

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
of the FPP manufacturer**

Part 1: General information about the inspection

Name of manufacturer	Meditab Specialities Pvt. Ltd.
Physical /postal address	J-4/2 Additional MIDC, Satara 415004, Maharashtra, India
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of: Non-sterile medicinal products: oral liquids (syrops, solutions and suspensions) and nasal inhalers
Focus of inspection	Oral solutions and oral suspension for treatment of HIV
Scope and type of inspection	Routine inspection, covering all aspects of GMP
Date of inspection:	10 – 13 March 2014

Part 2: Summary

General information about the company and site

Meditab Specialities is a Pvt. Ltd. Company established in year 1998 and the company is managed by professional board of directors. Meditab is 100% subsidiary company of Cipla Ltd.

Meditab has three manufacturing facilities located at:

- Satara
- Goa
- Daman

At Satara location, non-sterile oral liquids and nasal inhaler formulations were manufactured. Nasal inhalers were manufactured as Ayurvedic formulation; according to the company, a single Ayurvedic product was in production.

The corporate headquarters including Corporate QA were located at Mumbai.

According to Meditab's SMF, the site is located in non-chemical industrial zone. The site is at a distance of about 275 Kms from Mumbai.

The pharmaceutical manufacturing activities at Satara are licensed by the Food & Drugs Administration (FDA) of the Maharashtra State, India.

The products manufactured at the site were of two categories: Allopathic category and Ayurvedic category, and the facility for manufacturing these was divided into two separate areas as demonstrated on the floor plan, with separate ventilation systems.

The products manufactured were of non-toxic and non-hazardous nature. The Ayurvedic product contains volatile oils.

Besides WHO prequalified products, the product list included a number of preparations for relieving pain, symptoms of respiratory tract diseases, and an anti-depressant.

Background information

The total number of employees engaged on the site for Production, Engineering, QC/QA, Stores and Distribution were 142 employees.

Cipla central warehouse was used for distribution of medicinal products.

History of WHO or regulatory agencies inspections

The site was previously inspected by WHO inspection team on 11th to 15th September 2008 and 19th to 22nd April 2011.

Meditab had been audited and approved by various National & International Authorities including, but not limited to:

- MHRA (Medicines and Healthcare Products Regulatory Agency), UK:
- TGA (Therapeutic Goods Administration), Australia:
- MCC (Medicines Control Council), Republic of South Africa:
- The State Institute for Drug Control, Slovak Republic

The site was periodically inspected by Central Drugs Standard Control Organization and State Licensing Authority (Maharashtra) India.

Focus of the inspection

The inspection focused on the production and control of the prequalified products listed above.

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. Apart from some site-specific exceptions, written procedures used by Meditab followed Cipla Corporate SOPs and documents were copies of those SOPs.

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. There was a system for Quality Risk Management (QRM). Product quality reviews (called Annual Product Quality Review) were conducted for domestic market and export products.

PQR (Annual Product Quality Review)

APQR reports were prepared annually. The company had a schedule with product specific reporting periods. “Schedule for PQR preparation” also indicated customers, i.e. it was possible to identify whether the product had been produced for different customers (which also meant different product abbreviations).

The SOP “Annual product quality review (APQR)” was spot checked. It contained all parameters according to the current GMP requirements. The company correctly continued to comprise PQRs even if no new batches had been produced during the PQR period. PQRs were prepared until the batches were still within shelf-life and until the new data of on-going stability studies were generated.

PQRs provided sufficient overview. Open items from previous PQRs e.g. on-going changes were transferred to subsequent PQRs. No deviations were reported in these two PQRs. Yields did not raise concerns.

Quality Risk Management (QRM)

The SOP “Risk Management by Failure Mode Effects and Critical Analysis” was spot checked. 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 presented to the inspectors. Spot checks showed that the schedule was followed.

Risk Assessment (RA) files contained the following documents:

- Justification for selection of FMECA
- Actual RA
- Risk communication
 - Risk review
 - RA conclusion

For FMECA analysis 1-5 scoring system was used to specify severity, occurrence and detection.

The SOP “Root cause analysis” was spot checked. The SOP was applicable to all non-conformances as e.g. out of specifications (OOS), out of trends (OOT), deviations and complaints. The SOPs were applicable 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. Schedule for RA by FMECA for 2014 was presented to the inspectors.

Management review:

The SOP “Quality management review (QMR)” was spot checked. Quality Management Team (QMT) existed of team members from every department. QMR was conducted on a quarterly basis. QMR was also based on but not limited to the SOP “Quality Management System”.

The QMR report October to December 2013 was spot checked.

The following trends were attached to the MR:

- Complaints
- Deviations
- Out of specifications (OOS)/Out of trends (OOT)

Change control (CC)

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

Separate CC logs were maintained for:

- Document
- Facility
- Product
- System
- Equipment
- Others

Changes were classified as:

- Major
- Moderate
- Minor

The SOP specified that open change controls (pending for closure) were reviewed once in two months and reason for change being open was recorded in the log. Spot checks confirmed that CCs 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.

Deviation handling

The SOP “Deviation handling” and flow chart were spot checked. Deviations were categorized as planned and unplanned and classified as:

- Major - should be closed in 15 calendar days
- Minor - should be closed in 30 calendar days
- Repetitive deviations – were investigated and closed in specified time based on the classification i.e. Major OR Minor.

The deviation procedure was checked and found comprehensive detailing functional roles, operational roles and responsibilities of personnel involved in investigating deviations. The procedure defined deviations as unplanned cases of unexpected events that resulted in a departure from the approved procedure, document or established standard. 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.

Deviation registers for 2013 and 2014 were checked.

Deviations were trended and trends presented to the inspectors.

Corrective actions and preventive actions (CAPA)

The SOP “Corrective and preventive actions (CAPA)” and flow chart were spot 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 SOP “Cleaning of mixing cubicle” was checked. This described critical and non-critical areas. Critical being described as the area where there is a chance that the product is exposed and non-critical where there was very little chance of exposure. The facility cleaning procedure stipulated how to clean various items in the cubicle.

The SOP “Preparation, usage, storage and destruction of disinfectant, cleaning and deactivation solution” was spot checked. The SOP specified disinfectant solutions, cleaning solutions and deactivating solutions and how to prepare those solutions. Changeover of disinfectants was specified for the first fortnight and second fortnight.

The SOP “Disinfectants, cleaning agents and deactivating solutions” was spot checked. 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 of 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), version 08. Oral liquids process verification schedule was specified as at least one batch in two years. Process validation schedule for 2014 was shown to the inspectors.

Cleaning validation

Cleaning validation was performed and controlled under Cipla 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”. Frequency of re-validation of cleaning was established as 5 years, unless new equipment was purchased, in such situation a new assessment for worst case was conducted and depending on the result, a full validation (3 batches etc) or “verification” (1 batch) was performed.

Cleaning re-validation was planned for 2014.

Processing equipment, including process pipelines were made of SS. Large mixing tanks and holding tanks were cleaned as Clean in Place (CIP). Cleaning solution was prepared in the tank, tanks were provided with spray-balls; all other process equipment was cleaned manually (smaller vessels, sieves, mills etc.), including process pipelines (dismantled for cleaning). Cleaning of the filling equipment was not checked.

Separate validations had been conducted for separate units of process equipment train. Cleaning validation of three units of equipment was checked; all these units were cleaned manually. Each validation included 3 consecutive batches. Validations had been conducted in 2009-2010. Validation reports identified cleaning SOP versions and cleaning personnel (different operators for different batches), captured the results and conclusions, and were approved by QA.

Manufacturing vessel cleaning validation protocol/report was checked. Cleaning validation was performed on 3 consecutive batches.

Product transfer pipeline and in-line colloid mill cleaning validation protocols/reports were also spot checked.

Sampling plans were established and followed. It was noted that validation protocols prepared for future validations included also photos of sampling locations. The sampling methods used were both rinse water and surface swabs. Swab recovery studies were performed for stainless steel and demonstrated between 90% - 110% for most samples.

Chemical and microbiological analysis was undertaken and all complied with acceptance criteria.

Equipment Qualification

The Validation Master Plan for 2014 was reviewed. This was a schedule based on spread sheet with the years plotted out against the required validation activities. Equipment requalification period was established as not more than 5 years

The performance verification (PV) for cleaned equipment for filter press was checked. The clean equipment hold time was established not more than 7 days.

The schedule for periodic requalification of equipment was shown to the inspectors. The schedule indicated dates of completed qualification/requalification and requalification due dates. Spot checks confirmed that the schedule was followed.

Production equipment qualification

Filter press qualification.

The qualification file contained the following sections:

- User Requirement Specifications
- Design Qualification
- Factory Acceptance Test
- Equipment Qualification

- o Installation Qualification
- o Operational Qualification

Laboratory equipment qualification

Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) report Dissolution tester was spot checked. IQ, QO and PQ were done by analyst and approved by QC laboratory section head. The qualification file contained the following sections:

- User requirement specification
- User acceptance test
- Reinstallation qualification
- IQ
- OQ
- PQ

Standards used for equipment calibration along with certificates of analysis were shown to the inspectors.

Equipment maintenance was carried out yearly by contractors.

HVAC qualification

AHU 17 was installed to supply air to the bulk storage area and air lock no 1. The following tests were carried out for the Performance Verification:

- Installed HEPA filter integrity test
- Air velocity and air changes per hour
- Fresh air
- Return air quantity
- Duct leakage
- Clean up study
- Particle counts at rest and in operation
- Microbial count

T and RH studies were carried out once in 3 years and air flow pattern tests once in two years.

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

Process Validation

Concurrent validation was applied to scale-up of production capacity and commercializing. Mixing and filling were classified as critical process stages. Approved holding time for final bulk was established as 7 days.

2.5 COMPLAINTS

The handling of complaints was described in 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 Cipla Corporate QA. They logged, categorized and forwarded the complaints to the responsible site for evaluation. The investigation had to be performed within 30 day. A report was sent to the Cipla Corporate QA as a response after evaluation of the complaint. Cipla Corporate QA was responsible to give an answer to the customer.

There were separate complaint logs for export and local market. Complaints trend reports for the period July 2013 to December 2013 was spot checked.

2.5 PRODUCT RECALLS

The recall procedure was described in the SOP. The procedure was applicable to all drug products manufactured for local and export markets. Meditab sent their products to Cipla central warehouse for distribution. Management of recalls was the responsibility of Cipla 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:

- A (critical)
- B (major)
- C (minor)

Dummy recalls were carried by out by Cipla CQA, where also a schedule for recall procedure validation was kept for all Cipla sites and subsidiaries, including Meditab. Latest dummy recall involving Meditab product had been conducted in 2013. In the dummy recall, Meditab had the duty to identify the product and maintain communications with Cipla CQA. Dummy recall documentation was available at Meditab. In case of a real recall, Meditab would be responsible for investigations.

2.6 CONTRACT PRODUCTION AND ANALYSIS

The company stated that production was not outsourced.

Contract laboratories were used for certain tests for raw materials. The laboratories had official national approvals (Government level system related to general methods/equipment). Equipment available at the laboratories was known to Meditab. It was also explained that before outsourcing analytical testing related to medicinal products, certain approval must be obtained from national authority.

Apart from analytical testing, other activities were outsourced, e.g.:

- Pest and rodent control
- Calibration
- Factory garments laundry

Contracts with the two laboratories and the laundry company were checked. Contracts had been updated in 2013, they were laid out in a similar format, responsibilities were defined, and subcontracting was not allowed without consent from Meditab.

The laundry company had committed to wash Meditab's garments separately and ensure further separation by production departments; list of detergents was part of the contract.

Audits had been conducted and recorded; auditing and approval were managed by Cipla Corporate QA, Meditab personnel participated in audits.

2.8. SELF INSPECTION, QUALITY AUDITS AND SUPPLIERS' AUDITS AND APPROVAL

Self-inspections were performed routinely. The SOP "Self inspection", and schedule for 2013 and 2014 was spot checked. Self-inspection was carried out using check lists. The procedure contained detailed instructions for the qualification and training of the auditors as well as the preparation, performance and follow up of self-inspections. According to the schedule, all the areas were inspected 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 2013 and 2014 (till the date of inspection) had been completed as planned.

The documents in regard to a randomly selected self-inspection performed were available. Only the availability, no content was checked.

Audit team selection was the responsibility of QA.

Supplier management was organized and performed (including audits and approval) on Cipla Corporate level. Meditab used the corporate electronic database (web-based programme) for active ingredients and excipients, and paper based documentation for packaging materials suppliers.

According to Cipla procedures, API and primary packing materials manufacturers/vendors audits were carried out every 3 years, inactive starting materials audits were carried out every 4 years.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. 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, including staff on responsible positions to the level of operator (production) and analyst (laboratory).

The following Job descriptions were checked:

- Unit Quality Assurance head
- QA officer
- Production head
- Section head - Raw material – analytical group
- Production officer

Persons responsible in absence were specified in respective Job descriptions.

2.10 TRAINING

The SOP “Training” and training flow chart was spot 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 method.

Temporary workers were involved in secondary packaging. Temporary workers competency list was showed to the inspectors. Training was given by production officer and certified by Unit QA head. Training evaluation was done orally and by practical performance.

2.11 PERSONAL HYGIENE

The SOP “Personal health and hygiene” was spot checked.

According to the SOP, personnel should wear clean clothing suitable for the manufacturing activities and avoid direct contact with intermediates or finished products. 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 once in a year and as when required.

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. 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. Raw materials and printed packaging materials in the warehouse were stored in mobile racks and on pallets. Separate sampling areas were provided for APIs, inactive materials and packaging materials.

Weighing areas

Separate dispensing areas were used for inactive materials, for APIs and for primary packaging materials. Dispensing was carried out under laminar air flow conditions, except for secondary packaging materials.

Production areas

Production steps were sufficiently separated. The processing and in-process storage space did permit the orderly positioning of equipment and materials so as to minimize the risk of contamination 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.

The production area was established on two floors – the ground floor was called “tankage area”, the floor above it was called “operations area”.

Production areas were ventilated, with air-control facilities 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 were designed and laid out so as to avoid mix-ups or cross-contamination. The production areas were well lit.

Quality control areas

QC laboratories 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.

2.14 EQUIPMENT

Filling lines were called „mono-block” - comprising filling, sealing, stoppering. All production equipment was multi-use. WHO prequalified products could be processed and filled on any of the production lines.

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.

The SOP “Calibration and maintenance of analytical instruments/equipment” was spot checked.

The SOP “Calibration” was spot checked. The SOP was applicable to all measuring systems, instruments, testing equipment and process control equipment.

Production equipment calibration

Calibration SOP followed Cipla Corporate SOP. The schedule and tracking was maintained in an electronic database. A selected printout was checked; spot checks confirmed that the schedule was followed. Calibration was outsourced to a company with relevant national approval. Calibration documentation was checked for:

- Purified Water (PW) conductivity meter
- PW temperature sensor (on return)
- Production vessel
- Production vessel temperature sensor.

Calibration records and certificates contained sufficient data; reference instruments were identified and their certificates available. Meditab’s personnel were attending calibrations works and QA signed calibration acceptance certificates.

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

The SOP “Preventive maintenance procedure” and PM planner were spot checked. According to the SOP separate PM SOPs should be prepared for all equipment/instruments used for processing, testing and utilities. The SOP “Preventive maintenance of manufacturing vessels” and PM check list for manufacturing vessels were spot checked. According to the SOP PM of manufacturing vessels should be carried out once per month. Spot checks confirmed that PM planner was followed.

Computerized systems

GMP-related computerized systems 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

Utilities

HVAC system

A number of air handling units (AHU) were installed to supply air to warehouse, production and Quality Control (QC) laboratory facilities. During inspection attention was paid to AHUs No 10 and 19. The air supplied by these AHUs passed through the filter cascade:

- G4 (for the fresh air and returned air)
- F10
- EU 8
- H13

HEPA filters were installed in the plenum. Pressure differentials between filters were monitored daily. Filters were labelled and labels indicated cleaning date and cleaning due date. G4 and F7 filters were cleaned in the separate filters cleaning room. Filters were cleaned by using potable water and dried by using filtered compressed air. The SOP “Cleaning of air filter” was spot checked.

Pressure differentials between rooms were recorded manually. At the time of the inspection pressure differentials as shown by Magnehelics were within the established limits.

Purified Water (PW)

PW used in production was generated using RO and EDI at the final stages. Water was continuously circulated at ambient temperature. A calibrated flow meter was installed in the return loop. Conductivity was monitored online. PW system was sanitized weekly using hot water - not less than 85 °C at the return to the PW storage tank. Sanitization SOP gave instructions and also covered pump switch-over. PW system sanitization records were presented to the inspectors.

It was demonstrated on the diagram that the PW loop did not pass through the production area for Ayurvedic products.

PW sampling/trends

There were sufficient sampling points to monitor PW distribution. On random checks, PW testing results (chemical and microbial – total aerobic counts) were within specified limits, action and alert limits were specified and sampling schedule was followed.

Compressed air

Oil free compressors were used to generate compressed air. The compressed air was also used for product contact, e.g. for drying bottles. Compressors were located in a technical area; the air was filtered at user points.

Validation of compressed air was conducted annually. It included tests for oil, water, different gases, microbial contamination (Pinocchio air sampler). The latest validation report from August 2013 was checked, the required tests had been recorded and it had been concluded that the system was under control.

2.13 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.

Temperature and Relative Humidity distribution studies were carried out.

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

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 were 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.

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 SOP “Sampling” was spot checked. For sampling primary packaging materials and printed packaging materials, 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 LAF conditions.

Intermediate and bulk products

Not inspected in detail. Specifications were stipulated for final bulk, each batch was tested in QC at the bulk stage.

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 Cipla finished good warehouse located at Mumbai and Pune.

Rejected, recovered, reprocessed and reworked materials

Separate room was provided for storage of rejected materials and products, if any.

Recalled products and Returned goods

Till the date of inspection no products had been recalled.

Separate room was provided for storage of recalled and returned products, if any.

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 upon receiving of media. pH was checked after media sterilization.

Reference standards

Official reference standards were used as well as working reference standards prepared by the manufacturer. Reference standards were supplied by Cipla; Meditab conducted dispensing of working standards. Reference standards were properly labeled and stored.

Standards, standard solutions, working standards (WS) and chemical reference standards (RS) used for calibration of equipment 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.

The “Procedure for standard operating procedure” included instructions regarding the format, approval, distribution of copies (issuance record was kept, QA was responsible to exchange the copies, when new was 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 bulk and finished products.

Master formulae

Authorized master formulae were 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.

In production of bulk, critical times and temperatures were recorded. Entries were complete and signed off by personnel involved. Yield calculations were recorded after relevant process 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 utilities, such as the water systems. In general it complied with the guidelines on preparation of the SMF.

2.16 GOOD PRACTICES IN PRODUCTION

Production processes were not complex *per se*. Processes were well established. 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.

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 “Sampling”, “Receipt, registration and testing of samples”, “Reserve samples”, “Handling & Disposal of Quality control samples”, “Quality control of Raw materials, APIs & Excipients”, “Quality control of packaging materials” and “Quality control of finished products (drug products)”. 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. Glassware was cleaned using washing machine and dried at 60° C, volumetric glassware were dried in Infra-Red drying cabinet.

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

Batch release procedure included review by the QC; respective check-list was in use.

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

The SOP “Out of Specifications and Out of Trend investigation procedure” and flow diagram were spot checked. This procedure was based on FDA guidelines. The procedure was also applicable to bulk products and to stability testing.

OOS logs/registers and OOT logs/registers of 2012 and 2013 in chemical testing were checked.

Microbiology laboratory used out-of-alert and out-of-action limits for environmental monitoring and purified water. Respective logs/registers were kept. The company stated that no out-of-action results had occurred for several years.

In addition to OOS and OOT, a concept of analytical incidents was used. The SOP “Analytical Incidences investigation and resolution procedure” was spot checked. This procedure was not applicable for OOS and OOT results.

Incidents were trended; trend reports for 2012 and 2013 (chemical testing) were checked. Corrective actions were part of the trend reports.

OOS results had to be reported to Cipla Corporate QA. Incidents were managed within the site.

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 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. RS and WS were received from Cipla corporate.

Traceability of standards was ensured.

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

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.

Walk-in stability chambers were located in the QC unit. The access to the stability chambers was restricted. Stability chambers were connected to the software and in case of power failure, alarm was triggered. T and RH in the chambers were continuously monitored and recorded every 10 minutes. Printouts were taken every morning and checked.

The testing schedule and withdrawal (pull-out) time limits had been followed. Results for all established time-points, as applicable at the present, were reported. Established time points were: 0, 6, 12, 18, 24, 30 and 36 months. Duration of study was shelf-life 24 months plus 1 year. The scope of testing was adequate, including for example quantitative testing of related substances (single maximum impurity, total impurities) and preservatives, efficacy of antimicrobial preservation, viscosity. Raw data for CP2011 at 6 months' time point were randomly checked, no comments were made. The company had not obtained OOTs or OOSs. Some variability was noticed in the assay results, the company considered this to be normal variability for the product and method.

If a product receives an approval for extension of shelf-life, the company applies its general rule for on-going studies – shelf-life plus 1 year – based on the shelf-life assigned to a batch at the time of release.

Electronic data

SOP “Integration of chromatographic data” was spot 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. It was explained that till the date of inspection MI had not been used.

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

Microbiological laboratory

Media used was 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 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 Cipla corporate in cryovials. Cultures were cultivated to maximum four passages.

Loading patterns for the sterilisation of media were defined. The autoclave for media preparation was qualified and the sterilising process validated. Autoclave validation was outsourced. “Full validation” period was 2 years; within this period “verification” was stipulated in the procedures, involving one cycle of maximum load. Latest validation report from April 2012 for maximum load was checked. A sufficient number of thermocouples had been used, several of them inserted in simulated media.

Microbiological testing was done for each batch of finished product.

Waste from the microbiological laboratory was autoclaved in a dedicated, separate autoclave for 30 minutes and discarded.

Environmental monitoring

The SOP “Microbiological monitoring of environment in production area” was spot checked. Environmental monitoring (EM) was carried out using settle plates and active air sampling for fungi and aerobic bacteria. Settle plates were exposed for 1 hour. 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.

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 procedure “Database review of in-house isolates” for finished product, raw material, PW, potable water and compressed air were available and spot checked.

Validation of analytical methods

SOP “Validation and verification of analytical methods” was spot 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

Analytical method transfer

SOP “Transfer of analytical methods” was spot 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.

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, Meditab Specialities Pvt.Ltd. located at J-4/2 Addl. MIDC, Satara 415004, 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.