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Prequalification Team Inspection services
WHO INSPECTION REPORT
of the FPP manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Cipla Ltd
Corporate address of manufacturer	Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai-400013, India Web site: www.cipla.com Telephone: 91 22 24826000 Facsimile: 91 22 24826120
Inspected site	
Address of inspected manufacturing site if different from that given above	Cipla Ltd, Unit 1, PO Bhud, Upper Malpur Village, Tehsil, Nalagarh, Solan District, Himanchal Pradesh, 173 205, India D-U-N-S No. for Cipla Baddi site is 65-025-3839
Unit / block / workshop number	Unit I
Manufacturing license number	No MNB/05/109 & MB/05/110 issued 21/4/2015 manufacturing for sale drugs
CRM Inspection Record Number	INSP-2015-0126
Inspection details	
Dates of inspection	20 – 22 June 2016
Type of inspection	Routine inspection
Introduction	
Brief summary of the manufacturing activities	Manufacturing, packaging, quality control, stability testing, storage and distribution of: • Tablet • Tablet film coated

	• Capsule hard • Pellets • Meter dose aerosols Toxic or hazardous products, β-Lactams, cytotoxic drugs, hormones and steroids were not being manufactured at the site.
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, API's, natural products and Research Centre • Patalganga: FPPs, APIs and Research Centre • Kurkumbh: FPPs, APIs and Research Centre • Goa: FPPs • Baddi: FPPs • Sikkim: FPPs • Indore: FPPs • Vikhroli: Research Centre
History	The site was last inspected by WHO in February 2012. The site has also been inspected by the following regulatory authorities: • TFDA (Tanzania Food & Drugs Administration) – November 2008 • Medicinal Control Council, South Africa May 2009 • DACA, Ethiopia - December 2009 • NDA, Uganda: o May 2010 o May 2013 • TGA, Australia: o September 2010 o January 2014 o November 2015 • Medicine Control Authority of Zimbabwe: o December 2010 o August 2014 • Indian Food & Drugs Administration: o September 2006 o February 2009 o April 2011 o December 2013 o April 2015

	• MOH of Kenya:
	  o July 2011
	  o September 2015
	• MOH of Cambodia - November 2011
	• MOH of United Arab Emirates - May 2015
	• MOH of Ivory Coast - October 2015
	• MOH of Malawi - March 2016
	• MOH of Republic of Sudan:
	  o October 2010
	  o November 2015

Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Inspection covered oral solid dosage forms production, and quality control of: • Tablet • Tablet film coated
Restrictions	N/A
Out of scope	Block 16: Unit II, Lozenges was not inspected
WHO product numbers covered by the inspection	• HA 060 Lamivudine/Zidovudine Tablet, Film-coated 150mg/300mg • MA 064 Artemether/Lumefantrine Tablet 20mg/120mg • MA 120 Artemether/Lumefantrine Tablet 40mg/240mg • MA 121 Artemether/Lumefantrine Tablet 60mg/360mg • MA 122 Artemether/Lumefantrine Tablet 80mg/480mg

Abbreviations	AHU	air handling unit
	API	active pharmaceutical ingredient
	BDL	below detection limit
	BMR	batch manufacturing record
	BPR	batch packaging record
	CAPA	corrective actions and preventive actions
	CC	change control
	CFU	colony-forming unit
	CoA	certificate of analysis
	CpK	process capability index
	DQ	design qualification
	EM	environmental monitoring
	FAT	factory acceptance test
	FBD	fluid bed dryer

	FMEA	failure modes and effects analysis
	FPP	finished pharmaceutical product
	FTA	fault tree analysis
	FTIR	Fourier transform infrared spectrometer
	GC	gas chromatograph
	GMP	good manufacturing practice
	HACCP	hazard analysis and critical control points
	HPLC	high-performance liquid chromatograph
	HVAC	heating, ventilation and air conditioning
	IR	infrared spectrophotometer
	IQ	installation qualification
	KF	Karl Fisher
	LAF	laminar air flow
	LoD	limit of detection
	LOD	loss on drying
	MB	microbiology
	MF	master formulae
	MR	management review
	NMR	nuclear magnetic resonance spectroscopy
	NRA	national regulatory agency
	OQ	operational qualification
	PHA	process Hazard Analysis
	PM	preventive maintenance
	PpK	process performance index
	PQ	performance qualification
	PQR	product quality review
	PQS	pharmaceutical quality system
	QRM	quality risk management
	RA	risk assessment
	SOP	standard operating procedure
	TAMC	total aerobic microbial count
	TFC	total fungi count
	TLC	thin layer chromatography
	URS	user requirements specifications
	UV	ultraviolet-visible spectrophotometer

PART 2

Brief summary of the findings and recommendations

1. Pharmaceutical quality system

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

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 preparation of PQRs was managed in an annual schedule.

The PQR XXXX was discussed.

Management review (MR)

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

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.

The deviation procedure was found comprehensive detailing functional roles, operational roles and responsibilities of personal required investigating deviations. The procedure defined deviations as unplanned in that were unexpected events that resulted in a departure from the approved procedure, document or established standard 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.
The deviation logs were available for 2015 and 2016.

The deviation XXXX was 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, PQR, 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.

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, millieu/mother nature, measurement, machine and method).

Change control (CC)
The SOP "Change request", 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

The change control logs for years 2015 (June-December) and 2016 were available.

2. Good manufacturing practices 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. 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.

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.

Validation schedule for 2016 was presented to the inspectors. Periodic re-validation of finished products was carried out: at least one batch in three years.

Qualification

Qualification policy was specified in the VMP.

Process validation

VMP specifies that in case of change of source of API validation should be carried out for three consecutive batches. A specific process validation report was discussed.

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.

Swab and rinse samples were collected for all cleaning validation studies.

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.

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.

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.

Temperature mapping

The SOP "Temperature (T) and relative humidity (RH) distribution study" was discussed.

"Validation report for room Temperature and relative humidity study" XXXX was discussed. T&RH were recorded every minute for 7 continuous days in loaded conditions.

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.

Complaints trending was carried out 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.

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 authorization 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.

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.

7. Contract production, analysis and other activities

The SOP "Selection, evaluation and approval of contract testing laboratory" was discussed. List of approved contract laboratories was presented to the inspectors. Contract laboratories audits were coordinated by the CQA. According to the SOP each contract laboratory should be audit every 2 years.

Quality agreement with laundry service provider was discussed.

Consultants

The SOP "Service of consultants" was discussed. Consultants CVs were evaluated by the corporate senior management/site management. Criterions for selecting consultants were specified in the SOP.

8. Self-inspection, quality audits and suppliers' audits and approval

The SOP "Self inspection" and schedule for 2016 were discussed. Spot checks showed that schedule was followed.

Self-inspections were classified as:

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

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.

Items for self-inspection

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

- Quality system
- Production system
- Facility and equipment system
- Laboratory control system
- Materials system
- Packaging and labelling system

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.

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. 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.

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.

The organizational charts were available and discussed.

Job descriptions

Job descriptions were available for all personnel.

The job description of Unit Head (Unit 1) was discussed.

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. 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.

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.

Analyst training certificates were issued for each test.

11. Personal hygiene

Changing and washing followed a written procedure. The protective closing washing operations followed standard operating procedures. To enter the production section operators had to worn "boiler suits", head covers and factory footwear. 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.

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. Airlock doors were interlocked. Premises were cleaned and disinfected according to written procedures.

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. The warehouses were situated in the ground floor of the Building 4.

In the raw materials warehouse the received materials were stored first in the quarantine until sampling, testing and release in the SAP system. The approved materials were then moved to the approved warehouse.

Sampling areas

The sampling booths were under the supervision of QC, also responsible for cleaning.

Weighing areas

There were XX dispensing booths used for raw materials. The dispending was performed by the warehouse personnel under the control of production.

The SOP “Dispensing of active pharmaceutical ingredients and excipients”, SOP “Cleaning and line clearance of dispensing/sampling area” and SOP “Accessories cleaning” were discussed.

The SOP “Dispensing of packaging material” was discussed.
Sampling and dispensing tools were cleaned in the washing rooms. PW was used for the final rinse of the tools; compressed air and lint free cloth were used for tools drying.

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.

The SOP "Cleaning 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

The SOP was supplemented with detailed photos. Cleaning procedure was done according to the check list what was the part of the BMR/BPR.

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

Quality control 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.

13. 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.

The SOP "Analytical balance Model: "XX" was discussed.

Daily verification of balances was carried out using minimum and maximum weights. The following items were checked during monthly calibration:

- Linearity
- Accuracy
- Repeatability
- Sensitivity
- Eccentricity

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 "Cleaning of equipment during production on campaign basis" was discussed. This SOP specified equipment cleaning frequency: maximum allowed lots of working days.

The SOP "Equipment cleaning compression machine model XX" 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

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

The SOP "Cleaning of bins" was discussed. Cleaning procedure explained the following cleaning scenarios:

- Batch to batch
- Product to product

Metal detectors were installed on all compression 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.

Preventive maintenance (PM)

Major production and laboratory equipment were subject to planned preventive maintenance

The SOP "Planned preventive maintenance" was discussed. Equipment was categorized and PM frequency specified taking into account impact and severity.

PM was carried out: weekly/monthly/bi-monthly/quarterly/four months/6 monthly/annually.

The maintenance activities were summarized in "Annual PM Planners". Annual PM Planner of the compression area equipment for year 2016 was discussed.

The SOP "PM of compression machine", check list and PM planned were checked. Spot checks showed that planner was followed.

Calibration
The SOP "Qualification of equipment" was discussed. The SOP was applicable to equipment which were directly used in the manufacturing, packaging, dispensing and storage or used for supporting the production activities, for example HVAC system, compressed air, water system etc.

The SOP "Calibration" was discussed. The SOP specified calibration intervals for measuring systems, instruments, testing equipment and process control equipment.

The SOP "Qualification of analytical instruments and equipment" was discussed. The SOP explained new equipment and instruments qualification and re-qualification criterions.

Calibration schedules for QCL instruments and production instruments were checked. Spot checks showed that schedules were followed.

The qualification/re-qualification protocols and records of AHU XX and AHU YY were discussed.

Purified Water (PW)
The water system was regularly monitored by a sampling program covering all the user points.

The recent tests results (microbiology and chemical) of the user point XX were available in the LIMS system and discussed.

The microbiology sampling and testing was supported by the following SOPs:
- Water system monitoring
- Microbiology schedules
- User manual of environment and water monitoring in LIMS.

Compressed air (CA)
Not inspected

14. 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. 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.

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.

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

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.

The SOP "Reprocessing / reworking of batch" and flow chart were discussed. 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.

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.

Separate line clearance check lists were used for:

- Raw materials
- Primary packaging materials
- Secondary packaging materials

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. WS were qualified against the official RS. According to the SOP substance selected for qualification as a WS should have assay more than 99.5% and less impurities content. WSs were dispensed in the single use vials under the LAF cabinet located in the QC laboratory. WSs were used for assay, identification and impurities tests.

Working Standards (WS) and Reference Standards (RS) were available and mainly stored in cooling incubators at 2-8 °C. Hygroscopic standards and standards, for which storage conditions were specified as room temperature, were stored in desiccators. WS dispensed under the LAF in amber glass vials for single use. Usage of standards was documented. Standards inventory was electronically maintained. Traceability of standards was ensured.

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

Waste materials

Not inspected

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.

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. Finished goods codes were 8 digit codes generated sequentially on client level.

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.

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.

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.

16. 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 checked by workshop QA once per shift 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.

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.

Materials to the shifting, blending, granulation and coating cubicles were delivered via double door pass boxes. Each shifting, granulation and coating cubicle had individual equipment washing/drying rooms.

Packaging operations
Before packaging operations begins, 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.

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.

The analytical instruments were operated and the data processed by validated software's. In case of chromatographs the Chromeleon and LIMS was used.

The users and user privileges were defined in SOP and administered by the corporate IT.

The SOP "Good chromatography practices" was discussed. Manual integration policy was defined in the SOP "Integration of chromatographic data".

The SOP "Password policy for software in quality control" 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" 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.

Class "A" volumetric glassware was used.

The analytical instruments were qualified, calibrated and maintained regularly.

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.

The SOP "Functions and responsibilities of laboratory quality assurance" was discussed.

Analytical records review

The SOP "Receipt, registration and testing of samples" was discussed. The SOP was applicable for all samples analyzed (raw materials, APIs, packaging materials, finished products, intermediate products, stability samples etc.) in quality control laboratory (QCL).

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 ºC ± 2 ºC, RH 75% ± 5% (1 chamber)

and for long term:

- T 25 ºC ± 2 ºC, RH 60% ± 5% (2 chambers)
- T 30 ºC ± 2 ºC, RH 75% ± 5% (1 chamber)
- T 30 ºC ± 2 ºC, RH 65% ± 5% (2 chambers)

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.

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" with 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.

Separate SOP "Investigation of aberrations in microbiological test results" was available for microbial tests.

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. Trending of laboratory incidents was carried out once in four months.

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.

The investigation records of OOS XX and YY were discussed.

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.

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)

Microbial tests were carried out in two rooms 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 sterilization 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 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 and water for injection. 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.

Action and alert limits were. Trends for 2015 were discussed, trends were presented as graphs.

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. Tests results were trended monthly, six monthly and yearly.

Alert and action limits for tablet manufacturing area 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, what 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., Cipla Ltd, Unit 1, PO Bhud, Upper Malpur Village, Tehsil, Nalagarh, Solan District, Himanchal Pradesh, 173 205, India was considered to be operating at an acceptable level of compliance with WHO good manufacturing practices for pharmaceutical products.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

PART 5

List of GMP guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report* Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

2. WHO good manufacturing practices for active pharmaceutical ingredients. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report.* Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2.
   http://www.who.int/medicines/publications/44threport/en/

3. WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report*. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

4. WHO guidelines for sampling of pharmaceutical products and related materials. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

6. Supplementary guidelines on good manufacturing practices: validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4 http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Control Laboratories. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 1. http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report* Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3 http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report* Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines for drafting a site master file. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

16. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

17. WHO General guidance on hold-time studies *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report* Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

21. Guidance on good data and record management practices. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf