

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Cipla Ltd, Baddi
Unit	No 1
Physical address	Village Upper Malpur, P.O. Bhud, Tehsil Nalagarh, District Solan, Himachal Pradesh 173205, India
Postal address	As above
Telephone number	+91-1795 246051, +91-1795 246045
Fax number	+91-1795 246052
Summary of activities of manufacturer (e.g. manufacturing, packing).	Manufacturing, quality control and batch release of FPP: solid oral dosage forms (uncoated/coated tablets, hard gelatin capsules, pellets), metered dose inhalers and lozenges
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number	Prequalified product: - MA064: Artemether / Lumefantrine Tablets 20/120mg - HA 060: Lamivudine / Zidovudine tablets 150/300mg - HA267: Triomune 30 Tablets - HA352: Efavirenz Tablets 600mg - HA365: Lamivudine / Zidovudine and Nevirapine tablets 150 mg / 300 mg / 200 mg
Scope and type of inspection	Routine inspection, covering all aspects of GMP
Date of inspection:	27 - 29 February 2012
Project (if any):	Prequalification of Medicines Programme

Part 2: Summary

General information about the company and site

The facility inspected was Cipla Ltd, located at village Malpur, P. O. Bhud, Tehsil Nalagarh, District Solan, Himachal Pradesh 173205, INDIA, hereafter called Cipla Baddi. According to the Site Master File, Cipla Ltd has Corporate Headquarters in Mumbai Central, Mumbai 400008 India, plus manufacturing facilities and Research centres in the following locations:

1. Bangalore: FPPs, APIs, natural products and Research Centre
2. Patalganga: FPPs, APIs and Research Centre
3. Kurkumb: FPPs, APIs and Research Centre
4. Goa: FPPs
5. Baddi: FPPs
6. Sikkim: FPPs
7. Indore SEZ: FPPs
8. Vikhroli: Research Centre

The plant employed a total of 740 people.

History of WHO or regulatory agencies inspections

This was the second time the site of Cipla Baddi was being inspected by the WHO team. Previously the Baddi site was inspected by WHO in March 2009.

The manufacturing facility was licensed by the Drug Controlling Licensing Authority, Himachal Pradesh to manufacture solid dosage forms (Uncoated, Film Coated Tablets, Hard Gelatin Capsules and Pellets) and Inhalers (Pressurized Metered dose Inhalers).

According to the company presentation, the site was approved by the Tanzania Food & Drugs Administration, Medicinal Control Council; South Africa, Drug Administration and Control Authority, Ethiopia, National Drug Authority, Uganda, Department of Health and Ageing Therapeutic Goods Administration Australia and National Medicines & Poisons Board Secretariat General Republic of Sudan. It was also ISO 14001:2004 and ISO 18001:2007 certified.

Focus of the inspection

The inspection focused on the production and control of **HA352**: Efavirenz Tablets 600mg, **HA267**: Triomune 30 Tablets, **MA064**: Artemether / Lumefantrine Tablets 20/120mg, **HA 060**: Lamivudine and Zidovudine tablets 150/300mg, **HA365**: Lamivudine, Zidovudine and Nevirapine tablets 150 mg / 300 mg / 200 mg.

The inspection covered all the sections of the WHO good manufacturing practices: main principles for pharmaceutical products guideline, including quality assurance, premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control, utilities, manufacture and transfer of technology.

Inspected Areas

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

2.1 QUALITY ASSURANCE

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

Product Quality Review (PQR)

PQR reports were prepared annually. The first reporting period started from the month when the first batch was manufactured.

PQR for two products were reviewed.

Tabulated and graphical presentations of trends were available and were presented to the inspector. Trends were available for:

- API from different vendors
- Excipients
- Primary packaging materials

PQR was performed of acceptable standard.

Quality Risk Management (QRM)

QRM was implemented. Failure mode and effect criticality analysis (FMECA) were used for risk assessment.

9 FMECA studies were carried out in 2012 and 18 FMECA studies were carried out in 2011.

QRM was performed of acceptable standard.

Change control

The SOP on change control was spot-checked. Changes were classified as:

- Major change
- Minor change

The following types of changes were identified:

- Facility
- System
- Document
- Product

Change control trends were available and presented to the inspector.

Different types of changes were recorded in separate, monthly logs.

Monthly review practice for all change controls was introduced. A reason was given in case a change control was not closed out. A number of change controls reports were spot-checked.

Change control was performed of acceptable standard.

Deviation handling

The SOP on deviation handling was spot-checked.

Deviations were classified as:

- Planned
- Unplanned
- Major
- Minor
- Repetitive

Specific deviation reports were spot-checked. Root cause analyses were carried out by the company.

Deviation management was performed of acceptable standard.

Corrective actions and preventive actions (CAPA)

Standard Operating Procedure (SOP) for CAPA was spot-checked. CAPAs were reviewed periodically by the CAPA team. Implementation was approved by the Unit QA.

CAPAs 6 month review (trends) from 1 July 2011 to 31 December 2011 were available, were presented to the inspector and were spot-checked. No observations were made.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were 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.

Clean areas were cleaned frequently in accordance with an approved written programme and SOPs. Microbial monitoring was regularly undertaken.

2.4 QUALIFICATION AND VALIDATION

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

Cleaning validation

Worst case approach (solubility and potency) was used for the cleaning validation studies. Swab and rinse samples and microbial swabs were taken and analyzed.

Cleaning validation was carried out for the following surfaces:

- SS
- Acrylic
- Silicon
- PVC

Specific equipment cleaning validation report was spot-checked. Swab recovery was established. Equipment drawings showing the worst cleaning spots - difficult to access and clean were part of the validation report. Total equipment surfaces were calculated and calculations were available for major/critical production equipment.

Equipment Qualification

Electronic Multi-Channel Counter machine Design Qualification, Installation Qualification, Operational Qualification and Performance Qualification protocols and reports were available and presented to the inspector and the Performance Qualification report was spot-checked. Qualification was performed of acceptable standard.

2.5 COMPLAINTS

Complaints and other information concerning potentially defective products were reviewed according to written procedure and the corrective actions were taken. Complaints concerning a product defect were recorded and investigated. Attention was paid to establishing whether a complaint was caused because of counterfeiting. Consideration was given to whether other batches should be checked in order to

determine whether they were also affected. Decisions made and measures taken as a result of a complaint were referenced to the corresponding batch records

Complaint log for 2011 and specific complaint was spot-checked. Trends were carried out on periodic basis. Trends were available and presented to the inspector.

Complaints management was of acceptable standard.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was reviewed. The authorized person responsible for the execution and coordination of recalls was designated. . Till the date of inspection there was not product recall carried out.

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

Recalls management was of acceptable standard.

2.7 CONTRACT PRODUCTION AND ANALYSIS

The following activities were contracted out:

- Specific quality control laboratory tests
- Pest and rodent control
- Qualification of HVAC system
- T mapping
- Measuring equipment calibration
- Factory garments laundry

SOP audit of contract laboratory was spot-checked. Contract laboratories have been audited periodically. Five contract laboratories had been used. Specific contract was reviewed in details and conclusion was made that the contract was written following GMP guidelines. Contract laboratories were audited by CQA.

Contracts with pest controlling service provider, laundry service provider, calibration and validation service provider and laundry service provider audit report were spot-checked.

Reviewed contracts were of acceptable standard.

2.8 SELF INSPECTION AND QUALITY AUDIT

Self-inspections were performed routinely. The frequency at which self-inspections were conducted was stated in the procedure - A report was made at the completion of a self-inspection.

Self-inspection was carried out according to check lists. Observations were classified as:

- Critical
- Major
- Minor

Trends were carried out periodically, were available and were presented to the inspector. CAPAs were proposed and implementation was checked.

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

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

Self-inspection and approval of suppliers were of acceptable standard.

2.9 PERSONNEL

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

2.10 TRAINING

Training was provided in accordance with a written programme for personnel whose duties take them into manufacturing areas or into control laboratories.

The following types of training were identified:

- Factory induction programmer
- On the job training
- Scheduled and ongoing trainings
- Training of documents and changes
- Miscellaneous training

Training effectiveness was evaluated by questionnaires with objective and descriptive questions.

List of 25 training modules was presented. Some of training modules, like Hygiene and general GMP questionnaires were available in local language.

Specific personnel training files were reviewed. Training sessions were properly recorded and evaluated.

All training files were kept by QA. Certifications for work performances also were carried out by QA.

All analysts had to undergo validation for all certain tests they were certified to carry out.

Specific analyst personal validation protocol “Assay by HPLC” was spot-checked. Training was carried out of acceptable standard.

2.11 PERSONAL HYGIENE

Personnel employed received initial and regular training. Periodic health checks were carried out. Changing and washing followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. Smoking, eating, drinking, chewing, keeping plants, food, drinks, smoking material and personal medicines was not permitted in production, laboratory and storage areas. Wrist-watches, cosmetics and jewelry were not being worn in clean areas. The protective closing washing operations followed standard operating procedures. High performance of personnel hygiene was observed during the inspection.

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 did not open simultaneously.

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

The SOP for usage and cleaning of sampling room (active ingredient) and SOP usage of sanitising kit were spot-checked. No observations were made.

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. All materials in the warehouse were stored in mobile racks. Separate sampling areas were provided for APIs, inactive materials, liquids and packaging materials sampling.

Weighing areas

Dispensing was carried out in five dispensing areas. Two dispensing areas were used for APIs sampling, two for inactive materials sampling and one for liquids sampling.

Quality control (QC) areas

QC laboratories were separated from 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.

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

2.13 EQUIPMENT

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Production equipment was cleaned on a scheduled basis. Laboratory equipment and instruments were suitable for the testing procedures undertaken.

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

Preventive maintenance (PM) SOP for production equipment and annual PM planned schedule for 2012 was spot-checked. On spot-checks presented PM schedule was followed. Equipment had separate PM SOPs and check lists.

The SOP on calibration and maintenance of analytical instruments / equipment and calibration schedule (in house) for 2012 was spot-checked. On spot checks, presented schedule was followed.

The SOP on calibration for engineering instruments and instrument annual calibration schedule for 2012 was spot-checked. On spot-checks, the presented schedule was followed.

Extensive HVAC systems were installed, with separate AHUs. Each unit contained appropriate filters, finishing with a 0.3 micron HEPA filter in manufacturing areas. The system appeared well constructed and controlled.

Purified water was produced by passing potable water through softener, followed RO +EDI. Purified water was continuously circulated in a stainless steel loop at ambient temperature. Tank and loop were routinely sanitised. The system appeared well constructed and controlled.

The compressed air system was not inspected.

2.14 MATERIALS

Incoming 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.

Temperature and Relative Humidity distribution studies were carried out for all materials storage areas, stability chambers, incubators and refrigerators. Stability chambers, incubators and refrigerators were equipped with alarm system and T was recorded continuously using 4 T sensors. Data-logger printouts were checked every day.

The SOP on temperature (T) and relative humidity (RH) distribution study validation report for released materials area was spot-checked. Data loggers were used for T and RH recording. Data-loggers printouts and graphical presentation was available and presented to the inspector.

Starting materials

Starting materials were purchased from approved suppliers. Approved suppliers lists for starting materials (active and inactive) and packaging materials were available. For each consignment, the containers were checked for integrity of package and seal. Damage to containers and any other problem that might adversely affect the quality of a material recorded and reported to the QA department. Check-lists were used for materials receipt.

There were appropriate procedures in place to ensure the identity of the contents of each container of API. Bulk containers from which samples were drawn were identified. No observations were made.

Packaging materials

Packaging materials were purchased from approved suppliers. Printed packaging materials were stored in secure conditions. Each delivery of batch of printed or primary packaging material was given a specific reference number. No observations were made.

Intermediate and bulk products

Not inspected.

Finished products

Finished products were held in quarantine until their final release, and stored under conditions established by the manufacturer. No observations were made.

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were stored separately. No observations were made.

Recalled products

Recalled products were stored in designated storage area. No observations were made.

Returned goods

Returned goods were stored separately in a secure area. No observations were made.

Reagents and culture media

Records for the receipt and preparation of reagents and culture media were available. Reagents made up in the laboratory were prepared according to written procedures and appropriately labelled. Growth promotion tests were applied to verify the suitability of culture media each time they were prepared and used and upon receiving of media. Medias were prepared and sterilized following manufacturers instructions. pH was checked after media sterilization. No observations were made.

Reference standards

Official reference standards were used as well as working reference standards prepared by the manufacturer. Working standards were certified by the application of appropriate tests to ensure standardization. Reference standards were properly labeled and stored. Working standards were dispensed in 50 amber vials for individual use. No observations were made.

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.

Labels

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

Specifications and testing procedures

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

Master formulae

Formally authorized master formulas were available.

Master batch manufacturing record for specific product was spot-checked. No observations were made.

Packaging instructions

Authorized packaging instructions were provided for each product.

Batch processing records

Batch manufacturing records (BMRs) were kept 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 packaging records

A batch packaging record (BPR) was kept for each batch processed. 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.

BMR and BPR together with related analytical tests data sheets were stored for defined period.

BMR and BPR for specific product were spot-checked. No observations were made.

Standard operating procedures and records

SOPs and associated records of actions taken were available.

Assessment of the Site Master File

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

2.16 GOOD PRACTICES IN PRODUCTION

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

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

Packaging operations

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

2.17 GOOD PRACTICES IN QUALITY CONTROL

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

Control of starting materials and intermediate, bulk and finished products

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

The sampling SOP was spot-checked.

100 % sampling was carried out for ID test. Inactive starting materials which were not approved by WHO for reduced sampling were 100 % sampled for ID test.

AQL was applied for sampling of primary and secondary packaging materials.

Test requirements

Starting and packaging materials

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

In-process control

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

Finished products

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

Batch record review

QC records were reviewed as part of the approval process of batch release. Retention samples from each batch of finished product as well as related documents were kept for defined period. Finished products were kept in their final packaging and stored under the recommended conditions. Samples of active starting materials were retained for defined period. Retention samples of materials and products were of a size sufficient to permit two full re-examinations. Retention samples were stored under appropriate conditions.

The following documents related to specific product release were reviewed:

- Analytical test report
- Test data sheet (software Calculation sheet)
- Test data sheet (blank observation sheet)
- Chromatograms
- Check list for review of analytical report
- CoA

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

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

OOS and OOT SOP, flow chart and trends were spot-checked. SOP was written following US FDA guideline. CAPAs were proposed and very well implemented. Specific OOS investigation report was spot-checked.

Significant effort was made by CQA to avoid OOSs and OOTs caused by using wrong volumetric flasks and pipettes. Additional nonstandard size volumetric flasks and pipettes were ordered and received from the glassware manufacturer and introduced in practice.

Stability studies

The quality and stability of finished pharmaceutical product were evaluated. Expiry dates and shelf-life specifications were established on the basis of stability tests related to storage conditions. A written programme for ongoing stability determination was developed and implemented.

Stability and on-going stability samples were stored properly. Temperature in the incubators was continuously monitored. Incubators were equipped with alarm system.

Microbiological laboratory

The SOP for microbial air monitoring and trends for 2011 was spot-checked. Action and alert limits were specified. Environmental isolates were identified.

The SOP for sampling and monitoring of purified water and trends for 2011 were spot-checked. Action and alert limits were specified.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection listed in the Inspection Report, Cipla Ltd, Baddi (Unit No1) located at Village Upper Malpur, P.O. Bhud, Tehsil Nalagarh, District Solan, Himachal Pradesh 173205, India, was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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