

**Prequalification of Medicines Programme**  
**WHO PUBLIC INSPECTION REPORT**  
**Finished Product Manufacturer**

**Part 1: General information**

Name of Manufacturer	Cipla Ltd India
Unit number	<b>Units III, IV and VII</b>
Production Block	n/a
Physical address	Verna Industrial Estate Verna, Salcette, Goa 403 722 India.
Contact person and email address.	Mr. D. Singh dsingh@cipla.com
Date of inspection	2010-09-06 to 2010-09-09
Type of inspection	Re-inspection
Dosage forms(s) included in the inspection	OSDs, creams and ointments
WHO product numbers covered by the inspection	<i>Unit III:</i> Acyclovir 5% cream (HA048) <i>Units III, IV, VII (interchangeable):</i> Nevirapine 200 mg tablets (HA039), Lamivudine 150 mg tablets (HA043), Zidovudine 300 mg tablets (HA051), Duovir (HA060), Duovir-N tablets (HA365), Efavirenz 200 mg capsules (USFDA) and 600 mg tablets (HA352). Lamivudine & stavudine tablets for oral suspension (HA353 and HA354), Levofloxacin 250 mg tablets (TB205), Emtricitabine capsules (HA418)
Summary of the activities performed by the manufacturer	Production and control

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

Cipla Ltd has eight manufacturing facilities in India which are located in Bangalore, Baddi, Goa, Kurkumbh, Patalganga, Sikkim, Bommasandra and Indore. At the Goa site, the company

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employs about 2309 people in the areas of quality assurance, production, quality control, storage and distribution. Manufacturing was started at the Goa site in 2000 - 2001.

### ***History of WHO and/or regulatory agency inspections***

The Goa site had been previously inspected by several agencies including the USFDA, TGA (Australia), MCC (South Africa), MHRA (UK) and WHO (Geneva - prequalification programme), ANVISA (Brazil). The last WHO inspections were performed in August 2007 and August 2009 (data verification inspection for HA043, 049, 053, 039, 200, 210, 267, 275, 276, 60 and IN001).

### ***Focus of the inspection***

This inspection was planned as a routine GMP re-inspection of Units III, IV and VII. As about 3 years had elapsed since the last complete inspections of these units, a full re-inspection was performed. Specific focus was also placed on general compliance with GMPs for the production and control of WHO products being manufactured at the time of inspection. Other products covered by this inspection included some recently prequalified products like tablets, tablets for oral suspension, cream and capsule that were still in the process of being prequalified. This inspection also focussed on the confirmation of the equivalency and interchangeability of Units III, IV, VII, as this had been the object of recent variation applications that had been accepted on the basis of information from previous inspections and on documentary evidence.

### ***Inspected Areas***

On the first day of the inspection, the company made a presentation during which the layout of the different Units was explained. Unit III was used for tablets (coated & uncoated) as well as topical preparations (creams & ointments), Unit IV was used for tablets and hard shell capsules, while Unit VII was used for tablets and hard shell capsules. Both wet granulation and dry granulation approaches were used for manufacturing tablets and capsules.

The different Units at Cipla Goa were inspected about 7-8 times per year by different regulatory authorities.

Recent changes to Units III, IV and VII were presented, such as the upgrading of machinery (e.g., higher speed Fette tablet compression machines), new packaging machines (e.g., new blister packing machines) and an upgrading of the QC practices in Unit III and Unit IV. In Unit VII, there had been an expansion of the manufacturing areas (granulation and tablet compression areas) completed this year. All these changes had been qualified and all new equipment and new processing areas were now fully operational.

Each Unit had its own separate warehouse, QC laboratory and purified water system. However, the steam and compressed air used in Unit III and Unit IV was piped from a central utilities location.

In accordance with the tentative inspection plan, the quality system, quality management, quality policies, validation master plan and product quality review (done annually) were reviewed.

Other documents reviewed include:

- Site Master File.
- Change Control SOP (Version No. 21, Effective date 04.09.2010).
- Risk Management and Failure Mode and Effect Analysis ( FMEA ) SOP was reviewed (CQA-246, version No. 05, dated 14.07.2009).
- SOP for Deviation Handling (CQA-51, version No. 26, dated 13.03.2010).
- SOP for Product Quality Review (SOP No. CQA-97, version 17).
- Change control for changes to the analytical testing of the API (change control No. LD/CD/09/07/216).
- Change Control Log for documents (Annexure CQA-06/06).
- Change control documents for several WHO prequalified products.

Floor plans were examined (Annexure EP-044/A2) for Unit VII in preparation for the actual inspection of that Unit. This was followed by the examination of the schematic plans for the utilities (purified water and HVAC).

Inspectors then proceeded to the visit of Unit VII where the following areas were inspected:

- Receipt;
- Warehousing areas for starting and packaging materials (this also included the 2-8°C refrigerated store room;
- Sampling rooms (separate sampling rooms for actives and excipients);
- Dispensing rooms (separate dispensing rooms for actives and excipients);
- Manufacturing areas for floor 1, followed by manufacturing areas for floor 2;
- Purified water production room.

## **Day 2**

On the second day, after the inspectors had provided a summary of the observations from day 1, the company provided evidence of corrective actions relating to some of the observations raised on day 1.

The inspection of Unit VII was continued from day 1. Areas covered in Unit VII included sifting, manufacturing I (granulation with blending), in-process storage, in-process quality control, tools room, FBD bags storage, compression, packaging, finished product stores and utilities (HVAC and purified water) as well as the QC laboratory. Various documents were reviewed including complaints, CAPA, self inspection, deviations, planned preventive maintenance, area verification and AHU qualification (MSL02), schematic drawings and source data in validation and qualification.

The compressed air area for all units was also inspected on this day.

The next inspected Unit was Unit III, where the focus was placed mainly on the manufacture of Acyclovir 5% cream.

### **Day 3**

At the start of day 3, the company was provided with a summary of the observations arising from day 2.

Inspectors then proceeded to inspect the following areas:

- QC Unit III;
- Microbiology Unit II;
- Retention store Unit IV;
- Production areas Unit IV;
- HVAC Unit IV.

### **Day 4**

At the start of day 4 the company was provided with a summary of the observations arising from day 3.

The inspectors then proceeded to the inspection of the QC laboratory of Unit IV as well as other areas.

At the QC laboratory, various aspects of practices in quality control were quickly reviewed. Emphasis was placed on the retention samples storage area, which was checked for traceability by selecting a batch of interest and requesting that its location in the stores be shown. The calibration of the GC apparatus used for residual solvent testing was examined and was found to be adequate.

The inspectors then proceeded to the review of the documentation that had been requested on day 3. This included the following:

- Training records of the staff that was cleaning the HVAC pre-filters;
- Confirmation that the air compressors were oil-free (by looking at the engineering drawings), the quality of the compressed air as well as the certificate from the manufacturers of the air compressors;
- Consultation of the dissolution SOP EOP C001 entitled Dissolution Test Apparatus, Version No. 02;
- Verification of the adequacy of the SOP for HPLC testing with regards to the requirements for time in between the injection of system suitability standards for long runs (e.g., 80 min);
- Training of production officer who performed IPC counting of tablets;
- Verification of airflow patterns at Unit III and VII (especially because of the extension of part of Unit VII could de-balance the other areas); Qualification of the AHUs and airflow in the new part of Unit VII;
- Validation of the automatic rejection system of the blister packaging line;
- Complaints SOP (CQA-37, Version 22, Effective 29.06.2010);
- Complaint log for Unit IV for the period 16.02.2010 to July 2010;

- SOP for root cause analysis related to a complaint;
- Complaint investigation report for a randomly selected product;
- Recall procedure (CQA-32, effective date 05.03.2010);
- Pest control SOP;
- Technology transfer SOP No. CQA-05 and technology transfer report for HA365, as an example. Comparative dissolution profiles were also reviewed. Interchangeability for WHO products, SOP No. MT-624, dated 06.09.2010, was presented. It should be noted that this is a new SOP.
- Blank master production documents for the 600,000 batch size (CL/LA245/003/A./01). They were compared to those for the 110,000 batch size.
- Vendor audits and supplier approvals the supplier of foil as an example;
- Evaluation and Approval of Manufacturer SOP CQA-28, effective date 20.07.2010;
- SOP entitled "Audit of contract laboratory", SOP No. CQA-39, effective date 28.08.2010, version No. 10;
- Shanghai Desano early audit report, 10.10. 2007;
- Compressed air filter documents for the 1.0 micron filter, 0.1 micron filter (0.20AA coalescing filter);
- Training SOP entitled "Personnel Training", No. MT-384, issued on 18.12.2007;
- Training records (QA Head Unit VII);
- Questionnaire that was used to assess the training of a production officer on FMEA;
- Cleaning validation reports and protocols for the equipment that will be used to manufacture the commercial production batches of acyclovir 5%;
- Documentation related to 4 air compressors being used at the plant;
- AQL SOP Lidding Peelable Foil/ Lidding Foil was examined for level II;
- Qualification of Granulation area II of Unit III (Formal DQ and IQ);
- SOP for the Cleaning of Utensils (SOP CQA-254);
- SOP for qualification of blister reject unit;
- Microbiological testing results for excipients, purified water and monitoring of the environment revealed consistently acceptable results, which were trended;
- Testing performed on the food grade oil which was used to lubricate tablet tooling;
- Validation report for unit III;
- List of staff given training in relation to the updated SOP No. CQA-06 for change control;
- List of all products manufactured in 2010 and their respective number of batches;
- CAPA SOP, CQA-251, effective date 5.05.2010, along with its annexure. This was followed by consulting the list of CAPAs for year 2010 as well as some selected CAPAs.

## **2.1 QUALITY ASSURANCE**

Cipla had a documentation infrastructure consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance.

Based on the specific aspects reviewed in this inspection, it was considered that the system of quality assurance in the manufacturing units was appropriate to the manufacture of pharmaceutical products in that:

- (a) pharmaceutical products were generally designed and developed in a way that took account of the requirements of GMP;
- (b) production and control operations were generally clearly specified in a written form and GMP requirements were generally adopted;
- (c) managerial responsibilities were clearly specified in job descriptions checked;
- (d) arrangements were generally made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations were generally carried out;
- (f) satisfactory arrangements were in place to ensure, as far as possible, that the pharmaceutical products were stored by the manufacturer, in a manner so that quality was maintained;
- (g) there was a procedure for self-inspection and/or quality audit that regularly appraised the effectiveness and applicability of the quality assurance system;
- (h) deviations were generally reported, investigated and recorded;
- (i) there was a system for approving changes that may have an impact on product quality (change control);
- (j) regular evaluations of the quality of pharmaceutical products checked were conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

Cipla assumed responsibility for the quality of the pharmaceutical products to ensure that they were fit for their intended use, and complied with the requirements of the product dossier. Senior management was involved other staff in different departments at different levels within the company were committed to quality.

There was a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. This was documented and its effectiveness monitored. All parts of the quality assurance system were adequately staffed with competent personnel, generally suitable and sufficient premises, equipment, and facilities.

## **2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS**

As noted during the last inspections, the practices in the company provided assurance that products were consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product dossiers.

In general, manufacturing processes were clearly defined, systematically reviewed, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications.

Qualification and validation was performed where necessary. The necessary resources were available, including:

- (i) qualified and trained personnel;
- (ii) premises and space;
- (iii) suitable equipment and services;

- (iv) appropriate materials, containers and labels;
- (v) approved procedures and instructions;
- (vi) suitable storage and transport; and
- (vii) adequate personnel, laboratories and equipment for in-process controls.

Instructions and procedures were generally written in clear and unambiguous language, specifically applicable to the facilities provided. Operators were trained to carry out procedures correctly. Records were prepared during operations (production and quality control) providing documented evidence that all the steps required by the defined procedures and instructions were taken. Deviations were generally recorded and investigated. An appropriate history of batches was made, with only few exceptions. Materials and products were generally stored in accordance with their storage conditions with minimal risk to their quality.

### **2.3 SANITATION AND HYGIENE**

A high level of sanitation and hygiene was generally observed on site. The scope of sanitation and hygiene covered personnel, premises, equipment etc. An integrated, comprehensive programme of sanitation and hygiene was in place.

### **2.4 QUALIFICATION AND VALIDATION**

As found in the previous inspection, the company had a validation policy and programme described in a validation master plan. Key elements of qualification and validation were identified. There was documented evidence that the premises, supporting utilities, equipment and processes were subjected to design qualification, installation qualification, operational qualification and performance qualification where relevant. This was verified for selected areas, equipment and utilities. Process validation was also inspected for the above mentioned products and considered generally acceptable. Qualification and validation protocols and reports were reviewed during the inspection. Cleaning validation was in place and considered to be acceptable.

### **2.5 COMPLAINTS**

A procedure was in place, and followed, for the handling of complaints. Complaints about marketed products received (and selected for review in the inspection) were investigated, the cause investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

### **2.6 PRODUCT RECALLS**

An acceptable procedure was in place in order to initiate and handle recalls.

### **2.7 CONTRACT PRODUCTION AND ANALYSIS**

No contract manufacturing was carried out by the company. Acceptable contract agreements were in place for any analytical testing carried out by external laboratories. These laboratories

were audited every two years using a pre-prepared check-list. However, this check-list did not include a check that analytical method validation was acceptable to the company.

## **2.8 SELF INSPECTION AND QUALITY AUDIT**

The self-inspection programme was designed to detect any shortcomings in the implementation of GMP on site. A procedure and program for self inspection was in place and implemented. The team responsible for self-inspection consisted of personnel who could evaluate the implementation of GMP objectively. Reports were available following self inspections. There was a follow up system in place including reporting to management.

## **2.9 PERSONNEL**

The company had a sufficient number of qualified, experienced personnel to carry out the tasks for which it was responsible. Individual responsibilities were defined and recorded as written descriptions. Personnel interviewed and records checked reflected that they were aware of the principles of GMP. Unauthorized people were prevented from entering production, storage and quality control areas. Key posts for key personnel were occupied by full-time personnel. The heads of production and quality control were independent of each other.

## **2.10 TRAINING**

Personnel interviewed and records checked reflected that they received initial and continuing training. The SOP and programme for training as well as selected records for individuals were reviewed and inspected and considered to be acceptable. The training programme for casual staff required attention.

## **2.11 PERSONAL HYGIENE**

A high level of personal hygiene was observed in general by all concerned with manufacturing processes. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product at the time of inspection. Clean, protective clothing was worn by all persons entering production areas.

## **2.12 PREMISES**

The premises was generally located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of premises minimized the risk of errors and permitted effective cleaning and maintenance. Suitable measures were taken to avoid cross-contamination and facilitate cleaning in dust generating areas (e.g. weighing). Electrical supply, lighting, temperature, humidity and ventilation was in general appropriate for manufacture and storage of materials and products, and functioning of equipment. The premises were generally designed to ensure the logical flow of materials and personnel.

## **2.13 EQUIPMENT**

Equipment was generally located, installed, designed, constructed, adapted, and maintained to suit the operations to be carried out. The design of equipment made it possible to effectively clean and maintain these to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products. Equipment and instruments of an appropriate range and precision, suitably calibrated, were available for production and control operations.

## **2.14 MATERIALS**

Materials, including starting materials, packaging materials, solvents, process aids, reagents, labelling materials, cleaning, and lubrication were of a suitable grade and specification. All incoming materials were generally suitably controlled (quarantined, sampled, tested, released or rejected as relevant). The handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution was done in accordance with written procedures and, where necessary, recorded.

## **2.15 DOCUMENTATION**

The documents inspected were generally suitably designed, prepared, reviewed and distributed. Specifications and batch documents inspected were appropriate. All documents were approved, signed and dated.

## **2.16 GOOD PRACTICES IN PRODUCTION**

Production operations followed defined, written procedures and specifications. Deviations were recorded and handled in accordance with an approved procedure. Checks on yields and reconciliation of quantities were carried out. In general, materials, bulk containers, major items of equipment, rooms and packaging lines being used were labelled. In-process controls were performed. Controls were in place to prevent cross-contamination and contamination.

## **2.17 GOOD PRACTICES IN QUALITY CONTROL**

The quality control laboratories were suitably designed and equipped for the operations carried out.

There were adequate facilities, trained personnel and approved procedures for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and for monitoring environmental conditions (microbiology lab).

Qualification, calibration and validation was performed, records were maintained and deviations and Out of specification results were recorded and investigated.

## **2.18 UTILITIES**

The purified water systems were suitably designed, maintained, calibrated and monitored. Sampling and testing of water was done on a routine basis and results were satisfactory.

The HVAC systems were suitably designed. AHUs were installed and qualification activities were acceptable.

### **Part 3: Conclusion**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, reflected in the observations listed in the inspection report, **Cipla Ltd Units III, IV and VII**, located in Verna, Goa, India, are considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

The observations (non-compliances with guidelines) listed in the full inspection report were addressed by the company in a timely manner. The manufacturer responded to all observations and for each included a description of the corrective action implemented or planned to be implemented, and the date of completion or target date for completion. The corrective actions were assessed through evaluation of the response to each observation, were found to be acceptable and will be followed up during the next inspection which should be done within 3 years.

**Part 4: References**

1. *Quality Assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection.* World Health Organization, Geneva, 2007  
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2. WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report.* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 3  
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4. Supplementary 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. Fortieth Report.* Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 2  
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