

WHO PUBLIC INSPECTION REPORT (WHOPIR) of the FPP manufacturer

Part 1: General information about the inspection

Name of manufacturer	Cipla Ltd, Patalganga
Unit	Unit No I and Unit No II
Physical address	<p>Unit No I Cipla Limited Plot No. A – 33, A – 2 (Unit – I), MIDC Patalganga, 410 220 District Raigad, Maharashtra, India</p> <p>Unit No II Plot A-42 Cipla Limited Plot No. A – 42 (Unit – II), MIDC Patalganga, 410 220 District Raigad, Maharashtra, India</p>
Summary of activities of manufacturer (e.g. manufacturing, packing).	<p>Manufacturing, quality control and batch release of:</p> <ul style="list-style-type: none"> Non-sterile medicinal products: uncoated and film coated tablets, ointments, creams, gels and nasal sprays. Active Pharmaceutical Ingredients (APIs) and drug intermediates
Focus of inspection	Tablets, dispersible tablets and film coated tablets for treatment of tuberculosis, malaria and HIV
Scope and type of inspection	Routine inspection, covering all aspects of GMP
Date of inspection:	17 - 20 February 2014

Part 2: Summary***General information about the company and site***

The facility inspected was Cipla Ltd, located at Patalganga, A-42 MIDC Industrial Area, Patalganga, Raigad District, Maharashtra, 410 220, India, here after called Cipla Patalganga. Cipla Patalganga is situated in a Government sponsored Industrial Park at a distance of 80 km from Mumbai by road. The Manufacturing facility at Patalganga Unit I (Plot A-33) was commissioned in 1984 and set up for the manufacturing of APIs and Finished Formulations (Tablets, Topical Preparations & Nasal Sprays). The facility was extended under the same local Management in the year 2006 by a second Unit (Unit-II on Plot A-42) for the manufacturing of Active Pharmaceutical Ingredient (API) & Finished Formulations (Tablets). Further in the year 2013, the facility was again extended under the same local Management (Plot A-2). This Unit I extension, which is adjacent to Unit-I (Plot A-33), is set up for the manufacturing of Active Pharmaceutical Ingredient (API), Quality Control for Unit I and Unit I extension, as well as Pilot plant and Research and Development (R&D) laboratory for APIs.

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

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

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

Part 2: Summary***History of WHO or regulatory agencies inspections***

The site was previously inspected by WHO inspection team on 9 to 12 August 2010 for FPP manufactured in Unit I and on 21 to 24 February 2011 for FPP manufactured in Unit II.

Recently the site was inspected by the following authorities:

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

(this was for API)

Focus of the inspection

The inspection focused on the production and control of the products listed above. Particular attention was paid to the production and control of products under pre-qualification.

The inspection covered all the sections of the WHO GMP text, including quality assurance, premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control, utilities, manufacture and transfer of technology.

Inspected Areas

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

2.1 QUALITY ASSURANCE

A system for quality assurance in general was established. Production and control operations were clearly specified in written procedures, arrangements were made for the manufacture, supply and use of the correct starting and packaging materials. Necessary controls on materials, calibrations, and validations were carried out.

Annual Product Quality Review (APQR)

Product quality reviews (called Annual Product Quality Review) were conducted for domestic market and export products. APQR reports were prepared annually. The first reporting period started from the month when the first batch was manufactured. The SOP “Annual product quality review” was checked. The SOP was applicable for FPPs, APIs and intermediates. It contained all parameters according to the current GMP requirements. Numerous APQRs were reviewed and were generally acceptable.

Quality Risk Management (QRM)

There was a system for Quality Risk Management (QRM). The SOP “Risk Management by Failure Mode Effects and Critical Analysis” was checked. The SOP was used for Risk Management by Failure Mode Effects and critical Analysis. The SOP was applied in different areas e.g. development, manufacturing, testing, and distribution to evaluate the

risk inherent to a process. For root cause analysis, the fish bone method combined with the “five Why – Analysis” was used.

The SOP “Root cause analysis” was checked. The SOP was applied to all non-conformances as e.g. out of specifications (OOS), out of trends (OOT), deviations and complaints.

Risk Assessment (RA) files contained the following documents:

- Justification for selection of FMECA
- RA flow chart
- Risk assessment
- Risk communication
 - Risk review
 - RA conclusion

Planned and unplanned Risk Assessment (RA) was performed. The frequency for re-assessment of risk to products and systems was defined in the SOP. The annual schedule for planned risk assessment for 2014 was available for both Units. Separate registers containing the risk assessments performed in Units I and II were kept and cross-checked for the years 2013 and 2014 (up to the date of inspection). Numerous RA were reviewed and were generally acceptable.

Change control

The SOP “Change control”, flow chart and change control form were checked. 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. This was comprehensive and detailed checklists for staff to follow in the event of certain changes including what Quality System elements need to be amended (or considered) as a consequence of the change.

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.

The list of change controls logs from December 2010 to date were reviewed as a sample exercise. This was a log book format per unit, per category and per year or month as required.

Changes were classified as:

- Major
- Moderate
- Minor

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

In case of major changes regulatory authorities, customers and Marketing Authorisation holders for finished products should be notified. Changes were trended in the respective Finished Pharmaceutical Products APQRs.

Numerous change controls were reviewed and were generally acceptable.

Deviation handling

The SOP “Quality Management System deviation” and flow chart were checked. Deviations were specified as planned and unplanned and classified as:

- Major - should be closed in 15 calendar days
- Minor - should be closed in 30 calendar days
- .

The deviation procedure was reviewed and found comprehensive detailing functional roles, operational roles and responsibilities of personnel required investigating deviations. The procedure defines deviations as unplanned in that were unexpected events that resulted in a departure from the approved procedure, document or established standard. It is 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 Jan 2013. The implementation was inspected and found basic although acceptable.

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

Corrective actions and preventive actions (CAPA)

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

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

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices were generally implemented. The necessary resources were provided. Manufacturing processes were clearly defined and systematically reviewed. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and records were made during manufacture.

2.3 SANITATION AND HYGIENE

In general, premises and equipment were maintained at an acceptable level of cleanliness. The company had a standard operating procedure as the basis for its approach to personal hygiene and sanitation in its production facility.

Areas were cleaned frequently in accordance with an approved written programme and SOPs. Microbial monitoring was regularly performed.

The procedure for cleaning of the production cubicles was reviewed. This described critical and non-critical areas. Critical being described as the area where there was a chance that the product is exposed and non-critical where there was very little chance of exposure.

A corporate procedure specifying the detergents and disinfectants used was reviewed. This was reviewed against facility cleaning procedures. The procedure gave definitions of chemical disinfectant, cleaning agents and deactivating solutions. The criteria for selection of disinfectants which included assessment of the number and type of organisms to be controlled on the basis of trends microbiological environment monitoring/surface monitoring of concerned areas, spectrum of activity of commercially available disinfectants, concentration, application method and safety considerations for operators applying the disinfectants.

2.4 QUALIFICATION AND VALIDATION

The company identified what qualification and validation work was required. The key elements of a qualification and validation programme were defined in a validation master plan (VMP).

Cleaning validation

Cleaning validation was performed and controlled under corporate procedure “Cleaning validation and establishment of worst-case product”. 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 to an acceptable level, prevent possible contamination and cross contamination in subsequent products”. The procedure was also used to establish conditions for mixing products or equipment. The Cleaning Validation Matrix documented the validation activities to be performed during the year per equipment. Equipment trains were present identifying the equipment used. The cleaning validation frequency was stated to occur as every 5 years unless new equipment was purchased. In this case 3 consecutive validations would occur, captured as part of the change control mechanism. The matrix considered all product contact surfaces and consideration was given to non-contact parts which the product may migrate to such as gaskets

Equipment Qualification

The Validation Master Plan for 2014 was reviewed. This was a schedule based spread sheet with the years plotted out against the required validation activities. Equipment

Qualification was detailed as being required every 3 years for critical equipment and non-critical equipment every 5 years.

Laboratory equipment qualification

IQ, QO and PQ qualification report for analytical balance was spot checked. IQ, QO and PQ were done by the balance supplier. User requirement specifications were also checked.

The following analytical instruments were checked regarding usage and calibration:

- Karl Fisher
- pH meter
- Analytical balances
- HPLC
- GC
- FTIR
- UV
- Polarimeter
- Melting point
- Dissolution
- Disintegration
- Friability
- UV lamps used for TLC
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Equipment maintenance was carried out yearly by contractors.

Purified Water

Purified water (PW) system was installed in 2006 for Unit II and in 2003 for Unit I. PW used in production was generated using RO and EDI. Water was continuously circulated at ambient temperature. A calibrated flow meter was installed in the return loop. Conductivity, pH and TOC were monitored online. PW system was sanitized weekly using hot water (NLT 80 °C). Sanitization records were presented to the inspectors.

PW sampling/trends Unit I

Spot checked PW trend results (chemical and microbial – total aerobic counts) were within specified limits, action and alert limits were specified and sampling schedule was followed.

PW sampling/trends Unit II

Spot checked PW trend results (chemical and microbial – total aerobic counts) were within specified limits, action and alert limits were specified and sampling schedule was followed.

Pure steam

The SOPs “Sampling of water and steam condensate”, “Water analysis” and trend analysis were checked.

Steam sampling was done using steam trap or steam condenser. Steam was generated from PW. “Pure steam” chemical and microbial analyses were carried out as per USP and in house PW specifications. Sampling and testing of pure steam (MB and chemical) was carried out once a year during three consecutive days from all sampling points. Spot checked pure steam trend results were within specified limits, sampling schedule was followed

Compressed air

Oil free compressors were used to generate compressed air. The compressed air was used for technical purposes, but also for product contact, e.g. in coaters and Saizoner mixer granulators.

The SOP “Microbial monitoring of compressed gases and steam condensate” was checked. Sampling was done using Pinocchio Super Compressed Air sampler. Samples were taken once a year for three consecutive days from selected sampling points.

HVAC

AHU 07A was installed to supply air to the primary packaging rooms for Unit II packaging expansion. AHU was subjected to IQ and OQ which were carried out in July 2011. PQ was completed on 26 August 2011.

The air was supplied via filter cascade:

- G4
- F5
- F8
- Two H13

HEPA filters were installed in the plenum. Pressure differentials between filters were monitored daily.

Performance Verification report “Heating ventilation and air conditioning system” for AHU 7A was checked.

Related SOPs to the AHU performance qualification, raw data and instruments calibration certificates were spot checked.

Process Validation

Numerous process validation reports were reviewed and were generally acceptable.

2.5 COMPLAINTS

The handling of complaints was described in the SOP “Handling of product complaints”. The procedure as well as the flow chart and one complaint received in 2013 were checked. The SOP covered quality, medical and transport complaints for drug substances and drug products for the local market as well as export markets. Complaints were handled through Corporate QA. They logged, categorized and forwarded the complaints to the responsible site for evaluation. The investigation had to be performed within 30

days. A report was sent to Corporate QA as a response after evaluation of the complaint. Corporate QA was responsible to give an answer to the customer.

Registers for Unit I and II were available. Complaints were trended on a regular basis. Two types of complaints were defined: medical complaints (i.e. adverse event / adverse drug reaction, lack of efficacy) and technical complaints (e.g. empty containers, bad odour / taste, particulate matter, damage during transportation, coating defects, fill value, missing / broken product, label issues, variable data).

Numerous complaints were reviewed and were generally acceptable.

2.6 PRODUCT RECALLS

The recall procedure was described in the SOP. The procedure was applicable to all drug products manufactured for local and export markets. While Regulatory Affairs was responsible for the coordination with the QP/Quality Assurance of the concerned marketing authorisation holder, customer or concerned regulatory authorities, taking the decision for a recall was the responsibility of Corporate Quality Assurance. The procedure also included the notification of the local FDA and the notification of the customers as well as the assessing of the impact on other batches.

Recalls were classified as:

Classified as:

- I (critical)
- II (major)
- III (minor)

In the registers for recalls for Unit I (September 2012 – date of inspection) and Unit II (January 2013 – date of inspection), no recalls were logged.

Dummy recalls were carried out by CQA yearly for domestic and export markets. Dummy recall validation (export market) was spot checked.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Specific analyses were contracted out to other laboratories.

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
- Qualification of HVAC system
- Temperature mapping
- Measuring equipment calibration
- Laboratory equipment maintenance
- Factory garments laundry

Quality agreement with the company providing the laundry services was spot checked. According to the contract, laundry should be carried out following Cipla SOP “Washing of linen (non- sterile)”. Laundry was collected separately from different change rooms and also washed separately.

Quality agreement with the packaging material manufacturer as well as Inspection report was spot checked.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were performed routinely. The SOP “Self inspection”, schedule for 2013 and 2014 as well as the checklists for inspection of the QA department and tablet granulation were checked. The procedure contained detailed instructions for the qualification and training of the auditors as well as the preparation, performance and follow up of self-inspections. Separate schedules were prepared for self inspections of Units I and II for finished dosage forms. According to the schedule, all the areas were inspected every six months. 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.

The schedule for self-inspections for Units I and II for 2013 had been completed as planned.

The documents in regard to a self-inspection performed at Unit II/Packaging/Sep 2013 were available. Only the availability, no content was checked.

The system was in place for approving suppliers of starting materials - active and inactive and primary and secondary packaging materials.

Audit team selection was responsibility of CQA. API and primary packing materials audits were carried out every 3 years, inactive starting materials audits were carried out every 4 years.

The SOP “Evaluation and approval of manufacturer” and flow charts were checked. The SOP was applicable to the manufacturers and /or suppliers of API, packaging materials and excipients. SOP seen was updated and was effective from 15 February 2014. Paper based audit was included in the revised SOP to approve manufacturers of certain excipients and second packaging materials manufacturers.

On spot checks suppliers audit schedule was followed and reports were available.

2.9 PERSONNEL

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 were available for all personnel to the level of operator (production) and analyst (laboratory).

The following Job descriptions were reviewed:

- Unit Quality Head Unit I - responsible person for APIs and FPPs
- Unit Quality Head Unit II - responsible person for APIs and FPPs
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-
- Unit Quality Assurance Head Formulations Unit I - responsible person for release of starting materials, intermediates and finished products
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- Unit Quality Assurance Head Formulations Unit II - responsible person for release of starting materials, intermediates and finished products
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- Unit Quality Control Head Unit I – testing of APIs and Formulations
- Unit Quality Control Head Unit II – testing of APIs and Formulations
- Unit Head Formulations Unit I – Manufacturing of Formulations
- Unit Head Formulations Unit II – Manufacturing of Formulations

2.10 TRAINING

The SOP “Training” and training flow chart were checked. The SOP explained the training requirements for GMP and related training program for employees.

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

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

Analyst competency certificates were issued for each test.

2.11 PERSONAL HYGIENE

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

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

2.12 PREMISES

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. According with HVAC system qualification the final stage of the changing room was in the at-rest state, the same grade as the area into which it leads. Photos explaining changing procedures were available in all changing rooms; changing rooms were equipped with mirrors. Airlock doors were interlocked.

Premises were cleaned and disinfected according to written procedures. Records were maintained.

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. In Unit I, also narcotics were noted to be stored separately and under lock and key. All materials in the warehouse were stored in mobile racks. Separate sampling areas were provided for APIs, inactive materials, liquids and packaging materials.

Weighing areas

Dispensing at Units I and II was carried out in the warehouse in dedicated dispensing areas. Separate dispensing areas were used for inactive materials, for APIs and for primary packaging materials. Dispensing was carried out under laminar flow conditions, except for secondary packaging materials.

Production areas

According to the information received from the company, no highly sensitizing material, e.g. beta-lactams or biological preparations were used at Units I and II. No other types of products than pharmaceuticals were manufactured on site. 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 effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas were regularly monitored during both production and non-

production periods 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. The production areas were well lit, except if the open product had to be protected from light. In Unit I, space behind some secondary packaging lines was not sufficient. However, as soon as the nasal spray production will be transferred to another site, the manufacturing area for nasal sprays will be dismantled and the packaging area will be expanded.

Quality control areas

QC laboratories were common for API and FPP testing. The laboratories were located at Unit I-extension (serving Unit I as well as Unit I-extension) and Unit II. They were separated from the production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

Microbial laboratory was separated from production and QC laboratories. Separate air-handling units were provided for microbiological laboratories.

2.13 EQUIPMENT

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. Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments were suitable to the testing procedures undertaken.

Major production and laboratory equipment were subject to planned preventive maintenance.

The SOP “Preventive maintenance (PM) procedure” and PM planner were checked. According to the SOP separate PM SOPs should be prepared for all equipment’s/instruments used for processing, testing and utilities. The SOP “Preventive maintenance for Saizoner” and PM check list “Log book for Saizoner (Rapid Mixer Granulator) were spot checked. According to the Log book PM should be carried out every two and six months. PM planned for 2013 for Saizoner (Rapid Mixer Granulator) was checked. Spot checks confirmed that PM planner was followed.

Computerized systems

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

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

- Daily
- Weekly
- Monthly
- Yearly

2.14 MATERIALS

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).

Temperature and Relative Humidity distribution studies were carried.

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

“Temperature and RH humidity distribution study” (RM store Unit II) re-validation report and drawing was spot checked. The mobile racks were divided in 12 grids and 30 data loggers were used to record Temperature and RH. The study was carried out during seven consecutive days. Temperature and RH readings were taken every minute for 5 minutes interval according to the ISO 14644-3 guidelines.

Materials inventory was managed by using Inventory Management System (IMS). Access to the IMS was granted to store, QC and QA personnel. Access levels were different.

Starting materials

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials were available. 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.

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

Site transfer and code transfer for starting materials was possible and the prerequisites and procedures defined in the management system. Procedures and examples were reviewed.

Packaging materials

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.

The procedures for sampling, issue of packaging material to production and handling of returned packaging materials from production were reviewed.

For sampling, AQL testing according to 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 sampling of primary packaging materials was done under LF conditions.

Packaging materials, except rolls, were issued in exact numbers to production according to the work order. The FEFO principle was used (first expiry, first in, first out).

The return of excess material from production to stores was described. Depending on the type of packaging material, return was possible if more than the defined minimum amount had to be returned. For certain materials, no return to stores was possible. Production and stores responsibilities for the checking of the returned materials were described.

Intermediate and bulk products

Not inspected.

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.

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were stored separately.

Recalled products and Returned goods

Till the date of inspection no products were recalled. Separate, secure returned goods area was provided.

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. Medias were prepared and sterilized following manufacturers instructions. pH was checked after media sterilization.

Reference standards

Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were certified by the application of appropriate tests to ensure standardization. Reference standards were properly labeled and stored.

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

Waste materials

Not inspected.

2.15 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.

In the corporate technical guideline “Quality documentation policy” three levels of documents were defined, Level 1 - e.g. quality policy, Quality Manual, SOPs, QC procedures; Level 2 - unit specific documents regarding e.g. operation, cleaning, line clearance; Level 3 - quality control raw data, reports specific to a particular batch. A list of related documents was given for further reference.

The “Procedure for standard operating procedure” included instructions regarding the format, approval, distribution of copies (issuance record is kept, responsibility of QA to exchange the copies, when new is issued), handling of obsolete copies (original is stamped and archived) and review of documents.

Labels

Labels applied to containers, equipment and premises were clear and unambiguous.

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.

Master formulae

Authorized master formula was available.

Packaging instructions

Authorized packaging instructions were available.

Batch processing records

Batch manufacturing records (BMRs) 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.

Batch manufacturing record, Batch packaging report and Analytical test report for specific batches were checked. The information required was available. Entries were complete and signed off by personnel involved. Yield calculations were carried out after blending & lubrication, compression and coating (validated steps).

Batch packaging records

Batch packaging records (BPRs) were used for each batch packed. Before any packaging operation begins, checks were made that the equipment and work station were clear of previous products, documents or materials, and that equipment was clean and suitable for use. Checks were recorded and were part of the BPR.

Standard operating procedures and records

SOPs and associated records of actions taken were available.

Assessment of the Site Master File

The Site Master File was available in electronic form before the visit was made to the manufacturing site. It included detailed schematic plans and drawings of the buildings and utilizes, such as the water systems. In general it complied with the guidelines on preparation of the SMF.

2.16 GOOD PRACTICES IN PRODUCTION

Handling of materials and products were carried out in accordance with written procedures. Deviations from instructions or procedures were done in accordance with an approved procedure. Checks on yields and reconciliation of quantities were carried out. During processing, all materials, bulk containers, major items of equipment and rooms were labelled. Equipment spare parts as FBE filter bags, sieves, stereos and screens were stored secure in locked cabinets. Punches and dies were product dedicated and rotation was ensured.

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.

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.

2.17 GOOD PRACTICES IN QUALITY CONTROL

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.

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

Class A glassware was used in the laboratory.

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

In-process control records were maintained and formed a part of the batch records.

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

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

The release procedure for bulk finished products and packed finished product for dispatch was checked. Responsibilities and individual steps were described and masters for the following checklists were included: “QA checklists for review of batch manufacturing record”, “QA checklist for review of batch packaging record”, QA batch record review sheet” and “Batch release certificate”. In the QA checklists for review of BMR and BPR, no explicit control point for the completed “Checklist for document review by production and packaging” performed by production was included.

Out of Specification (OOS) and Out of Trends results (OOT)

Out-of-specification results and out of trend results obtained during testing of materials or products were investigated in accordance with an approved procedure. Records were maintained. OOS and OOT trends were available and presented to the inspector.

OOS and OOT SOP, flow chart and trends were spot checked. SOP was written following US FDA guideline.

OOS Register for FPPs, Unit I 2014 & 2013 were reviewed.

OOT register for FPPs, Unit I and Unit II 2014 & 2013 and trending were reviewed.

Reference standards

Working Standards (WS) and Reference Standards (RS) were available and mainly stored in separate, locked refrigerators 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. WS were adequately labelled. Standards inventory was electronically maintained.

Traceability of standards was ensured.

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

Stability studies

Expiry dates and shelf-life specifications were established on the basis of stability tests related to storage conditions.

The performance of stability studies was described in the SOP. The company followed the requirement of USP and ICH guidelines. For new products as well as subsequent batches, the type of study (long-term or accelerated), the number of batches and the frequency for testing were defined. Time limits for withdrawal of samples and testing were defined.

Four stability walk-in chambers and four stability chambers were located in the laboratory of the Unit II. The access to the stability chambers was restricted. Stability chambers were connected to the software and in case of power failure, alarm was triggered. Temperature and RH in the chambers were continuously monitored and recorded every 10 minutes. Printouts were taken every morning and checked.

Electronic data

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

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

Microbiological laboratory

Media used was either bought “ready-made” or prepared in-house from dehydrated media. Media preparation sheets were available for the different media used. Storage conditions and time of use of prepared media was defined. In-house prepared media and

bought “ready-made” media were tested for sterility and growth promotion according to the pharmacopoeia method using the organisms described and in-house organisms. The standard cultures used were received from corporate organisation in cryo-vials. Cultures were cultivated to maximal five passages.

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

The performance of microbiological testing was described in the SOP “Microbiological examination of non-sterile products”. The harmonised method was used. The routine method used was the pour-plate method. Total aerobic microbial counts, total yeast microbial counts and tests for specific microorganisms were performed. Testing methods were validated including product influence on growth.

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

Environmental monitoring

The SOP “Microbiological monitoring of environment in production area” was checked. Environmental monitoring (EM) was carried out using settle plates and active air sampling for fungi and aerobic bacteria. Settle plates were exposed. EM was carried once in two months on rotation basis – one month settle plate method and one month active air sampling method. EM schedule was presented to the inspectors and based on spot checks performed, the schedule was followed.

Study report “Exposure period for settle plate monitoring” was checked.

Unit II & Unit I

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

The SOP “Identification and maintenance of in-house isolates” and the list of in-house isolates were spot checked. Isolates were identified from PW, potable water and environment. The document “Database review of in-house isolates” was checked:

Non-pathogenic organisms were identified. Isolates identified were from normal house flora.

Validation of analytical methods

The SOP “Validation and verification of analytical methods” was checked.

For the verification of Pharmacopoeia methods the following parameters were verified:

- Specificity
- Repeatability
- Linearity and range

- Accuracy
- Solution stability.

For the analytical method validation the following parameters were validated:

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

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

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

Analytical method transfer

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

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

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

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection listed in the Inspection Report, Cipla Ltd, Patalganga Unit No I located at Plot A-33, A-2 (Unit- I) MIDC, Patalganga, Raigad District, Maharashtra, 410 220, India and Unit No II, located at Plot A-42 MIDC Patalganga, Raigad District, Maharashtra, 410 220, India, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.



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.