



**Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Cipla Ltd.
Unit	Unit I
Physical address	Plot D 7 MIDC Industrial Area, Kurkumbh Village, Taluka-Daund, Pune District, Maharashtra, 413 802, India
Postal addresses	As above
Date of inspection	7 – 12 and 14 – 15 March 2016
Type of inspection	Routine inspection
Dosage form(s) included in the inspection	• Tablets film coated • Capsules hard • Soft gel capsules • Oral paste
WHO product numbers covered by the inspection	• HA056 Ciprofloxacin (hydrochloride) Tablet, Film-coated 100mg • HA057 Ciprofloxacin (hydrochloride) Tablet, Film-coated 250mg • HA058 Ciprofloxacin (hydrochloride) Tablet, Film-coated 500mg • HA059 Ciprofloxacin (hydrochloride) Tablet, Film-coated 750mg • HA207 Fluconazole Capsules, hard 50mg • HA208 Fluconazole Capsules, hard 150mg • HA209 Fluconazole Capsules, hard 200mg • HA489 Lamivudine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 300mg/300mg • MA064 Artemether/Lumefantrine Tablet 20mg/120mg
Summary of the activities performed by the manufacturer	Manufacturing, packaging, quality control, stability testing, storage and distribution of: • Tablets film coated • Capsules hard • Soft gel capsules • Oral paste



Part 2: Summary

General information about the company and site

Cipla Ltd is 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 Quality Assurance and Research & Development) is located in Mumbai. Cipla has manufacturing facilities and research centres in the following locations:

- Bangalore: FPPs, APIs, natural products and Research Centre
- Patalganga: FPPs, APIs and Research Centre
- Kurkumbh: FPPs, APIs
- 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 is being continuously upgraded as per their needs. The site is located in an industrial park, approximately 70 km from Pune city. The site inspected was Cipla Ltd, Kurkumbh, Unit I (D-7), MIDC, Kurkumbh, 413 802, District Pune, Maharashtra, India.

The total number of employees engaged on the site for Production, Engineering, QC/QA, Stores and Distribution (Pharma Unit I and II) were 810 employees. 156 employees were involved in quality control activities, 82 in quality assurance activities and 506 in production activities.

History of WHO and/or regulatory agency inspections

The site was last inspected by WHO in November 2011. The site has also been inspected by the following regulatory authorities:

December 2009	Ministry of Health, Ethiopia
January 2010	Australian Pesticide and Veterinary Medicines Authority (APVMA)
October 2010	Medicines Control Council (MCC), SA
November 2010	National Health Surveillance Agency ANVISA, Brazil
November 2011	WHO (UNICEF)
November 2011	United States Food and Drug Administration (USFDA)
July 2011	Ministry of Health, Sudan
August 2012	National Drug Authority (NDA), Uganda
August 2012	Korea Food & Drug Administration (KFDA)
January 2012	Ministry of Health, Morocco
April 2013	Medicines and Healthcare Regulatory authority (MHRA) – UK
June 2013	Australian Pesticide and Veterinary Medicines Authority (APVMA) (Desktop review)
May 2014	United States Food and Drug Administration (USFDA)



March 2015	National Health Surveillance Agency ANVISA, Brazil (Desktop review)
September 2015	Ministry of Health Pharmacy And Poisons Board , Kenya
September 2015	Ministry of Health Egypt

Focus of the inspection

The inspection focused on general principles of GMP and the production and control of the products listed above.

Inspected Areas

- Quality Assurance
- Sanitization and hygiene
- Qualification and validation
- Complaints
- Recalls
- Supplier qualification
- Personnel
- Training
- Personal hygiene
- Premises
- Equipment
- Materials
- Documentation
- Production
- Quality control

3.1 PHARMACEUTICAL QUALITY SYSTEM (PQS)

Principle

In general PQS was implemented. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results taken into account in batch release and regular reviews of the quality of pharmaceutical products were conducted. Periodic management reviews were performed.

Quality Risk Management (QRM)

The SOP “Risk Management by Failure Mode Effects and Criticality Analysis (FMECA)” and flow diagram were discussed. The SOP was used for Risk Management by Failure Mode Effects and criticality 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).

Risk assessment (RA) register for 2016 was presented to the inspectors.



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

A number of RAs were checked.

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.

Finished products PQR trends were presented as tabulated data and graphs.

The PQR HA489 Lamivudine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 300mg/300mg for period 1st October 2014 to 30th September 2015 was reviewed.

APIs and excipients material codes were manufacturer related.

The PQR for Fluconazole capsules 150 mg for period 1st August 2014 to 31st July 2015 was reviewed.

PQRs were approved by the unit quality assurance head. Reviewed PQRs were well documented.

Management review (MR)

The SOP “Quality Management Review (QMR)” was reviewed. Management review (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.

QMR report, dated January XX, Unit I (Formulation I and II) was discussed. QMR was well documented; trends were presented as graphs, bars and pies.

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 personnel 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 and were 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 software; “Smart solve”. This had been purchased and supplied by “Pilgrim” customised for Cipla. This had been implemented since February 2013. Deviations related to production/packaging were recorded in the related batch manufacturing records/batch packaging records.

Deviation logs for 2015 and 2016 were presented to the inspectors

Deviations were trended on monthly basis (considering 6 months back); trends for February 2016 were discussed. 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).

A number of deviation records were discussed.

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 what 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
- 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.

A number of change requests (CR) 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.

CAPA logs for 2015 and 2016 were presented to the inspectors.

A number of CAPAs were discussed.

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 and tools to be used were specified. Tools to be used were:

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

3.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Manufacturing processes were clearly defined and systematically reviewed. Qualifications and validations were performed. Necessary resources were provided and records were made during manufacture. Significant deviations were recorded and investigated, root causes were determined and corrective and preventive action were implemented. A system was available to recall any batch of product from sale or supply and complaints about marketed products were examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products.

3.3 SANITATION AND HYGIENE

The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facilities. Areas were cleaned frequently in accordance with an approved written program and SOPs. Microbial monitoring was regularly performed.



3.4 QUALIFICATION AND VALIDATION

Validation Master Plan (VMP)

The key elements of a qualification and validation program were defined and documented in the Validation Master Plan (VMP). VMP was discussed. 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.

Qualification

Qualification policy was specified in the VMP.

Process validation

Last three consecutive batches validation for Lamivudine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 300mg/300mg was carried out in October 2010 (1st batch), August 2011 (2nd batch) and July 2012 (3rd batch). Periodic re-validation was carried out in January 2013.

Lamivudine/Tenofovir disoproxil (fumarate) Tablet, Film-coated 300mg/300mg packing process validation was carried out for three consecutive batches and was completed in 2013.

Cleaning validation

The SOP “Cleaning validation and establishment of worst case product” was discussed. The SOP was applicable to cleaning procedures of equipment and accessories used in manufacturing of pharmaceutical products. The procedure was comprehensive and its purpose described as “to prove that the equipment cleaning procedure can consistently clean the previous product, cleaning agent and microbial residues and solvent/solution to an acceptable level, prevent possible contamination and cross contamination in subsequent products”. Worst case product was defined using the following criterion:

- Product having least solubility
- Product having least therapeutic dose (potent drug)
- Product having least permitted daily exposure - PDE value (Toxic drug)

Worst product for calculation of acceptance criterion was specified as: product having minimum batch size and maximum daily dose.

The cleaning validation frequency was stated to occur as every 5 years for one batch. Swab and rinse samples were collected for all cleaning validation studies.

The matrix considered all product contact surfaces and consideration was given to non-contact parts which the product may migrate to such as gaskets and sleeves.



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.



Hold time studies

The SOP “Storage period for dispensed raw materials, in-process and bulk finished products” was discussed. Hold time studies were carried out for all products and following processing steps.

In case if the batch has to be packed after exceeding the established hold time for the bulk finished product, deviation should be initiated and batch should be reanalyzed as per specification and the batch should be monitored for long term stability.

Summary of hold time study Lamivudine and tenofovir disoproxil fumarate tablets 300/300 mg was discussed. The hold time studies were carried out for three consecutive batches.

Temperature mapping

The SOP “Temperature (T) and relative humidity (RH) distribution study” was discussed. Initially T and RH mapping studies were carried out seasonally and periodic re-validation was carried out every three years for one season. As an example for T&RH mapping raw material warehouse validation reports were discussed.

Validation report XXX “T and RH distribution study in critical, non-critical and cold storage areas” was discussed. T and RH studies were carried out according to the ISO 14644-3 and WHO guidelines.

3.5 COMPLAINTS

The SOP “Handling of product complaints” and flow chart were discussed. The SOP was applicable to 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. Complaints were logged, categorized and forwarded 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

Complaints were trended every 6 months. Trends for the period July – December 2015 were discussed. Trends were presented tabulated and as bars:
Complaints registers for 2015 and 2016 were presented to the inspectors.

A number of complaint investigations were discussed.

3.6 PRODUCT RECALLS

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.

3.7 CONTRACT PRODUCTION AND ANALYSIS

Production activities were not contracted out for export market. For local market production activities were 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.



3.8 SELF INSPECTION, QUALITY AUDITS AND SUPPLIERS AUDITS AND APPROVAL

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

Self-inspections were classified as:

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

Non-conformances were classified as:

- Critical
- Major
- Minor

The documents prepared for every self-inspection included the 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.

Separate check lists were used for inspection of different departments and different activities, for example: granulation, compression, and packaging.

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.

Supplier's audits and approval

The SOP "Evaluation and approval of manufacturer" and flow chart 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, lead auditor should be preferably from QA or CQA.

The SOP "Vendor audit management" was discussed. Audits were carried according to the yearly audit calendar. API/API starting material/intermediate/primary packaging materials/printed secondary packaging materials/sterile packaging material vendors' audits was carried out every 36 months. Excipients vendors' audits were carried out every 48 months. Frequency for existing certified vendors (manufacturer/supplier) was based on the risk rating of individual vendors.



Vendors audit schedule for 2016 was presented to the inspectors.

A number of audit reports were reviewed.

3.9 PERSONNEL

General

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Responsible staffs, specific duties were recorded in written job descriptions. Personnel were aware of the principles of GMP and received initial and continuing training, including hygiene instructions, relevant to their needs. Steps were taken to prevent unauthorized people from entering production, storage and QC areas.

Job descriptions

Job descriptions were available for all personnel.

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.

Personnel hygiene

The SOP “Health and hygiene requirements” was checked. 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.

To enter the production section operators had to wear “boiler suits”, head covers and factory footwear. In production cubicles (e.g. shifting, blending, granulation, compression, coating) operators had to wear overgrown, head cover/face mask, overshoes and gloves.

3.10 PREMISES

General

Exposed surfaces were smooth, impervious and unbroken. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. Airlock doors were interlocked. Pharma Unit I was visited during the course of inspection. QC laboratory and QA department as well as materials warehouses were located at the ground floor. Production facilities were located at first floor of the building. Utilities: HVAC system and purified water system were located on the top floor of the building.

Each production section (e.g. granulation, compression, and coating) had separate tools rooms and equipment washing rooms.

Premises were cleaned and disinfected according to written procedures.

The SOP “Cleaning procedure for cubicles in Pharma manufacturing areas” was checked. The procedure was common for all production cubicles/rooms. Cleaning procedures explained the following cleaning scenarios:

- Batch to batch
- Product to product

Cleaning procedure was done according to the check list what was the part of the BMR/BPR.

The SOP “Supplementary procedure from sampling” was discussed. This SOP described API / raw materials / intermediates / Packaging materials / finished product sampling rooms/LAF booths cleaning procedure.



The SOP “Cleaning procedure for dispensing area” and rooms cleaning log were discussed. Line clearance was done.

Ancillary areas

Rest and refreshment rooms were separate from manufacturing and control areas.

Storage areas

Storage areas were of sufficient capacity. Receiving and dispatch bays protected materials and products from the weather. Segregation was provided for the storage of rejected, recalled, or returned materials or products

Separate warehouse was provided for storage of solvents and liquids. This warehouse was not visited during the course of inspection.

Sampling areas

Separate sampling areas were provided for sampling of APIs, inactive materials, primary and secondary packaging materials. APIs, inactive materials were sampled under LAF. Line clearance was carried out after each sampling operation by stores officer and checked by production officer.

It was explained that solvents and liquid materials were sampled in the warehouse in separate sampling place, provided with air exhaust. Solvents were sampled using dedicated air operated or barrel pumps.

Weighing areas

Dispensing for APIs/inactive materials was carried out in dispensing rooms under LAF. Dispensing was carried out by stores officer and checked by production officer. Materials were dispensed in poly bags and stored in stainless steel containers.

The SOP “Dispensing of API and excipients” was discussed. The SOP defined dispensing sequence: API → inactive materials. Line clearance was done after dispensing of each batch of API.

Sampling and dispensing tools were cleaned in the separate washing room located in the warehouse. PW was used for the final rinse of the tools, compressed air was used to remove remaining water and afterwards tools were placed in infra-red dryer. After drying tools were placed in poly bags and stored in stainless steel cabinets.

Production areas

The premises were laid out in such a way as to allow the production to take place in areas connected in a mostly logical order, corresponding to the sequence of the operations and to the requisite cleanliness levels. The working and in-process storage space did permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps. Interior surfaces (walls, floors and ceilings) were found to be

smooth and free from cracks and open joints. They did permit easy and effective cleaning and disinfection. Production areas were ventilated, with air-control facilities (including filtration of air to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, relative humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas were regularly monitored to ensure compliance with their design specifications. The packaging areas for the pharmaceutical products were designed and laid out so as to avoid mix-ups or cross-contamination.

Quality control areas

Unit I (Plot D-7) had two chemical / instrumental laboratories one for APIs manufacturing units and one for formulation manufacturing units. APIs manufacturing units and formulation manufacturing units had common microbiological laboratory. All laboratories were located at different buildings and were separated from the production areas. Separate AHU provided air to the laboratories.

Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

3.11 EQUIPMENT

General

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Balances were verified daily, full scale calibration was carried out monthly. Daily verification of balances was carried out using minimum, middle and maximum weights.

This procedure was applied for all balances checks on site. Standard weights and respective calibration certificates were presented to the inspectors.

Production equipment was cleaned on a scheduled basis.

The SOP “Equipment cleaning Fette compression machine” was discussed. Different SOPs were available for different production equipment cleaning. The SOP was supplemented with photos of difficult to clean equipment parts. Cleaning procedure explained the following cleaning scenarios:

- Batch to batch
- Product to product
- Cleaning after campaign production

The SOP “Cleaning of bins” and SOP “Accessories cleaning” were discussed. Cleaning procedure explained the following cleaning scenarios:

- Batch to batch (dry cleaning)
- Product to product (cleaning by detergent, scrubbing and PW)

Metal detectors were installed on all compression/capsuling machines.



Laundry and drying machine were provided for washing/drying finger bags. Cleaned finger bags were placed in poly bags and stored in SS cabinets. Dedicated finger bags were used for each product.

Finger bags and screens integrity was checked.

QC released food grade oil was used for punches and dies lubrications. Dedicated punches and dies were used for each product. Punches and dies were stored in metal cabinets. Punches and dies rotation was insured, visual checks were carried out before issue to the production. Calibrated punches and dies checking tools were available as well as punches and dies polishing equipment.

Laboratory equipment and instruments were suitable to the testing procedures undertaken.

Production and laboratory equipment were subject to planned preventive maintenance

Preventive maintenance (PM)

The identification of the production equipment was based on SOP “Allocating Code Numbers to New Equipment”. The maintenance policy was defined in the SOP “Preventive Maintenance Procedure”.

The maintenance activities were summarized in annual schedule. The maintenance protocol and maintenance records (monthly/quarterly/6 monthly) of the compression machine XXX located in YYY were discussed.

Calibration

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 procedure of the balances was defined in the SOP “Calibration Procedure”. The calibration protocol and records of the balance XXX were discussed.

The SOP “Dissolution test apparatus with auto-sampler” operating procedure and dissolution tester Labindia No XXX calibration certificate, calibration data sheet and check list for review of analytical report were discussed. Physical calibration was carried out quarterly and chemical every 6 months.

Heating, ventilation and air conditioning system (HVAC)

The environmental conditions in the production areas were controlled by HVAC system. The clean rooms classification was “Class D (ISO 8)”. 109 air handling units (AHU) were used to provide clean air production areas, warehouses and QC laboratory.



The AHUs supplying air to the production cubicles, sampling and dispensing rooms consisted of the following filter cascade:

- Primary filter G4
- Secondary filter F7
- HEPA filter H13 (installed in the plenum)

The AHUs supplying air to the warehouses consisted of the following filter cascade:

- Primary filter G4
- Secondary filter F7
- Final filter F8

Primary and secondary filters were cleaned in separate room using compressed air, after cleaning, filters integrity was checked. Primary, secondary and HEPA spare filters were available. Spare filters were store in a separate room.

100% fresh air was used for fluid bed dryers (FBD) and coating machines. Each FBD and coating machine had its own AHU, what consisted of the following filter cascade: G 4 → F 7 → HEPA 13.

The pressure cascade was based on an air bubble method meaning the pressure in the processing cubicles at least 10 Pa less than the corridor. The layouts, qualification and monitoring protocols and reports of AHU XXX supplying Compression cubicle No YYY were discussed.

The SCADA building management system was used to control the temperature, monitor the humidity, switch on/off the AHUs and record the status (EE-B17).

Purified Water (PW)

PW was produced by reverse osmosis (RO). In the loop water was circulated continuously. PW storage tank and distribution loop sanitization was carried out every 2 weeks using hot water NLT 80 °C. The following on-line check we carried out continuously:

- UV intensity and working hours
- TOC
- Conductivity (supply and return)
- pH (supply and return)
- Velocity (supply and return)
- Temperature (supply and return)

PW system was equipped with sound alarm system.

PW system daily log for March 2016 was discussed. Daily checks and sanitisation records were checked.



3.12 MATERIALS

General

Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution. Materials and products were stored under the appropriate conditions. Food grade oil was used for punches and dies lubrications.

Materials in the warehouses were stored in mobile racks (compactor storage).

SAP system was used for materials management. SAP system was validated at the corporate level and implemented to all Cipla units.

Temperature and Relative Humidity distribution studies were carried.

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.

Starting materials

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials were available in SAP system. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material recorded and reported to the QA department. Check-lists were used for materials receipt. Received goods were compared with purchase order. Upon receipt “Goods receipt” (GR) number was assigned by the SAP system and note was sent to the QC Laboratory, analytical report number (ARN) was automatically generated and sampling was done according to the different materials sampling plan.

Separate warehouses were provided for materials what should be stored in humidity controlled environment (RH 40 – 60 %) and materials what that should be stored in cold place (2 – 8 °C).

Appropriate procedures were in place to ensure the identity of the contents of each container of API. Bulk containers from which samples were drawn were identified.

Materials were issued to the production following “First expire – first in – first out” principle.

The SOP “Dispatch of materials to other Cipla units” was discussed.

Finished products

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer. After QC release finished products were transported to the finished good warehouse located at Mumbai. Finished goods were transported in air conditioned trucks. Data loggers were placed in each consignment and print outs were taken at the Mumbai warehouse. It was said that transportation process had been



validated; validation documentation was not checked during the course of inspection. Transportation of finished goods was contracted out.

Rejected, recovered, reprocessed and reworked materials

Each warehouse had separate, locked rejected materials storage room.

The SOP “Handling of returned products” and flow chart were discussed. Returned goods were received at the central warehouse in Mumbai and afterwards shifted to the respective units. Upon receipt returned products were kept under lock and key in required storage conditions. Returned goods were inspected by the team comprising from QA, production and QC.

The SOP “Reprocessing / reworking of batch” and flow chart were discussed. This SOP was applicable to the batch of drug product not confirming to predetermine specification/any abnormal observation during the processing. According to the SOP reprocessing and reworking should be performed only in exceptional cases. In case of reprocessing / reworking prior approval should be taken from customer-

Packaging material

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure locations. Each delivery of batch of printed or primary packaging material was given a specific reference number. Packaging materials testing laboratory was located in the warehouse. Packaging materials files contained artworks, specifications, positive and negative samples and shade cards.

For sampling, AQL testing procedure according to the ISO 2859-1 was used. The inspection levels for visual inspection and analysis were defined. For the different types of packaging materials parameters were defined and categorized as critical, major or minor.

The SOP “Dispensing of packaging materials” was discussed. The SOP was applicable to primary and secondary packaging materials. Line clearance was done by stores officer and checked by production officer.

Reagents and culture media

Records for the receipt and preparation of reagents and culture media were available. Reagents made up in the laboratory were prepared according to written procedures and appropriately labelled. Growth promotion tests were applied to verify the suitability of culture media each time they were prepared and used and upon receiving of media. Media were prepared and sterilized following manufacturer’s instructions. pH was checked after media sterilization.

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 3 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.

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 was maintained by the corporate working standard cell (CWSC), CWSC was also responsible to allocate production Unit which is responsible for standardisation of the WS, dispensing and distribution of the WS to another units. WS were qualified against the official RS. WSs were used for assay, identification and impurities tests.

WS protocol XXX for Lamivudine USP was discussed.

Working Standards (WS) and Reference Standards (RS) were available and mainly stored in 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. Temperature in the chamber was continuously monitored and recorded every 10 minutes. Printouts were taken every morning and checked.

3.13 DOCUMENTATION

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date. Records were made or completed when any action was taken.

Specifications and testing procedures

Testing procedures were validated and were appropriately authorized and dated. Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products as well as for intermediate and bulk products.

Specifications for starting and packaging materials, finished products and intermediates

Specifications for starting and packaging materials, finished products and intermediates were available and contained required information about the materials (e.g. material code)

Master formulae

The SOP “Product identification and master batch document numbering system” was discussed. This SOP was applicable for all formulations manufactured in all units of Cipla, associates and loan license units. The SOP described scenarios for creating of product codes and for changing existing product codes.



Master batch records (MBRs) were identified by material code (bulk finished goods/finished goods), production version and document version.

Batch manufacturing records (BMR) / batch packaging records (BPR)

BMRs and BPRs were used for each batch processed. Before any processing begins, checks were made that the equipment and work station were clear of previous products, documents, or materials, and that the equipment was clean and suitable for use. Checks were recorded and were part of the BMR.

A number of BMRs were discussed.

Batch numbering system

The SOP “Batch numbering system for inward and in-house produced material (formulation) was discussed. According to the SOP batch/lot numbers consisted of unique combination of numbers, letter and/or symbols that identifies a batch/lot and from which the production and distribution history can be determined. Batch numbers were allocated by the SAP system.

Standard operating procedures (SOP) and records

Generally various SOPs and records of actions taken were available for all activities carried out on site. Records were kept for major and critical equipment.

3.14 GOOD PRACTICES IN PRODUCTION

General

In general production operations followed defined procedures. Deviations from procedures were recorded and investigated. Checks on yields and reconciliation of quantities were carried out. Materials, bulk containers, major items of equipment, rooms and packaging lines being used, were labelled to identify the product or material being processed and the batch number. Access to production premises was restricted to authorized personnel. In-process controls were performed by operators and discussed by workshop QA within the production area. Friability test, hardness, content uniformity, weight variation and disintegration tests were carried out in IPC laboratory.

Before processing operations was started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Necessary in-process controls and environmental controls were carried out and recorded.

Bulk granules/ tablets (uncoated and coated) were stored in in-process storage room in mobile racks (compactor storage) or shelves. Inventory of the stocks was managed by the SAP system. One person from production was assigned to monitor SAP system daily and in case validated hold time (3 months) was reached, products were quarantined.

Dispensing operations

Dispensing operations were carried out in warehouse.



Prevention of cross-contamination and bacterial contamination during production

Precautions were taken to prevent the generation and dissemination of dust by provided airlocks, pressure differentials, and air supply and extraction systems. In general contamination and cross-contamination of starting material or of a product by another materials or product were avoided. Production areas were subject to periodic environmental monitoring.

Processing operations

Before processing operations were started, steps were taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation. Time limits for storage of equipment after cleaning and before use were stated and based on validation data. Significant deviations from the expected yields were recorded and investigated.

Measuring, weighing, recording, and control equipment and instruments were serviced and calibrated at specified intervals and records maintained.

Separate bins contained the dispensed material for individual batches.

Packaging operations

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously. The line clearance was performed and recorded in the BPRs. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

3.15 GOOD PRACTICES IN QUALITY CONTROL

General

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively and reliably carried out. QC personnel had access to production areas for sampling and investigation as appropriate.

Class “A” volumetric glassware was used.

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.

The SOP “Password policy for software in quality control” 1035-B-0012, version 2 (C) was discussed. The SOP was applicable for generating, processing, acquiring electronic data and /or controlling instruments / equipment having the password security option. The SOP “User management policy software: Chromeleon” UMCS001A, version 1 and privileges distribution chart were discussed.



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 systems 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.

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

The SOP “Sampling of water and steam condensate (LIMS)” was discussed. The SOP was applicable to potable water, purified water, water for injection and steam condensate.

Laboratory data partly was managed by LIMS. LIMS implementation at the QC laboratory should be finalized by end of March.

High pressure liquid chromatographs (HPLC) and gas chromatographs (GC) were connected to the Chromeleon software.

Control of starting materials and intermediate, bulk and finished products

Tests followed the instructions given in the relevant written test procedure. The tests results were checked independently before the material or product was released. Samples were representative of the batches of material from which they were taken.

Test requirements starting and packaging materials

Before releasing a starting or packaging material for use, the QC manager ensured that the materials have been tested for conformity with specifications. An identity test was conducted on a sample from each container of starting material. Each batch of printed packaging materials was examined following receipt.

In-process control (IPC)

Each production section (e.g. granulation, compression, and coating) had separate IPC laboratory. IPC laboratory belonged to the production department and IPC tests were carried out by production personnel. IPC tests were carried out routinely according to the product specific BMR/BPRs.

Test requirements - finished products

For each batch of medicines product, there was an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

Batch record review/batch release procedure

The SOP “Batch release system of formulations” was discussed. The SOP was applicable for release of bulk finished products for packaging and packed finished product dispatch/pilot bio-study/bio-study/non-commercial purpose or sales purpose. Bulk finished goods and finished goods batch release was done by head Unit Quality or next delegated person from QA. Goods were released using the SAP system.



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.

Analytical records review

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.

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 at Cipla corporate. Analytical results were entered to the software by analysts. Master certificates were available in the software for all products.

Stability studies

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.

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

Stand-by chamber was available and qualified for the following conditions:

- T 25 °C ± 2 °C, RH 60% ± 5%
- T 30 °C ± 2 °C, RH 65% ± 5%
- T 30 °C ± 2 °C, RH 75% ± 5%

Expiry date allocation

The SOP “Allocation of manufacturing date and expiry date for products” was discussed. The SOP was applicable for bulk finished products and finished products. According to the SOP manufacturing date is date of mixing API(s) with excipient(s). If more than one intermediate



product was used in a particular batch of bulk finished/ finished product, then the manufacturing date of intermediate having “earliest manufacturing date” was considered as the manufacturing date of bulk finished/finished product.

Out of specification results (OOS)

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 and bars and pies.

Discussed trends were detailed and gave a lot of useful information, for example:

- Distribution of OOS results
- OOS due to analyst/product/material/method/specification/instrument
- Test wise distribution, etc.

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

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.

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.

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.

Finished product retention samples were stored at the Pharma Unit I general warehouse in separate room. Samples were stored in mobile racks (compactor storage). Temperature limits were set up 20 – 25 °C, relative humidity NMT 65%. “Location tracking software” was used to indicate samples location, quantity and time of destruction.

Sampling procedure

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. Classification of defects was given in individual packaging materials specifications.



Microbiological laboratory (MB)

Microbiological laboratory was located at the Pharma Unit II. Two testing rooms were used; testing room I – for PW analysis and testing room II – for product analysis. Separate room was provided for bacterial endotoxins test. Microbial tests were carried out in LAF cabinets. Separate room was used for cultures handling.

Media used was either purchased “ready for use” or prepared in-house from dehydrated media. Media preparation and sterilisation records were available for the different media used. Storage conditions and time of use of prepared media was defined. In-house prepared media and purchased “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 “ready for use”. “Ready for use” Medias were purchased for EM tests and partly for PW tests. Medias for microbial limit test were prepared on site.

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 discussed.

The SOP “Preparation and disposal of microbiological culture media” and SOP “Establishment of alert/action limits” were discussed.

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 monthly, six monthly and yearly. Trends for 2015 were discussed, trends were presented as graphs. Alert and action limits were specified.

The SOP “Microbiological monitoring of environment in production area” was discussed. The SOP was applicable to environment in production areas. Active air sampling method and settle plate methods were used. Settle plates were exposed for 1 hour and air sample volume was 250L. Tests results were trended yearly.

Alert and action limits were specified. Trends for 2015 were discussed, trends were presented as graphs.

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



Part 4: 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, a Cipla Ltd., Unit I, located at Plot D 7 MIDC Industrial Area, Kurkumbh Village, Taluka-Daund, Pune District, Maharashtra, 413 802, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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.