World Health Organization

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WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Cipla Ltd, Patalganga
	Unit No I and Unit No II
	Unit No I Cipla Limited Plot No. A – 33, A – 2 (Unit – I), MIDC Patalganga, 410 220 District Raigad, Maharashtra, India **Unit No II** Plot A-42 Cipla Limited Plot No. A – 42 (Unit – II), MIDC Patalganga, 410 220 District Raigad, Maharashtra, India
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of: • Non-sterile medicinal products: uncoated and film coated tablets, ointments, creams, gels and nasal sprays. • Active Pharmaceutical Ingredients (APIs) and drug intermediates
Active Pharmaceutical Ingredient(s) included in the inspection	Lamivudine (APIMF001) Artesunate (APIMF004) Artemether (APIMF043) Lumefantrine (APIMF075) Moxifloxacin (APIMF091)
Scope and type of inspection	Routine inspection, covering all aspects of GMP
Date of inspection:	10 - 14 February 2014
Project (if any):	Prequalification Programme

Part 2: Summary

General information about the company and site

The facility inspected was Cipla Ltd, located at Patalganga, A-42 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India, here after called Cipla Patalganga**.** Cipla Patalganga is situated in a Government sponsored Industrial Park at a distance of 80 km from Mumbai by road. The Manufacturing facility at Patalganga Unit I (Plot A-33) was commissioned in 1984 and set up for the manufacturing of APIs and Finished Formulations (Tablets, Topical Preparations & Nasal Sprays). The facility was extended under the same

local Management in the year 2006 by a second Unit (Unit-II on Plot A-42) for the the manufacturing of Active Pharmaceutical Ingredient (API) & Finished Formulations (Tablets). Further in the year 2013, the facility was again extended under the same local Management (Plot A-2). This Unit I extension, which is adjacent to Unit-I (Plot A-33), is set up for the manufacturing of Active Pharmaceutical Ingredient (API), Quality Control for Unit I and Unit I extension, as well as Pilot plant and Research and Development (R&D) laboratory for APIs.

Cipla Ltd. has its Corporate Headquarter in Mumbai Central, Mumbai 400008 India, plus manufacturing facilities and Research centres in the following locations:

Bangalore:	FPPs, API's, natural products and Research Centre
Bommasandra	APIs
Patalganga:	FPPs, APIs and Research Centre
Kurkumb:	FPPs, APIs and Research Centre
Goa:	FPPs
Baddi:	FPPs
Sikkim:	FPPs
Indore:	FPPs
Vikhroli:	Research Centre

Cipla Ltd. manufactures and markets a wide range of intermediates, Active Pharmaceutical Ingredients (API's) and Finished Formulations.

Part 2: Summary

History of WHO or regulatory agencies inspections

The site was previously inspected by WHO inspection team on 14th February 2011 to 17th February 2011 for APIs manufactured in Unit II.

Recently the site was inspected by the following authorities:

- Joint Inspection by Central Drugs Standard Control Organization, Government of India & Local Food and Drug Administration
- ISO 14001 & OHSAS 18001 for safety and environment
- United States Food & Drug Administration (USFDA)
- Therapeutic Good and Administration, Australia
- Medicines and Healthcare Regulatory Agency (MHRA)
- Korean Food & Drug Administration

Focus of the inspection

The inspection focused on the production and control procedures of

- Lamivudine (APIMF001
- Artesunate (APIMF004)
- Artemether (APIMF043)
- Lumefantrine (APIMF075)
- Moxifloxacin (APIMF091)

It was explained to the inspectors that above mentioned APIs were not manufactured at Unit I. Company was planning in the nearest future to manufacture those APIs also in the Unit I, therefore Unit I was also inspected.

For WHO, above listed APIs during the inspection were manufactured at Unit II.

Inspected Areas

The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text:

- Quality management
- Qualification and validation
- Complaints and recalls
- Self-inspection
- Personnel training
- Premises
- Equipment
- Materials
- Documentation
- Production
- Rejection and reuse of materials
- Quality control

2.1 QUALITY MANAGEMENT

In general, a system for managing quality was established. The Quality Unit was independent of production. QU was headed by the Quality Assurance Head Unit II who supervised the whole quality management system (QMS) at Cipla Patalganga.

Product quality review (PQR)

The SOP "Annual product quality review (APQR)" was checked. The SOP was applicable for FPPs, APIs and intermediates. It contained all parameters according to the current GMP requirements.

The following PQRs for 2013 were reviewed:

- PQR for Lumefatrine (APIMF075)
- PQR for Artemether (APIMF043)
- Moxifloxacin (APIMF091)

Responsibilities – job descriptions

The following Job descriptions were reviewed:

- Unit II Quality Assurance Head
- Unit II Unit Quality Assurance Head (APIs)
- Unit II Officer (Reviewer and observer APIs)
- Unit II Officer (Documentation, Validation & Qualification APIs)

Change control (CC)
The SOP "Change control", flow chart and change control form were checked. The SOP was applicable to all changes (addition/revision/deletion/transfer) related to products, documents, systems, facilities, equipment, instruments and others like changes what does not fall under the changes defined above.

Changes were classified as:
- Major
- Moderate
- Minor

The SOP specified that change control should be closed . All during the inspection reviewed changes were closed within the specified time limit.

In case of major changes regulatory authorities, customers and Marketing Authorisation holders for finished products should be notified. Changes were trended in the respective API APQRs. The following change control logs were presented to the inspectors:
- CC log for documents
- CC log for product
- CC log for systems
- CC log for facility
- CC log for equipment
- CC log for instrument

Separate registers were used for changes in the different areas.

Deviations
The SOP "Quality Management System deviation" and flow chart were checked. Deviations were specified as planned and unplanned and classified as:
- Major
- Minor

Deviations were trended and trend analysis presented to the inspectors. Spot checks confirmed that deviations were closed within specified time limit.

Corrective action and preventive action (CAPA)
The SOP "Quality Management System CAPA" and flow chart were checked. The SOP was applicable to all non-conformances, Out of Specifications (OOS), Out of Trends (OOT), deviations, internal and external audits, complaints, recalls, batch failures, APQR, items from quality management review, risk management, rejection of batches and other sources of quality data. CAPA team leader, team members and CAPA reviewer team were specified, CAPA register was presented to the inspectors.

According to the SOP CAPAs should be closed within 180 calendar days. Spot checks confirmed that CAPAs were closed within the specified time limit.

Risk assessment (RA)
The SOP "Risk Management by Failure Mode Effects and Critical Analysis" was checked. The SOP was used for Risk Management by Failure Mode Effects and critical Analysis. The SOP was applied in different areas e.g. development, manufacturing, testing, and distribution to evaluate the risk inherent to a process. For root cause analysis, the fish bone method combined with the five Why - Analysis was used.

Responsibilities of the quality and production units
Responsibilities of different departments were described in the SOP "Organisational chart and job responsibilities".

Internal audits (self-inspection)
The SOP "Self inspection", schedule for 2013 and checklist for inspection of the Quality Assurance (QA) department were checked. The procedure contained detailed instructions for the qualification and training of the auditors as well as the preparation, performance and follow up of self-inspections. According to the schedule, all the areas were inspected .

Supplier approval
The SOP "Selection, evaluation and approval of manufacturer", flow chart for approval of new manufacturers, flow chart for audit of manufacturer, flow chart for approval of manufacturer of other raw materials/packaging material and flow chart for additional item to be purchased from already approved manufacturer were checked.

Approved manufacturers of starting materials/final intermediate products/ primary packaging material manufacturers were re-evaluated every three years by questionnaire and site audit. Other raw materials and packaging materials manufacturers were re-evaluated every four years by questionnaire.

Manufactures audits were carried out by trained persons. Audit schedule for API starting materials manufacturers/suppliers was presented to the inspectors.

Audit observations were classified as:
- Critical
- Major
- Minor

2.2 PERSONNEL

Personnel qualifications
There was an adequate number of personnel qualified, trained and experienced to perform and supervise the manufacture of intermediates and APIs.

Training
The SOP "Training" and training flow chart were checked. The SOP explained the training requirements for GMP and related training program for employees. The following trainings were specified in the flow chart:
- Factory induction training/QC induction training

- On-the-job training
- Working under supervision
- Training evaluation (questionnaire and testing), if required re-training
- Training certificate
- Scheduled trainings (for all employees) – twice per year
- Training on changes
- External training (for management)

Training effectiveness was evaluated by multiple choice questionnaire and open questions.

Analyst competency was assessed by a personal validation protocol. Analysis was carried out in parallel by trainee and trainer. Results were compared and RSD was specified. Analyst competency certificates were issued for each test.

Personnel hygiene
The SOP "Personal health and hygiene" was checked. According to the SOP, personnel should wear clean clothing suitable for the manufacturing activities and avoid direct contact with intermediates or APIs. Diseases should be reported. Smoking, eating, drinking, chewing and the storage of food and personal medicines was restricted. Jewellery was not allowed. Medical checks were carried out twice per year.

Laundry of protective clothing was carried out by a contractor. Agreement with the company providing the laundry services was spot checked. According to the contract, laundry should be carried out following Cipla SOP ¨Washing of linen (non- sterile)". Laundry was collected separately from different change rooms and also washed separately.

Consultants
The SOP "Services of consultants" was spot checked. Consultants had sufficient education, training, and experience. A list of consultants was maintained stating the name and type of service provided by these consultants. Consultants CVs were maintained separately.

2.3 BUILDINGS AND FACILITIES

Design and construction
Buildings and facilities used in the manufacturing of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Buildings and facilities had adequate space for the orderly placement of equipment and materials. Pressure differentials between different production rooms were monitored. Change room doors were interlocked.

The SOP "Microbiological monitoring of environment in production area" was checked. Environmental monitoring (EM) was carried out using settle plates for fungi and aerobic

bacteria. EM trends from July 2012 till December 2013 were checked. Spot checked EM trend results were within specified limits, action and alert limits were specified.

Utilities
HVAC
Air to the "controlled areas" was supplied via 12 air handling units (AHU). During the inspection attention was paid to the AHU No 4. Air was supplied via filter cascade:

Pressure differentials were monitored; filters were cleaned once per week and changed upon requirement. Filtered compressed air was used for filter cleaning; filter cleaning were carried out in separate room.

Purified water Unit II
Purified water (PW) system was installed in 2006. Purified water (PW) used in production was generated using RO and EDI. Water was continuously circulated at ambient temperature. Calibrated flow meter was installed in the return loop. Conductivity and pH were monitored online. TOC tests were carried out in the QCL. PW system was sanitized weekly using hot water. Sanitization records were presented to the inspectors.

The SOP "Sampling of water and steam condensate "Water analysis" and trend analysis for two sampling points was spot checked. Samples from these sampling points were taken on a weekly basis. From other user points, samples were collected according to the sampling schedule - 2 sampling points fortnightly, rotated every quarter. Spot checked PW trend results were within specified limits, action and alert limits were specified.

PW Unit I extension
PW for usage in Unit I extension was generated by ion exchange and mixed bed method. During the inspection PW system qualification (monitoring) was in Phase III.

PW system Qualification protocol/report was spot checked.

PW system mixed bed, water storage tank and distribution loop were made from electro polished SS L 316. Orbital welding was applied for joints; boroscopic reports were available for 10% of the joints. Welder qualification certificate was shown to the inspectors. There were 4 user points in the API production unit, in total there were16 sampling points.

Containment
Highly sensitizing materials were not manufactured on site.

Lighting
Lighting was adequate.

Sewage and refuse
Not inspected.

Sanitation and maintenance
During the inspection, no special attention was paid to sanitization and maintenance of the premises. On spot checks sanitization and maintenance was found to be adequate.

2.4 PROCESS EQUIPMENT

Design and construction
Equipment used in the manufacture of intermediates and APIs was of appropriate design and adequate size, and suitably located for its intended use. Major equipment such as reactors and centrifuges, and permanently installed processing lines used during the production of an intermediate or API were appropriately identified.

Equipment maintenance and cleaning
Preventive maintenance (PM)
The SOP "Preventive maintenance procedure (PM)", planner and schedule were checked. The SOP "Preventive maintenance of reactor" also was checked. PM SOPs were available for all equipment used for processing, testing and utilities. Spot checks showed that the planned schedule was followed.

Cleaning
Cleaning of production equipment was described in the SOPs. The procedures were available e.g. for reactors, centrifuges or FBD, SS transfer line, flexible hose pipes and various accessories. Where applicable the procedure described the batch to batch as well as the product change over cleaning.

FDB bags were dedicated for the product. They were cleaned and checked for integrity after use.

Calibration
The SOP "Calibration", planner, and schedule were checked. Spot checks showed that the planned schedule was followed.

Equipment qualification
Fluid Bed Dryer (FBD) used in production of Praziquantel API (Unit I extension) Qualification protocol/report was spot checked.

Laboratory equipment calibration
Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) reports for analytical balance were spot checked. IQ, QO and PQ were done by the balance supplier. User requirement specifications were also checked.

The following analytical instruments were checked regarding usage and calibration:
- Karl Fisher
- pH meter
- Analytical balances
- HPLC
- GC

- FTIR
- UV
- Polarimeter
- Melting point
- Dissolution
- Disintegration
- Friability
- UV lamps used for TLC

Standards, standard solutions, working standards (WS) and chemical reference standards (RS) used for calibration of above mentioned equipment's were traceable.

Equipment maintenance was carried out yearly by contractors.

Class A glassware was used in the laboratory.

Computerized systems
GMP-related computerized systems (ERP) were not used in production.

HPLCs, GCs and automatic titrators were connected to the validated software. Back up of electronic date was carried out regularly:

Back up was done to another server located at the Unit I. Yearly back up was done to the server located at Vikrholi site. Computers were password protected; individual passwords were changed every 90 days.

2.5 DOCUMENTATION AND RECORDS

Documentation system and specifications
Documents related to the manufacture of intermediates and APIs were prepared, reviewed, and approved. Specifications were established and documented for raw materials, intermediates and finished API. Acceptance criteria were established and documented for in-process controls. The company had many corporate level documents what were applicable either for both – FPPs and APIs or APIs.

Equipment cleaning and use record
Inspected records were adequate.

Records of raw materials, intermediates, API labeling and packaging materials
Some records inspected were found in order.

Master production instructions (MPI)
Master production instructions had been established and appropriately approved.

Batch numbering system
The SOP "Batch numbering system" was reviewed.

Batch production records
Batch production and packaging records were called Process Data Sheets (PDS).

The PDS for one of product along with the Analytical test report and API specification were checked. The PDS was issued, checked and authorised by the respective responsible persons. According to the manufacturing instruction, the batch was dried in two FDB runs, milled, sifted and filled in drums without another blending step. Each drum was sampled from top, middle and bottom and a composite sample of all samples was withdrawn and analysed. During the inspection, the company presented a newly prepared document to perform a validation study to prove the homogeneity of the batch.

The PDS, analytical raw data and related documents were spot checked for the one of API validation batch.

Laboratory records
Receiving of samples, allocation of A.R. number, testing, checking and release of the different materials were described in laboratory procedures. The handling of dry chemicals and reference standards as well as the preparation of solutions and working standards was done according to approved procedures.

Control of laboratory test results
The SOP "Functions of Laboratory Quality Assurance" was checked. The SOP explained the steps for the verification and approval of the laboratory test reports and status labels received from Quality Control along with the relevant specification/SOP as a final review. A check list for the verification of the QC report was used. The QC report verification was done by Laboratory QA.

Batch production record review/batch release procedure
The SOP "Batch release" and flow chart for manufacturing and blending batch release were reviewed. After completion of production process Batch release check list was used. QA was responsible for filling Batch release check list and reviewing of PDS. After completion of checking PDS, Specimen Batch Release certificate was issued and signed by QA.

Electronic data
The SOP "Integration of chromatographic data" was checked. The SOP was applicable for HPLC and GC chromatograms. Manual integration (MI) was allowed only for the test for Related Substances and Residual Solvents. Before MI was performed the analyst should receive approval for MI of chromatogram. To receive approval analysts had to use a specific form. MI form had to be signed by the Section head and afterwards approved by the Laboratory QA head and Reviewer.

Audit trial functions were activated; date and time functions were locked.

2.6 MATERIALS MANAGEMENT

There was one warehouse used for storage of APIs, raw materials and primary packaging materials

Solvents were stored in solved yard.

Material code

The material code in the raw materials warehouse was allocated by the inventory management system. The SOP "Use of request item for requesting for RMCA code" was spot checked. The material code was made up of five digits and contained alpha-alpha or alpha-numeric combination. The system ensured the single use of one code. Logging new material into the system was the responsibility of QA.

2.7 PRODUCTION AND IN-PROCESS CONTROLS

Production operations

During inspection the following stages of one of product were manufactured:

- Reduction
- Preparation of Sulphuric acid solution
- Drying

During inspection condensation reaction step of one of API was carried out.

Other products under the scope of inspection were not manufactured during the inspection.

Dispensed staring materials were transported from the warehouse to the production unit in closed cages. Stainless steel and glass line reactors were used for production. The production process mainly was carried out in closed systems. Basically, products were transferred to the next production step by gravity. Filter bags, FBD bags and product transfer pipes were product dedicated.

Last steps of production were carried out in a "controlled area¨.

In-process sampling (IPC) and controls

In process checks, pH and TLC, were carried out in the in process control laboratory.

Blending batches of intermediates or APIs

The SOP "Blending of batches" was reviewed. Only batches meeting the specifications were blended. Blending was recorded on separate Blending PDS. The expiry/retest date of the blended batch was based on the manufacturing date of the oldest batch in the blend. Blended batch numbering register for 2013 was presented to the inspectors.

2.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

On random checks no issues were noticed.

Packaging materials
Primary packaging materials were stored in the raw materials warehouse in good order.

Label issuance and control
Labels applied to the containers were printed by shift manager, label samples were attached to the PDSs.

2.9 STORAGE AND DISTRIBUTION

Warehousing procedures
The warehouse and solvent yard were found to be in good order. On random checks, materials stored in the warehouse had safety data sheets and inventory cards.

Solvents used for the manufacture of APIs under the scope of inspection were stored in the solvent yard in stainless steel (SS) underground tanks. Pipelines were adequately identified. Solvents were transferred to the production units by identified pipelines.

Solvents were delivered in dedicated transport tankers. Tanker cleaning certificates were available. Samples of solvents were taken from transport tankers and released for filling into storage tanks after Quality Control (QC) release. After mixing fresh solvent with the remaining solvents in the storage tanks samples were taken, analyzed and released by QC. Solvents from tankers were transferred to the storage tanks using fixed SS “couplings” what were located under the roof.

APIs starting materials and finished APIs warehouse was inspected. Almost all starting materials were stored in locked metal high bay racks according to the specified storage temperature. Some starting materials were stored in “water reactive chemicals room”.

In the cold room (T 2-8 °C) T was recorded continuously by using 8 T probes. T printouts were taken twice per day.

Materials to be stored at T 15-25°C were stored in the air conditioned room.

The SOP “Temperature and relative humidity (RH) distribution study” was checked. According to the SOP T and RH distributing studies should be carried out every 3 years after seasonal validation.

Validation report “Temperature and relative humidity distribution study” was presented to the inspectors. T&RH were recorded using 9 Thermo Couples for 7 continuous days.

Materials were brought to the warehouse via material entrance and de-dusting area. Materials flow diagram and check list for the receipt of raw materials were presented to the inspectors. Sampling of raw materials was carried out in an ISO 8 class sampling room. The SOP “Sampling” was spot checked. 100% identity tests using NIR equipment were carried out for all key starting materials. Pool sample consisted of no more than 5 individual samples. Line clearance was done and recorded before sampling.

After sampling, materials were held in quarantine area until release by QC.

Dispensing of raw materials also was carried out in the warehouse. There were two different dispensing rooms. One dispensing room was used for dispensing of charcoal and catalysts and one for dispensing of other raw materials. Dispensing of raw materials was carried out in an ISO 8 class room. Line clearance was done and recorded before sampling.

Primary packaging materials were stored in separate high bay racks. New centrifuge and FBD filter bags were store in the same warehouse.

Separate storage was provided for finished APIs under appropriate storage conditions.

Receipt and quarantine
Materials were held under quarantine until they were sampled, tested and released for use. Separate room was provided for storage of rejected starting materials. In the chemicals warehouse, a segregated locked area was provided for solvents in drums.
Solvents delivered in tankers were kept “on hold” until the QC release.

Sampling and testing of incoming production materials
Containers from which samples were withdrawn were marked to indicate that a sample has been taken.

Materials management was found to be in good order.

Distribution procedures
APIs were released for sale after QA approval. The APIs prequalified by WHO were not sold to other parties but used to manufacture finished dosage forms within Cipla sites.

2.10 LABORATORY CONTROLS

Procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data were available. Laboratory records were maintained. Appropriate specifications were established for APIs and intermediates.

Specifications included testing of impurities - organic impurities and residual solvents. Reagents and standard test solutions were prepared and labelled following written procedures and current GMP guidelines. “Valid up to” dates were applied for analytical reagents and standard solutions.

HPLC columns were product dedicated and were stored properly in locked metal shelves. New columns performance was verified against the CoA.
HPLC columns, HPLC,s GCs and automatic titrators log books were maintained electronically.

Reference standards
Working Standards (WS) and Reference Standards (RS) were available and mainly stored in separate, locked refrigerators at T 2-8 °C. Hygroscopic standards and standards, for which storage conditions were specified as room temperature, were stored in desiccators. WS were qualified against chemical RS and dispensed under the LAF in amber glass vials for single use. Usage of standards was documented. WS were adequately labelled. Standards inventory was electronically maintained.

Traceability of standards was ensured. Raw data for the qualification of working standard of one of product was checked.

Standards storage fridges were connected to the software and in case of power failure, an alarm was triggered. T in the fridges was continuously monitored and recorded every 10 minutes. Printouts were taken every morning and checked.

Investigation of Out of specification results
The SOP "Out of Specifications and Out of Trend investigation procedure" and flow diagram were checked. This procedure was based on FDA guidelines. Separate OOS and OOT registers were maintained for each laboratory (Unit I and Unit II). OOS register for Unit II was checked. OOT register was presented to the inspectors.

Microbiological Testing
Media used was either bought "ready-made" or prepared in-house from dehydrated media. Media preparation sheets were available for the different media used . Storage conditions and time of use of prepared media was defined. In-house prepared media and bought "ready-made" media were tested for sterility and growth promotion according to the pharmacopoeia method using the organisms described and in-house organisms. The standard cultures used were received from corporate organisation in cryo-vials. Cultures were cultivated to maximal five passages.

Loading patterns for the sterilisation of media were defined. The autoclave for media preparation was qualified and the sterilising process validated. The report and data for the last autoclave re-validation was checked. Chemical (temperature) and bio indicator testing was performed in 16 locations throughout the autoclave.

Microbiological testing was done for the new drug products only and not on a routine basis. The performance of microbiological testing was described in SOP "Microbiological examination of non-sterile products". The harmonised method was used. The routine method used was the pour-plate method. Total aerobic microbial counts, total yeast microbial counts and tests for specific microorganisms were performed. Testing methods were validated including product influence on growth.

Waste from the microbiological laboratory was autoclaved in a dedicated, separate autoclave and discarded.

Testing of intermediates and APIs
Laboratory tests were performed for all intermediates in the QCL, except pH and TLC. In-process samples were taken and analyzed in production unit in-process control laboratory by the shift officer. Instrumentation and facilities were adequate to conduct the tests required for intermediates and finished APIs. Impurity profiles were established and tested.

Particle sizes were analysed by laser diffraction method.

Certificates of analysis
Certificates of analysis (CoA) were issued for each batch of API.

Stability monitoring of APIs
Stability testing schedule was available and shown to the inspectors.
The performance of stability studies was described in SOP. The company followed the requirement of USP and ICH guidelines. For new products as well as subsequent batches, the type of study (long-term or accelerated), the number of batches and the frequency for testing were defined. The procedure also covered reprocessed or reworked batches. Time limits for withdrawal of samples and testing were defined. Stability protocols and reports were checked. The pull out register and raw data were inspected for selected batches, time points and tests. No deficiencies from current guidelines were observed.

Ongoing stability studies were carried out for all APIs under the scope of inspection.
The following APIs ongoing stability samples were stored at T 30 ± 2° C and RH 65 ± 5%
Four stability walk-in chambers and four stability chambers were located in the laboratory of the Unit II. The access to the stability chambers was restricted. Stability chambers were connected to the software and in case of power failure, alarm was triggered. T and RH in the chambers were continuously monitored and recorded every 10 minutes. Printouts were taken every morning and checked.

API validation batches had been placed for accelerated and long term stability studies. Stability studies schedule for API was presented to the inspectors.

Expiry and retest dating
Supporting stability information was available for expiry/re-test dates assigned. 2 years re-test period or 5 years expiry dates we assigned for APIs after completion of stability studies.

Reserve/retention samples
Retain samples were stored under lock and key. Access to the storage room was controlled. One storage room was used for retain samples of raw materials (new room) the other for retain samples of APIs and finished drug products manufactured at Patalganga site. Samples for two full analytical analyses were kept for 10 years in case of APIs and one year after expiry for finished drug products. The retain samples store rooms were temperature monitored. T was recorded once per day.

VALIDATION

Validation Master Plan

The general policy on validation was described in the "Validation Master Plan". It covered manufacturing of APIs and formulations and contained responsibilities and general concepts for qualification of premises and equipment as well as validation of processes, cleaning, analytical methods and computerized systems. For computerized systems, a separate VMP was prepared, which was not inspected. Re-validation was considered for changes as well periodically.

Qualification

The performance verification report "HVAC system" for specific Air Handling Unit was checked. AHU performance verification (PV) tests were done by external party following Cipla SOPs. According to the SOP performance verification should be carried out every 2 years, on spot check PV schedule was followed.

Process validation programme

One of product process validation Protocol/report was checked. Validation was carried out for 3 consecutive batches for the process optimization. The new process analytical test results were compared with the tests results of the previously manufactured batches.

One of product manufactured at Unit I, A-2 (extension) process validation protocol/report for the first 3 consistently manufactured batches was available. Revision of the protocol/report by the company was in process during the inspection.

Cleaning validation

The master validation protocol and report for API worst case selection for cleaning validation" for API was checked. Worst case product for every cleaning procedure (different solvents) was determined and cleaning validation performed. Swab and rinse method were used for sampling. Analytical methods were validated. The results supported the conclusion of a validated cleaning process. According to internal procedure, cleaning verification will be carried out on one batch per two years.

Study protocol "Hold time of cleaned equipment" was spot checked.

Validation of analytical methods

The SOP "Validation and verification of analytical methods" was checked.
For the verification of Pharmacopeia methods the following parameters were verified:

- Specificity
- Repeatability
- Linearity and range
- Accuracy
- Solution stability.

For the analytical method validation the following parameters were validated:

- Specificity
- Repeatability

- Intermediate precision
- Linearity and range
- Accuracy
- Robustness
- Solution stability

The last analytical method validation was carried out on 8 August 2012 for one of API Related Substances by HPLC. Validation Protocol/report was spot checked. Validation was carried out according to the method of analysis.
The following tests were carried out:

- Specificity and SS
  - Limit of detection
  - Limit of Quantification
  - Linearity and range
  - Repeatability
  - Intermediate precision
  - Accuracy
  - Robustness
  - Solution stability

Analytical method transfer
The SOP "Transfer of analytical methods" was checked. Two types of method transfer (MT) were applicable:

- Comparative MT (comparison of the results from transferring laboratory and receiving laboratory
- Extended MT (in case if results obtained by comparative testing did not meet predefined acceptance criteria.

The last analytical method transfer was carried out on 11 September 2012 Comparative method transfer was done by two analysts. "The test of Related Substances protocol and method transfer report" was spot checked.

2.11 REJECTION AND RE-USE OF MATERIALS

Rejection
Intermediates and APIs failing to meet established specifications were rejected.

Reprocessing and reworking
The SOP "Reprocessing and Rework" was checked. The SOP specified responsibilities and the process for reprocessing and rework of APIs or intermediates. The R&D department was involved in developing suitable steps for reworking of batches. Quality Assurance was responsible for review of the proposed steps and approval of reprocessing and rework. Further QA was responsible for preparation and issuing the PDS to production. Decision on assessment of quality or requirement to carry out stability studies on the basis of scientific rationale was delegated to QA department. Reference to the procedures on stability studies and allocation of expiry dates were included in the procedure. For rework, concurrent validation of the process had to be carried out.

Recovery of materials and solvents
Solvents were recovered at the production facility. The procedure, responsibilities, and controls were described in SOP "Solvent recovery". The solvents were distilled in the same reactor and re-used providing that they met the specifications for the intended use. The recovered solvents were collected in a clean vessel, sampled and analysed. A new AR No was allocated. Recovered solvents were only used according a validated procedure after trials by the R&D department and only for the same product and same predefined step. Traceability was ensured. Recovered solvents were discarded when not meeting the specifications/after the end of the campaign without forecast for a new production or after one year.

Returns and rejects
A separate locked room was provided for storage of returned and rejected finished products.

Waste management
Disposal of different waste generated in production was described in SOP "Disposal of waste". It was applicable to all departments and listed the type of waste, the source of waste as well as the disposal company the waste was sent to. The disposal of used filters was described in SOP "Handling of air filters".

2.12 COMPLAINTS AND RECALLS

Handling of complaints was described in the SOP "Handling of product complaints". The procedure as well as the flow chart and one complaint received in 2013 were checked. The SOP covered quality, medical and transport complaints for drug substances and drug products for the local market as well as export markets. Complaints were handled through Corporate QA. They logged, categorized and forwarded the complaints to the responsible site for evaluation. The investigation had to be performed within 30 day. A report was sent to Corporate QA as a response after evaluation of the complaint. Corporate QA was responsible to give an answer to the customer.

Handling of returns was described in the SOP "Handling of returned materials". The scope of the procedure covered APIs as well as intermediates. Receiving, labelling, storage, investigation and reporting were described in detail. The close-out period was defined as 30 working days. No returns were received in 2013.

Recall procedure was described in the SOP "Recall procedure for API". The decision for a recall had to be taken by Corporate QA. The procedure also included the notification of the local FDA and the notification of the customers as well as the assessing of the impact on other batches. No products were recalled in the last years. Dummy recalls were performed at least once in five years to evaluate effectiveness of recall. The last dummy recall was carried out in May 2013.

2.13 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Production activities were not contracted out.

Specific analyses were contracted out to other laboratories. Responsibilities were laid down in contracts. Contract laboratories were audited on a regular basis.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection listed in the Inspection Report, Cipla Ltd, Patalganga **Unit No II**, located at A-42 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, was considered to be compliant with WHO GMPs for Active Pharmaceutical Ingredients published by WHO for the scope of activities listed below:

Manufacture and packaging of Active Pharmaceutical Ingredients

- Lamivudine (APIMF001
- Artesunate (APIMF004)
- Artemether (APIMF043)
- Lumefantrine (APIMF075)
- Moxifloxacin (APIMF091)

All the non-compliances observed during the inspection that were listed in the full report 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.