- Bommasandra

The manufacturing facilities at Cipla Kurkumbh were started in 1994, and it is being continuously upgraded as per their needs. The site is located in an industrial park, approximately 70km from Pune city. There are three manufacturing units at Kurkumbh site: Unit I (D-7), Unit II (D-27) and Unit III (D-22). The breakup of various manufacturing blocks (either known as Bulk Drugs / BD or API) within each unit and the corresponding products are as followed:

Unit I	BD-I (finishing area)	Lamivudine, Oseltamivir phosphate, Lumefantrine
	BD-II (finishing area)	Atazanavir sulphate, Darunavir ethanolate
	BD-V	Fluconazole
Unit II	API-I	Lamivudine, Tenofovir, Tenofovir Disoproxil Fumarate, Emtricitabine, Efavirenz
	API-II	Tenofovir Disoproxil Fumarate
Unit III	BD-I	Lamivudine, Nevirapine, Tenofovir Disoproxil Fumarate, Emtricitabine, Stavudine, Nevirapine hemihydrate, Oseltamivir phosphate, Abacavir sulphate
	BD-III	Nevirapine, Tenofovir Disoproxil Fumarate, Emtricitabine, Stavudine, Nevirapine hemihydrate, Abacavir sulphate
	BD-IV	Tenofovir Disoproxil Fumarate, Emtricitabine

It is to be noted that Unit-I manufactures both non-sterile APIs and non-sterile finished pharmaceutical products in different manufacturing blocks. From the site master file, it was also noted that the site manufactures Levonorgestrel and other hormone APIs on this site in a dedicated facility.

Since the last inspection site had submitted three APIMFs to WHO (Atazanavir sulphate APIMF189, Darunavir Ethanolate APIMF251 and Efavirenz APIMF253). All these three APIMFs are currently under review.

History of WHO and/or regulatory agency inspections

The site was last inspected by WHO in February 2011. The site has also been inspected by several regulatory authorities such as TGA, USFDA, and KFDA:

- | | |
|-------------------------------------|--------------------|
| – 10-12 February 2011 | WHO (Geneva) |
| – 7-11 May 2012 | Korean FDA (Korea) |
| – January 2013 (desktop inspection) | TGA (Australia) |
| – 19-23 May 2014 | FDA (USA) |

The main scope of the last USFDA inspection was finished dosage manufacturing but it was claimed that USFDA had also inspected their respective APIs (Lamivudine Form I). EIR has been received from USFDA in which Active Pharmaceutical Ingredients is included.

Focus of the inspection

The inspection focused on the production and control of APIs listed under Part 1, General Information. The inspection covered most of the sections of WHO GMP guidelines for active pharmaceutical ingredients, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

Day 1, 19th August 2014

- Introductions
- Exposition of the WHO inspection procedure by the lead inspector
- Site presentation by the site management.
- Manufacturing authorization
- Regulatory inspections
- Changes since the last inspection
- Organisational charts
- Product Quality Reviews
- Material management (RMCA software)

Day 2, 20th August 2014

- Feedback of day 1
- Self-inspection
- Training
- Supplier qualification
- Change control
- Investigation of OOS results

- Tour at Unit III (D-22), sections Bulk Drug (BD) I and IV (including storages wet chemistry and powder processing areas)

Day 3, 21st August 2014

- Feedback on day 2
- Instrumentation (qualification, calibration, maintenance, cleaning)
- HVAC system
- Water systems
- Cleaning and cleaning validation
- Tour, Air Handling Unit (AHU) in Unit III
- Tour, Purified water system for Unit III (BD-I & BD-IV)

Day 4, 22nd August 2014

- Feedback on day 3
- Review of trending of potable water and purified water for Unit III
- Quality control laboratories and test records (office and tour)
- Reprocess, rework
- Blending
- Handling of Returned Material
- Batch release
- Documentation system
- Closing meeting

2.1 QUALITY MANAGEMENT

The quality management system was generally well established, documented and implemented. The site organizational structure was reviewed and was acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified.

Corporate QA (located in Mumbai) responsible for the harmonization in corporate level, strategic decisions, supplier evaluation (including vendor audit program) preparation and distribution of CQA SOPs, recording the incoming complaints and managing the investigation. Site QA responsibility of quality assurance of unit QAs are harmonized by the site QA head who reports to the Corporate QA. The Site QA Head did not have supervisory tasks and responsibilities on the independent Unit QA heads, except of high level managerial role. The manufacturing units had independent QA departments (refer to Unit QA) responsible for the operational QA tasks and functions, such as batch release, investigations (deviation, change), etc. The unit QA departments consisted of two sections “Quality compliance and systems”, “Quality operations”.

The product quality reviews were prepared unit wise, according to SOP. The Unit QA Heads were responsible for assuring that all the requirements of APQR are fulfilled and to approve the APQR.

2.2 PERSONNEL

The total staff of the site (Unit I, II, III and formulation) was 1645 persons. The total staff for API units at the time of inspection was 952. The units (including manufacturing and quality control) were operated in 3 shifts. The personnel hygiene rules were defined in SOP. The personnel entering the manufacturing area had to wear clothes appropriate for the classification of the area and the operation. Used garments were cleaned daily by a contract laundry. The manufacturing units/departments were responsible for the preparation of the organization charts and the job descriptions. Each unit had separate Unit QA Head who eventually reports to Site Head QA. Quality assurance department was divided into “Compliance system” and “Quality operation” following to the recent restructuring of within Cipla Ltd corporate

SOP on training was reviewed and noted that flow chart on training was available which states training requirement for new staff as well as for the existing staff. The individual departments were responsible for the execution of training activities. The procedure stated that medium for training is English and local language if certain staff does not understand English. For contract staff, a separate training protocol is prepared in English (but based on their need can translate into local language). Training modules on cGMP, cleaning validation and others were prepared in English but not in local language for operators.

2.3 BUILDINGS AND FACILITIES

Wet chemistry and powder processing operations were performed in manufacturing sections (Bulk drug-BD) of the manufacturing units (see part 1). Besides the manufacturing workshops each unit had separate quality control, storage (incoming materials, solvents and finished products) organizations, facilities and utilities (HVAC, water system, etc.).

Two types of water were used in the site: potable water (general use and cleaning, including powder processing areas) and purified water (as process water in wet chemistry). The municipal water was pre-treated to gain potable water meeting the WHO specification. The feed water for the purified water system was the potable water. Unit I had three Unit II & III two water systems. The microbiology and chemical testing trends of the potable water system (Unit III) for year 2013 were reviewed and available.

2.4 PROCESS EQUIPMENT

The process equipment were multipurpose, the cross contamination avoided by means of campaign manufacturing and thorough (validated) cleaning procedures. The critical equipment were qualified, re-qualified if appropriate (after changes, major modifications, every 5 years, etc.) and maintained regularly

2.5 DOCUMENTATION AND RECORDS

There were different level SOPs used: corporate, site and unit. The corporate and site level SOPs were managed by the site QA (implementation and training before the effective date predefined by the corporate QA), but the handling of unit procedures was belonging to the unit QA. The format, identification coding, preparation, distribution, review, and retention of SOPs and other documents was defined. The master copy of the SOPs was retained for unlimited period.

2.6 MATERIALS MANAGEMENT

Every material (including raw materials and active substances) received a unique identification number representing the quality, supplier (in case of raw materials) and the manufacturing process (in case of active substance). The material codes are generated automatically (random 5 digit code) by means of RMCA (Raw Material Creation Application) software. Every shipment/batch of the incoming materials is identified, recorded in the IMS software, sampled, tested, released and labelled accordingly.

A procedure on selection, evaluation and approval of manufacturer provided purpose for the selection, evaluation and approval and re-evaluation of raw manufacturers. The procedure was applicable to manufacturers of raw materials including API starting materials, final intermediates and other raw materials. The CQA was responsible for the material vendor management and for the strategic decision of to decide on the inclusion of a new supplier.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

The production operations were defined and recorded in Process Data Sheets-PDS equal to batch manufacturing records. Every unit possessed own in-process laboratories belonging to the unit quality control by organization. TDF has three different manufacturing processes (Process A, B and C).

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

The packaging of the APIs was performed in the controlled environment (Class D, ISO 8) of the powder processing facilities. Packaging materials were controlled (received, tested, handled, released, stored) similarly to the other raw materials.

2.9 STORAGE AND DISTRIBUTION

The storage facilities and practices of the Unit III were inspected. The warehouse was common for the raw material, packaging materials and finished products (active substances). The ambient temperature part of the warehouse had moveable shelving system. Separate cubicles were available for cold storage (2-8⁰C, rooms: 1019, 1021), returns/rejects (room 1018), sampling and dispensing (3 rooms for chemicals + 1 for packaging materials). For starting materials, the storage condition was set to ambient

without providing upper/lower limit. The finished goods store was controlled for temperature (15-30⁰C) and humidity (NMT 70%) and cold store at 2-8⁰C. Inventory Management System (IMS) is currently being used for the material inventory and also running parallel SAP system which will be used full fledged from 1 September 2014.

2.10 LABORATORY CONTROLS

The quality control (chemical) facilities and practices of the Unit III were inspected. The QC laboratory consisted of 4 sections: API, Stability, Chromatography and Raw material. The sampling was the task of the QC personnel. The incoming samples were recorded in a register (common for all raw materials, intermediates and finished products) and an AR number generated (as a serial number of the forthcoming entry in the logbook). Total quality control software was used in lab for issuance of analytical worksheets.

2.11 VALIDATION

The applicability of the manufacturing processes were justified by prospective, retrospective or concurrent validation studies, as well as re-validations. The validation protocols contained the acceptance criteria, control, test procedures, process steps, assessment of results, etc. The validation report was approved by the unit QA head.

2.12 CHANGE CONTROL

Change control was handled according to SOP. Changes were classified as major, moderate and minor with examples given for each. The need to notify regulatory authorities was included in the procedure. The change control apply for product, document and process related changes. The changes were identified by unique codes, issued by the unit, indicating the unit number, the year and a monthly repeated serial number. The file of the change controls together with the records was available.

2.13 REJECTION AND RE-USE OF MATERIALS

Reprocessing and Reworking provides procedure on when a batch can be reprocessed or reworked following out of specification or failure. QA approval is sought before a batch can be reprocessed and or reworked. The reprocessed and reworked batches shall be subjected to stability testing. It is stated that appropriate approval should be sought from respective regulatory authorities and changed be included in DMF. A unique batch number is assigned differentiating from the original batch number to differentiate reprocessed or reworked batch. A logbook for reprocessing and reworking was maintained.

Handling of Returned Material was reviewed and noted that procedure has a flow chart. The procedure provided guidance on how to handle return material, verification and testing of material upon return, redistribution if material received intact after ID test, if not reprocessing/reworking where applicable before further decision taken on

return material. It was noted that no separate batch number assigned to the returned material if no reprocessing or reworking was done.

2.14 COMPLAINTS AND RECALLS

The complaints and recalls were handled according to SOP. They were categorized as technical or medical and the possibility of counterfeit was included. The log of the complaints was managed unit wise. Any complaints that may arrive at any part of CIPLA is first recorded by the CQA then forwarded to the concerned site/unit. The deadline for investigation/feed back to the customer is 30 days. The investigation records of the complaint regarding the product: Oseltamivir phosphate was available. (CQA identification:

2.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

The contract manufacturing was restricted to solvent regeneration. The activity was contracted out to two Indian manufacturers. The contract partners were evaluated by questionnaire and on-site audit.

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, APIs manufactured at *Cipla Ltd, Unit I, II, III, Kurkumbh, India* were considered to be manufactured in compliance with WHO GMP 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.