

**Prequalification Team  
WHO PUBLIC INSPECTION REPORT  
(WHOPIR)  
Active Pharmaceutical Ingredient (API) Manufacturer**

**PART 1: GENERAL INFORMATION**

|                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| Name of Manufacturer                                           | Cipla Ltd.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Units                                                          | Unit I, II & III                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Physical address                                               | Cipla Plot D 7 (Unit I), plot D 22 (Unit III), Plot D 27 (Unit II) MIDC Industrial Area, Kurkumbh Village, Taluka-Daund, Pune District, Maharashtra, 413 802, India                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Postal address                                                 | As above                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Date of inspection                                             | 7 – 12 and 14 – 15 March 2016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Type of inspection                                             | Routine GMP inspection                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Active Pharmaceutical Ingredient(s) included in the inspection | <p><b>Prequalified APIs</b></p> <ul style="list-style-type: none"> <li>• APIMF001 Lamivudine anhydrous</li> <li>• APIMF025 Tenofovir Disoproxil fumarate</li> <li>• APIMF251 Darunavir Ethanolate</li> <li>• APIMF253 Efavirenz</li> <li>• APIMF073 Oseltamivir monophosphate</li> <li>• APIMF075 Lumefantrine</li> <li>• APIMF189 Atazanavir</li> <li>• APIMF251 Darunavir Ethanolate</li> <li>• APIMF003 Stavudine</li> <li>• APIMF007 Nevirapine anhydrous</li> <li>• APIMF154 Nevirapine hemihydrate</li> <li>• APIMF199 Abacavir hemihydrate</li> <li>• APIMF061 Emtricitabine</li> <li>• APIMF295 Sofosbuvir</li> <li>• Fluconazole CEP 2007</li> </ul> <p><b>API under assessment</b></p> <ul style="list-style-type: none"> <li>• Dolutegravir Sodium</li> </ul> |
| Production Lines                                               | Chemical Synthesis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Summary of the activities performed by the manufacturer        | <p>Production and quality control of intermediates and finished non-sterile APIs.<br/>No toxic or hazardous substances were handled or manufactured</p> <p>Hormone APIs were manufactured at Unit III, Block Bulk drug II (dedicated)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

### ***General information about the company and site***

Cipla Ltd was a public limited company established in 1935. It manufactures and markets wide range of pharmaceutical formulations and active pharmaceutical ingredients (APIs). The corporate headquarter (including corporate QA and R&D) was located in Mumbai. Cipla has manufacturing facilities and research centres in the following locations:

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

The manufacturing facilities at Cipla Kurkumbh were started in 1994, and it was being continuously upgraded as per their needs. The site was located in an industrial park, approximately 70 km 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 total number of employees engaged on the site (Unit I, II and III) for Production, Engineering, QC/QA, Stores and Distribution were about 1814 employees. 324 employees were involved in QC activities, 152 in QA activities and 1021 in production activities.

### ***History of WHO and/or regulatory agency inspections***

The site was last inspected by WHO in August 2014. The site has also been inspected by the following regulatory authorities:

|                               |                                                                             |
|-------------------------------|-----------------------------------------------------------------------------|
| August 2014                   | WHO (Geneva)                                                                |
| May 2012                      | Korean FDA                                                                  |
| May 2015 (desktop inspection) | TGA (Australia)                                                             |
| May 2014                      | FDA (USA)                                                                   |
| February 2015                 | COFEPRIS - Federal commission for the protection from sanitary risks Mexico |

### ***Focus of the inspection***

The inspection focused on the production and quality control operations related to the APIs: APIMF001 Lamivudine anhydrous, APIMF025 Tenofovir disoproxil fumarate, APIMF251 Darunavir Ethanolate, APIMF253 Efavirenz, APIMF073 Oseltamivir monophosphate, APIMF075 Lumefantrine, APIMF189 Atazanavir, APIMF251 Darunavir Ethanolate, APIMF003 Stavudine, APIMF007 Nevirapine anhydrous, APIMF154 Nevirapine hemihydrate, APIMF199 Abacavir hemisulfate, APIMF061 Emtricitabine, APIMF295 Sofosbuvir, Fluconazole CEP 2007, under assessment Dolutegravir Sodium.

**Inspected Areas**

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials
- Complaints and recalls
- Contract manufacturers (including laboratories)

**PART 3: INSPECTION OUTCOME****3.1 QUALITY MANAGEMENT (QM)**Principles

The quality management system was established and maintained according to the Cipla Corporate policy. It was reflected in amongst the organizational structure/reporting line, documentation system, the IT systems used corporate level (SAP, LIMS), common database of materials, supplier evaluation, handling of complaints, R&D support, etc.

Management review (MR)

The SOP “Quality Management Review was discussed. MR team was led by the Head site quality. MR team consisted of the members of every department. QMR was conducted monthly at unit level.

Internal audits (self-inspection)

The SOP “Self inspection” and schedule for 2016 were discussed.

Self-inspections were classified as:

- Scheduled
- On demand
- As-hoc inspections (unplanned)

Non-conformances were classified as:

- Critical
- Major
- Minor

The documents prepared for every self-inspection included filled in checklist, a report, a compliance report of the area concerned including the assessment of the inspectors and QA. For tracking, corrective actions were logged into the CAPA system.

### Items for self-inspection

According to the SOP self –inspections should cover the following areas:

- Personnel department
- Storage of raw materials, packaging materials and finished goods
- Production and in-process control
- Labelling control
- QC
- QA
- Documentation
- Details of personnel of various departments
- Validation and revalidation program
- Calibration of instruments/measurement systems
- Complaints management
- Recall procedure
- Maintenance of buildings and equipment
- Water purification system
- Documents related to regulatory affairs
- Control on contract analysis
- Engineering
- Discharging of residues
- Corporate quality functions
- Drug safety

### Self-inspection team

The SOP specified composition of the inspection team and contained detailed instructions for the qualification evaluation, certification and re-evaluation of existing inspectors as well as the preparation, performance and follow up of self-inspections.

### Frequency of self-inspection

Separate schedules were prepared for self-inspections of different departments. According to the schedule, all the areas were inspected every six months.

### Self-inspection report

Lead inspector was responsible for drafting the self-inspection report. Report was signed by all inspectors.

### Follow-up action

Compliance of critical non-compliances should be submitted within 2 working days and major/minor non-compliances within 15 working days after receipt of the report. CAPAs were submitted by the user department and evaluated by the QA.

### Product Quality Review (PQR)

The SOP “Annual product quality review” was discussed. The SOP was applicable to all drug products, APIs and Intermediates. PQR was carried out as per yearly (month wise) schedule. Process capability was calculated using CpK index.

Specific PQRs for year 2015 were discussed.

### Quality Risk Management (QRM)

SOP “Risk Management by Failure Mode Effects and Critical Analysis” and flow diagram were discussed. 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 / review processes throughout the life cycle of drug substance, drug products, including equipment, facilities, system, raw materials, solvents, packaging, labelling and manufacturing operations which were likely to affect the product or process and any other activity which was directly or indirectly affecting product quality. Rating from 1-5 was used to define risk priority numbers (RPN).

According to the SOP risk assessments should be reviewed every three months in case if RPN categories are critical and major and every three years if RPN categories are moderate and minor. RAs review was carried out according to the yearly schedule.

## **3.2 PERSONNEL**

### Personnel qualifications

There were an adequate number of personnel qualified to perform and supervise the manufacture of intermediates and APIs. The responsibilities of personnel engaged in the manufacture of intermediates and APIs were specified in writing.

### 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 flow chart was following:

- Induction training
- Department induction training
- On-the-job training
- Working under supervision
- Training evaluation/personnel validation
- Training certificate
- Scheduled trainings/training on changes/miscellaneous trainings
- External training

Training effectiveness was evaluated by multiple choice questionnaire and open questions. According to the SOP re-training should be considered under the following circumstances:

- If deficiencies were noticed in working during self-inspection, audits or performance review, OOT, OOS an incidents with analytical error, deviations, complaints etc.,
- If any participant failed to meet acceptance criteria for training evaluation.

Training records were maintained by respective departments. Department wise training schedule for 2016 was presented to the inspectors.

Analyst competency was assessed by a personal validation protocol. Analysis was carried out in parallel by trainee and trainer.

There were several types of analyst validation protocols:

- Weighing and pipetting

- Dissolution/IR/UV
- HPLC assay and related substances
- etc.

Analyst training certificates were issued for each test.

#### Consultants

The SOP “Service of consultants” was discussed. Consultants CVs were evaluated by the corporate senior management/site management. Criteria for selecting consultants were specified in the SOP. List of consultants were shown to the inspectors.

#### Personnel hygiene

The SOP “Health and hygiene requirements” was checked. The SOP was applicable for formulation units and API units at Kurkumbh (Unit I, II and III).

According to the SOP all personnel should undergo medical examination prior to recruitment, health of the personnel, which may affect product quality was monitored on an ongoing basis. Any employee returning after long absence (more than 3 days) due to the sickness was required to present a medical fitness certificate. Personnel suffering from illness such as skin rashes, colds, and open lesions to the body were required to report the department head and were excluded from working in the clean and critical areas. Smoking, eating, drinking, chewing and the storage of food and personal medicines and smoking was prohibited in the manufacturing areas. Regular medical examination was carried out once per year.

Changing and washing followed a written procedure. The protective clothing washing operations followed standard operating procedures.

### **3.3 BUILDINGS AND FACILITIES**

#### Design and construction

The design and construction of the buildings and facilities did not change since the last WHO inspections.

The numbering/identification of the facilities were described in SOP, production facilities (cubicles) were cleaned following a general SOP.

The return air ducts were cleaned at product changeover. Prevention of cross contamination was explained in the SOP.

#### Purified Water System

The purified water was used for wet chemistry/synthesis process steps only. In the final processing areas potable water was used for cleaning purposes.

The water system did not change since the last inspection and was regularly monitored.

## HVAC

### **HVAC systems**

There were two types of air supply systems in place in the final steps of production:

- “Single pass” systems with SB (supply blower) and EB (exhaust blower) in the centrifuge-crystallization rooms, operating with 100% fresh air.
- Air handling units in the powder processing areas with circulation and at least 10 % fresh air.

The system was initially qualified / approved on 18/07/08 then re-qualified last time on 29/02/16.

The pressure cascade was based on an air bubble method meaning the pressure in the processing cubicles at least 6 Pa less than the corridor.

There were layouts available indicating the air supply systems.

The pressure difference of pre-filters and HEPA filters of the AHUs were monitored by pressure gauges located at the service areas. The return air filters were washed fortnightly.

## **3.4 PROCESS EQUIPMENT**

### Design and construction

The design and construction of the process equipment was in-line with the corresponding manufacturing processes.

### Equipment qualification, maintenance and cleaning

Balances were verified daily, full scale calibration was carried out monthly. Daily verification of balances was carried out using minimum, middle and maximum weights. The following items were checked during monthly calibration:

- Spirit level
- Repeatability
- Uncertainty
- Eccentricity

This procedure was applied for all balances checks on site.

The identification of the production equipment was based on SOP BDQA-08 v.05, 05/05/14.

The maintenance policy was defined. The maintenance activities were summarized in annual schedule. The maintenance protocol and maintenance records (quarterly/annual) of the fluid bed dryer (FBD) were discussed.

Following the installation and qualification the process equipment were approved for usage by means of “Handover certificate”.

The policy on the calibration of measuring devices (including temperature indicators and controllers, pressure gauges, magnehelic gauges, etc.) was common for the API and FP

departments. The calibration protocol and records of temperature sensors (XXX) and displays (YYY) connected to the FBD ZZ were discussed.

The equipment cleaning procedure depended on the solubility of the material/API. There were 5 different type of cleaning agents used together with the corresponding procedures.

The cleaning validation (policy defined in the VMP) was based on the risk based approach, taking the solubility of the API into consideration.

Every unit had their Master sampling plan and record for cleaning validation.

#### Computerized systems

The site activities were supported by validated IT systems:

- CipDox (document management and change control)
- Pilgrim (deviation management)
- SAP (material management, GRN, inspection lot number)
- LIMS, recently installed and still under installation in some areas
- QCMS (Quality Control Management Software) for controlling reference materials (stock, usage).
- Chromeleon software for control of chromatographs, data acquisition, processing and record (together with back up and archive).

### **3.5 DOCUMENTATION AND RECORDS**

#### Documentation system and specifications

There were corporate, site and unit level SOPs in place. The corporate SOPs were available in the CipDox software. The appointed QA person of the site has “read only” access to the system.

#### Batch production records and packaging records (BMR/BPR)

The approved master production instructions/batch manufacturing records were available for the productions. The following batch manufacturing records were discussed.

Batch manufacturing records of Efavirenz were discussed.

The SOP defined the procedure of generation, issuance and recording of the batch numbers. The batch numbers were generated “automatically” by the SAP system, issued unit-wise, indicating the nature of the production. The issuance of the batch number and batch manufacturing records was recorded in logbooks.

The BMRs were printed out from the SAP indicating the date of printing. Issuance of the additional pages (the similar way) was controlled and based on “reprint request”.

#### Laboratory control records

The system of laboratory control records was hybrid. It was basically paper based, but the test raw data of the instrumental analyses was also available electronically and the forms serving

of recording the tests were pre-defined electronic documents and printed out from the computer.

#### Out of specification (OOS) and out of trends (OOT)

The SOP “Out-of-specification and out-of-trend investigation procedure” flow diagram and laboratory investigation report were discussed. The SOP was applicable to all chemical/instrumental tests carried out in QC laboratory. The SOP was based on MHRA guideline “Out of specification investigations”. OOS/OOTs/laboratory incidents were trended quarterly. Trends for 2015 were discussed. Trends were presented as bars and pies.

Following to the generation of the identification code in the LIMS system, the investigation was recorded paper based.

The analytical methods were validated according to the corporate policy.

The validation protocols and reports of the XXX assay test (HPLC) were discussed.

The SOP “Analytical incidences investigation and resolution procedure”, flow chart and analytical incidence investigation report were discussed. This procedure was applicable to all analytical incidences that may occur during Analysis, calibration or identified during document review. Definition of the analytical incidences was given as: “Non-conformance observed (other than OOS/OOT) during the performance of a test procedure or identified during review such as instrument malfunctioning, analyst error, procedural error, variation of results among replicate determination, abnormal response or pattern of standard or sample, system suitability failure of any kind of other error. Trending of laboratory incidents was carried out once in four months.

Separate SOP “Investigation of aberrations in microbiological test results” and OOS registers were presented to the inspectors.

The SOP “Batch failure investigation” and flow diagram were discussed. The SOP was applicable to batch not confirming to predetermine quality control specifications. OOS/OOT batch BMR and supporting documents were reviewed as per check list. According to the SOP impact on other batches/products/items should be assessed by QA.

### **3.6 MATERIALS MANAGEMENT**

#### General controls

The SOP “Procedure for material identification and coding” was discussed. The SOP was applicable to all raw materials, intermediates semi-finished goods – API, packing material – labels, packaging materials – others. The SOP specified steps how to generate material codes in the SAP system. API codes were manufacturer specific and the same for all Cipla units.

#### Qualification of the suppliers

The SOP “Evaluation and approval of manufacturer” and flow charts were discussed. The SOP was applicable to the manufacturers of API, packaging materials and excipients used in manufacturing of finished products. The SOP described the quality system requirements to select, evaluate and approve manufacturer of all materials used in the manufacture of medicinal/drug products.

Two stage approaches was used for approval of manufacturer:

- Stage I – primary evaluation of manufacturer
- Stage II – approval of manufacturer

According to the SOP material should be procured for registration/feasibility batches only after satisfactory primary evaluation, whereas manufacture should be approved, prior to commercial use of product.

Two evaluation criteria's were applied:

- Site audit based – applicable to all manufacturers of API, sterile excipients, sterile packaging materials, primary packaging materials and printed packaging materials.
- Paper based.

Vendor quality management was carried out by Corporate QA.

According to the SOP auditors should be qualified for the job and should have appropriate experience and lead auditor should be preferably from QA or CQA.

The SOP “Vendor audit management” was discussed. Audits were carried out according to the yearly audit calendar. API starting material/intermediate/primary packaging materials vendors’ audits was carried out every 36 months. Frequency for existing certified vendors (manufacturer/supplier) was based on the risk rating of individual vendors.

The qualification records of the supplier of XXX were discussed. The date of the initial qualification was 13/03/07. The forthcoming re-qualifications were on 2009/2011/2015. The last qualification (based on a site audit held on 05/06/14) was approved on 19/03/15.

#### Receipt and quarantine

Every manufacturing unit had its warehouses handling raw materials, packaging materials and APIs.

The material management was supported by SAP system.

Following to the physical check of the incoming materials (recorded on a check list) the information on the shipment was entered to the SAP system, where an internal ID (SAP batch number) and a GR note was generated “automatically.

The status of the material was indicated on the label and also available in the SAP system. The dispensing of the released materials was performed by the warehouse personnel under the control of the production.

#### Sampling and testing of incoming production materials

The SOP “Sampling” was discussed. The SOP was applicable to all API, API starting materials, raw materials, excipients, ancillary materials, packaging materials, bulk finished and packed finished products sampling. Sampling of primary packaging materials was carried out according to the ISO 2859-1 standard, general inspection level was specified level – II (critical – 0.65, major – 1.0 and minor – 2.5). Classification of defects was given in individual packaging materials specifications. Samples for identity tests for key starting materials were collected from all containers and analyzed individually.

### 3.7 PRODUCTION AND IN-PROCESS CONTROLS

#### Production operations

The production operations were performed according to approved batch manufacturing records including IPC controls.

#### In-process sampling and controls

There were in-process laboratories located in the production (wet chemistry/synthesis) areas capable to perform tests like pH and Thin Layer Chromatography (TLC). The intermediates were sampled and tested by the QC laboratories.

#### Blending batches of intermediates or APIs

The requirements against blending were defined in SOP. Only released batches can be blended and the blending process has to be validated. The manufacturing date of the oldest blended batch serves as the manufacturing date of the blend.

#### Contamination control

There were air supply systems, gowning procedures, material and personal flow provisions in place for contamination control.

#### Deviations

The SOP “Quality Management System deviation” and flow chart were discussed. The SOP was applicable for deviations observed during any stage of receipt, handling, storage, dispensing, processing, testing, manufacturing, packaging operations, transportation, systems, software operations, facility, validations qualifications, calibrations, maintenance and documentation involved in drug product, drug substance and its intermediate. Deviations were specified as planned and unplanned and classified as:

- Major
- Minor
- Repetitive deviations:
  - o Major
  - o Minor

The deviation procedure was reviewed and found comprehensive detailing functional roles, operational roles and responsibilities of personal required investigating deviations. The procedure defined deviations as unplanned in that were unexpected events that resulted in a departure from the approved procedure, document or established standard. It was discovered after the occurrence. Major deviations were described as any departure from any established standard which may have an impact upon the identity, quality, purity, stability, safety, physical characteristics and efficacy of the product or process.

Deviations were captured by the “Smart solve”. The software had been purchased and supplied by “Pilgrim” customised for Cipla. “Smart solve” had been implemented since January 2013.

Deviations related to production/packaging were recorded in the related BMRs/BPRs.

Deviations were trended on monthly basis (considering 6 months back). Trends were presented as tabulated, bars and pies by departments, areas of deviations, total deviation

count by month, deviation count by category (planned/unplanned) deviation count by type (major/minor) and deviation count by count by status (open/closed/in work).

The handling of deviations was supported by the Pilgrim software (SOP 1035-G-0008 v.02, 30/09/15).

The investigation records of the specific deviations were discussed.

#### Corrective Actions and Preventive Actions (CAPA)

The “Quality Management System CAPA” and flow chart were discussed. The SOP was applicable to all non-conformances, OOS, Out of Trends (OOT), OOAC (out of action limit), OOAL (out of alert limit), deviations, audit findings, analytical incidents in laboratory, complaints, recalls, batch failures, APQR, items from quality management review, risk management, rejection, Quality Council meeting, and other sources of quality data. Operation roles, 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.

#### Root cause Analysis (RCA)

The SOP “Root cause Analysis” was discussed. The SOP was applicable for investigation the root cause of product complaints, OOS, OOT, deviations and other non-conformance which are likely to affect the product or process. The root cause investigation team was specified and tools to be used were specified. Tools to be used were:

- 5 why analysis,
- Fish bone diagram (6 M approach – man, material, millieu/mother nature, measurement, machine and method).

### **3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES**

#### General

The packaging, identification and labelling procedures of APIs and intermediates did not change since the last inspection.

### **3.9 STORAGE AND DISTRIBUTION**

#### Warehousing procedures

The storage and distribution procedures and facilities did not change since the last inspection.

### **3.10 LABORATORY CONTROLS**

#### General controls

The quality control testing of the API’s raw materials and intermediates (including stability testing) were performed in QC laboratories independent from the production.

Access to the IT systems was controlled having the user groups, user privileges identified and setup.

The reference materials used in the API laboratory were stored in cold chamber (2-8 °C) or in desiccators at room temperature (below 25 °C).

Up to the end of 2015 the stability samples (with location and other data) were controlled in logbooks (Sample Location Chart). Since the implementation, the data are available in the LIMS.

The retention samples were stored under controlled conditions (below 25 °C).

#### Testing of intermediates and APIs

The quality specification, test methods and test records of the Atazanavir sulphate were discussed.

#### Qualification of analytical equipment

The qualification policy of the analytical equipment was described in SOP. Accordingly, the qualification was applicable for the new equipment and the re-qualification was due in case of major change in the system and calibration with pre-defined frequency.

The High Performance Liquid Chromatograph (HPLC) was qualified accordingly and regularly calibrated. Last calibration on 21/10/15 was discussed.

#### Analytical method validation

The SOP “Validation and verification of analytical methods” was discussed. The SOP was applicable for validation of quantitative and semi-quantitative analytical test procedures for APIs, raw materials, API starting materials and intermediates, excipients and drug products (formulations) analyzed.

According to the SOP validation was applicable to:

- Non-pharmacopoeial (non-compendial) chemical test methods
- Modified pharmacopoeial methods

verification was applicable to:

- Pharmacopoeial (non-compendial) chemical test methods
- Validated pharmacopoeial (non-compendial) chemical test methods in case of outsourced drug substances or drug products
- Method modified with change in method parameters within permitted range to meet system suitability requirements
- Change in analytical instruments with different mechanism having impact on method.

Validation and verifications in general was applicable to most common types of analytical procedures:

- Identification tests
- Limit test for the control of impurities
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product.

The following parameters were used in method validation/verification:

- Specificity and selectivity

- Precision
- Repeatability
- Intermediate precision
- Reproducibility
- Linearity
- Range
- Accuracy
- Solution stability
- Robustness
- Limit of detection
- Limit of quantification
- Lower limit of quantification

The SOP was very comprehensive document and specified validation/verification scenarios for different test methods and techniques – experimental design and acceptance criteria. The validation protocol XXX “Microbiological examination of non-sterile products/microbial contamination in non-sterile products (plate count method)” was discussed. The validation protocol was applicable to all finished products/raw materials that are required to be analyzed as per the harmonized method.

#### Certificate of Analysis (CoA)

The SOP “Preparation of certificate of Analysis” was discussed. This SOP was applicable for API, excipients, intermediates, formulations, packaging materials and raw materials.

CoA’s were generated by T.O.T.AL QC software. The software was developed by Cipla corporate and also validated by Cipla corporate. Analytical results were entered to the software by analysts. Master certificates were available in the software for all products.

#### Batch release

The QA head and the section heads (Quality Operations and Quality Compliance) were authorized to release intermediates and APIs.

The batch release was documented in a check list then recorded in the SAP system. The batch release records of batch XXX were discussed.

The raw materials were released by the laboratory QA reporting to the QA Head.

The release was recorded in the LIMS, SAP and documented in hard copies of Goods Received Note and the CoA. The release documents of the raw material XXX were discussed.

The SOP “Functions and responsibilities of laboratory quality assurance” was discussed. According to the SOP verification and reconciliation of electronic data and random audit trail review to be done and crosscheck. The check list for verification of QC report was attached to the SOP.

The SOP “Receipt, registration and testing of samples” was discussed. The SOP was applicable for all samples analysed (raw materials, APIs, packaging materials, finished products, intermediate products, stability samples etc.) in quality control laboratory (QCL). The check list for review of analytical report was attached to the SOP and specified that: all the corresponding raw data related to the tests are reviewed and attached to the report.

The SOP “User management policy software: Chromeleon” and privileges distribution chart were discussed.

The SOP “User management and password policy for SAP landscape and master workflow tool were discussed. SOP was applicable for all users of the SAP landscape.

The SOP “Good chromatography practices” was discussed. Manual integration policy was defined in the SOP “Integration of chromatographic data”. According to the SOP manual integration was prohibited. In case of constraints in integration, deviation shall be filled, analytical development laboratory and Corporate QA shall be approached for further guidance.

#### Stability monitoring of APIs

The SOP “Stability studies” was discussed.

The following conditions were applied for accelerated studies:

- T 40 °C ± 2 °C, RH 75% ± 5% (APIs and formulations)
- T 25 °C ± 2 °C, RH 60% ± 5% (APIs)

long term

- T 25 °C ± 2 °C, RH 60% ± 5% (APIs and formulations)
- T 30 °C ± 2 °C, RH 65% ± 5% (APIs)
- T 5 °C ± 3 °C (APIs)

One batch per year was placed on long term stability monitoring programme. Samples were packed in market simulated conditions.

#### Hold time studies

There was a general protocol in place for the hold time study of the wet materials.

The hold time study of the Dolutegravir sodium and Sofosbuvir together with the Schedule for year 2015 were discussed.

#### Reserve/retention samples

The SOP “Reserve samples” was discussed. The SOP was applicable to raw materials, APIs, excipients, intermediates, printed primary packaging materials and drug products (formulations) in the final packs.

#### Reference standards (RS) and working standards (WS)

The SOP “Laboratory reference standards” was discussed. The SOP was applicable to all standards used in the laboratory (pharmacopoeial standards, test standards, working standards, analytical standards, chemical standards and volumetrically standards). Purchase of the pharmacopoeial referenced standards was carried out by corporate office and distributed to the respective units. Working standards lists were maintained by the corporate working standard cell (CWSC), CWSC was also responsible to allocate production Unit

which was responsible for standardisation of the WS, dispensing and distribution of the WS to another units. WS were qualified against the official RS. WS were dispensed in the single use vials under the LAF cabinet located in the QC laboratory. WSs were used for assay, identification and impurities tests.

WS protocol XXX Lamivudine USP was discussed.

Working Standards (WS) and Reference Standards (RS) were available and mainly stored walk in chamber at 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. Standards inventory was electronically maintained. Traceability of standards was ensured.

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

Expiry dates for solid and liquid reagents were specified based on historical data. For solid reagents expiry date was specified 3 years from date of receipt and 2 years after date of opening. For liquid reagents expiry date was specified 2 years from date of receipt and 1 year after date of opening. Hygroscopic reagents expiry date was specified 6 months after date of opening.

For the reagent solutions prepared in laboratory 3 months expiry date was assigned and for volumetric solutions 1 month. Volumetric solutions were standardized before used.

The SOP “Backup and restoration of electronic data in server” was discussed. Backup of data was carried out according to the schedule on netback server. Servers for LIMS and SAP were located at corporate office in Mumbai; servers for other laboratory software’s were located on site. Tapes were used for backups. Till the date of inspection no data was destroyed.

#### Microbiological laboratory (MBL)

The SOP “Water Analysis” was discussed. The SOP was applicable to potable water, purified water (PW). Pour plate method was used for total aerobic microbial count (TMAC) determination - potable water and Membrane filtration for TMAC – PW and WFI. Tests for in house pathogens were carried out for potable and PW. Tests results were trended yearly.

The SOP “Microbiological monitoring of environment in production area” was discussed. The SOP was applicable to environment in production areas. For API manufacturing blocks “clean area” settle plate method was used. Settle plates were exposed for 30 minutes. Tests results were trended yearly.

Alert and action limits were specified.

Action and alert limits for PW and EM were based on historical data, which was reviewed once in two years.

### **3.11 VALIDATION**

#### Validation policy

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). VMP was revised annually or when major changes happened. VMP was approved by Corporate QA. The document was applicable to: finished dosage forms and API and all manufacturing process, supporting systems like facility, utilities, equipment, computerized systems, cleaning process, analytical methods, and microbiological testing methods. VMP specified re-validation and re-qualification criterion as:

- Periodic verification
- Re-validation after changes

Validation schedule for 2016 was presented to the inspectors. Periodic re-validation of API's was carried out: at least one batch in five years.

#### Qualification

Qualification policy was specified in the VMP.

#### Approaches to process validation

The Validation Master Plan summarised the validation policy of the company at Corporate level including API and FP manufacturing units. Specific validation records were discussed.

### **3.12 CHANGE CONTROL (CC)**

#### Change control (CC)

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

The procedure was comprehensive in describing the responsibilities of the personnel involved in the evaluation of the change and comprehensive in the definitions of different changes that could occur.

Changes were classified as:

- Major – may have direct impact on the identity, quality, purity, potency, strength, stability, and safety, efficacy of physical characteristics of the product or drug substance.
- Moderate
- Minor

CR logs were presented to the inspectors.

CRs types were related to:

- Documents
- Product
- Facility
- System
- Equipment

- Instrument
- Other

CipDox system was used for recording of CRs. The system was implemented in March 2015. The software was operated by the corporate according to the SOP.

### **3.13 REJECTION AND RE-USE OF MATERIALS**

#### Reprocessing and reworking

Based on the SOP reprocess and reworking were allowed if the material (API or intermediate) failed to meet the requirement. The batches manufactured by reprocessing and reworking needs to be validated and their stability to be proved.

#### Recovery of materials and solvents

The recovered/regenerated solvents had the unique item codes, specifications and their usage was indicated in the batch manufacturing records. Only solvents from the same product and same process step can be reused.

There were two cases of regeneration in place: in-situ and by a contract partner. A solvent recovery plant in Unit III was under installation.

#### Rejected materials

The rejection of the raw materials and packaging materials was the responsibility of the QA head.

The investigation serving as a base for rejection was described in a corporate SOP.

### **3.14 COMPLAINTS AND RECALLS**

The SOP “Handling of product complaints” and flow chart were discussed. The SOP was applicable to for complaints received from customers (local and export) medical professionals, regulatory authorities and to ensure that appropriate corrective and preventive actions were taken. Complaints were handled through Corporate QA. They logged, categorized and forwarded the complaints to the responsible site for evaluation. Both corporate QA and Unit QA should log each incoming complaint within 1 working day upon receipt. After receipt and logging of complaint at the respective unit, an investigation team comprising of representatives from production and QA departments should review the complaint. Complaints were classified as:

- Critical
- Non-critical
- Confirmed
- Non-confirmed

A specific complaint XXX was discussed.

The SOP “Recall procedure” was discussed. The procedure was applicable to all drug products manufactured by the company for local (sale and physicians sample) and overseas/export markets. Corporate QA was responsible for evaluation of need of the recall, inform regulatory authorities (class I and class II recalls) and qualified persons (QP)/QA of

concerned marketing authorisation holders. The procedure also included the notification of the local authorities and the notification of the customers as well as the assessing of the impact on other batches.

Recalls were classified as:

Classified as:

- Class I - recall should be executed immediately
- Class II - recall should be executed within 48 hours
- Class III - recall should be executed within 5 working days

In case of export market the recall should be executed as per the respective regulatory authority requirements. Recall execution time for export markets was specified in respective technical agreements between Cipla and customers.

All changes brought in the recall process, procedure, documentation, communication and organizational structure should be addresses through a CC procedure.

Recall validation was carried out by dummy recalls. If the actual recall has not been carried out within 2 years, dummy recall should be carried out for local and export market. Dummy recalls were carried by out by CQA for one representative manufacturing site, covering all sites one by one. Site where actual product recall had not been carried out was selected for mock recall.

### **3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)**

Production activities were not contracted out.

The following activities were contracted out:

- Specific quality control laboratory tests. Responsibilities were laid down in contracts. Contract laboratories were audited on a regular basis.
- Pest and rodent control
- Measuring equipment calibration
- Laboratory equipment maintenance
- Factory garments laundry

The SOP “Audit of contract laboratory” was discussed. Contract laboratories audits were coordinated by the CQA. According to the SOP each contract laboratory should be audit every 2 years.

Contract of analysis between Cipla and XXX was discussed. Both parties’ responsibilities were laid down in the contracts.

#### **PART 4: CONCLUSION**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned:

- APIMF001 Lamivudine anhydrous
- APIMF025 Tenofovir Disoproxil fumarate
- APIMF251 Darunavir Ethanolate
- APIMF253 Efavirenz
- APIMF073 Oseltamivir monophosphate
- APIMF075 Lumefantrine
- APIMF189 Atazanavir
- APIMF251 Darunavir Ethanolate
- APIMF003 Stavudine
- APIMF007 Nevirapine anhydrous
- APIMF154 Nevirapine hemihydrate
- APIMF199 Abacavir hemisulfate
- APIMF061 Emtricitabine
- APIMF295 Sofosbuvir
- Fluconazole CEP 2007
- Dolutegravir Sodium

manufactured at Cipla Ltd., Unit I, Unit II and Unit III located at Plot D 7, Plot D 27 and Plot 22 MIDC Industrial Area, Kurkumbh Village, Taluka-Daund, Pune District, Maharashtra, 413 802, was 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.