

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

**Part 1: General information**

Name of Manufacturer	Cipla Ltd India
Unit number	Indore SEZ
Production Block	I and IV
Physical address	Plot 9& 10 , Pithampur, Indore, India
Contact person and email address.	Mr D Singh dsingh@cipla.com
Date of inspection	2010-08-16 to 2010-08-19
Type of inspection	Routine (new)
Dosage forms(s) included in the inspection	OSD and syrups (Unit I and Unit IV)
WHO product numbers covered by the inspection	Duovir N (HA365) and Lamivudine oral solution 50 mg/5 ml (HA053) (Variation applications: additional manufacturing site)
Summary of the activities performed by the manufacturer	Production and control

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

Cipla Ltd is a public limited company established in 1935. It is managed by a board of directors. It manufactures a range of APIs and FPPs. The corporate head office is located in Mumbai central. The manufacturing sites are located in various states in India.

Cipla Ltd India Indore SEZ was located on plot 9, 10 and 15 of the Indore SEZ Phase II, Pithampur, district Dhar in Madhya Pradesh.

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

Cipla has been inspected several times by WHO and various Drug regulatory Authorities. However this site in Indore is new - and this was the first inspection by an international team of inspectors.

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

The inspection focused on the production and control of tablets (Unit IV) and syrups (Unit I). The inspection covered various sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities. The inspection was done as applications for variations had been received to include this site as an additional manufacturing location for Cipla products.

### ***Inspected Areas***

On arrival, the inspectors were met by company representatives and were taken to the board room.

The inspectors started with an opening meeting and explained the procedures of the prequalification programme briefly. The inspectors further introduced themselves. This was followed by an introduction of representatives from the company. The company then made a presentation of the site located in ISEZ Pharma zone Phase II.

This Cipla site was located on plot 9, 10 and 15. Activities included plot 9 (FFS, PFS and aerosols), plot 10 - tablets. Eye drops, nasal and prefilled syringes. (This means mainly Unit I - FFS, eye drops, respules, LVP; Unit II - aerosol; Unit III - PFS, eye drops and nasal preparations and Unit IV- OSD (Tablets, Effervescent tabs, Pellets, HGC).

The tentative plan for day 1 was as follows:

<b>Day 1</b>		
Morning	<b>Opening meeting</b> <ul style="list-style-type: none"> <li>• Introductions</li> <li>• Attendance Record</li> <li>• Confirmation of scope of inspection and inspection plan</li> <li>• Company overview and presentation (about 15 minutes)</li> <li>• Description of manufacturing and product range</li> </ul>	
	<b>Personnel</b> <ul style="list-style-type: none"> <li>• Organization Chart</li> <li>• Job descriptions for key personnel</li> <li>• Training procedures and records</li> </ul> <b>Buildings and Facilities</b> <ul style="list-style-type: none"> <li>• Design and construction</li> <li>• Site layout</li> <li>• Personnel and material flow</li> </ul>	

	Lunch	
Afternoon	<b>Quality Management</b> <ul style="list-style-type: none"> <li>• Product Quality Review</li> <li>• Complaints</li> <li>• Recalls</li> <li>• Deviation control</li> <li>• Change control</li> <li>• Contract agreements</li> <li>• Supplier approval / qualification</li> <li>• Document Control</li> <li>• Self inspection</li> <li>• Batch document preparation, flow charts</li> </ul>	
	Summary of the observations of the day	

The inspectors started by reviewing the documentation relating to the quality system. These included:

- The organization charts
- Job descriptions
  - Production responsible Unit IV (training needs identified, not continued training)
  - Unit head - Unit IV
  - QA
  - QC
- CQA-62 (other duties of production)
- SOP and registers for
  - Complaints
  - Recalls
  - Deviation control
  - Change control
    - Change control (P10/05/009)
  - Reprocessing/reworking
  - Utilization of recoveries
- CQA 246 Risk management
- CQA 308
- Training record on risk assessment (FMEA) for two employees
- FMEA for bottle pack
- Mock recall of 2009
- Contracts with contract laboratories (2 labs were checked)
- Self inspection
- Root cause identification for a shaft break down in Unit II

The day was ended by giving feed back on the observation made during the course of the day.

The tentative inspection plan for day 2 was as follows:

<b>Day 2</b>		
Morning	<b>Engineering &amp; Services:</b> <ul style="list-style-type: none"> <li>• Preventive Maintenance</li> <li>• Calibration</li> </ul> <b>HVAC</b> <ul style="list-style-type: none"> <li>• Design &amp; construction including documentation</li> <li>• Operation and maintenance</li> <li>• IQ/OQ/PQ</li> <li>• Monitoring and testing</li> </ul> <b>Water for Pharmaceutical use</b> <ul style="list-style-type: none"> <li>• Design &amp; construction including documentation</li> <li>• Operation and maintenance</li> <li>• IQ/OQ/PQ</li> <li>• Monitoring and testing</li> </ul>	
	Lunch	
Afternoon	<b>On site inspection (Utilities and Production)</b>  <b>Warehouse(s) and Production</b> <ul style="list-style-type: none"> <li>• Receipt, handling and storage</li> <li>• Materials and finished products</li> <li>• Sampling</li> <li>• Weighing/dispensing/issuing</li> </ul>	
	Summary of observations for the day	

After arrival on the second day, the company was given the summary of the day's goals for inspection (AHU's, Water system, passivation, etc...SOP for the calibration schedule, the SOP for the sampling of water, testing of the water, trends for the qualification of the water system, in accordance with the inspection plan that had originally been sent to the company).

The company was reminded that inspectors would like to see the SOP for product quality review.

#### Areas examined during the day

The inspectors reviewed documents related to material and personnel flow, area classification, HVAC ducting, pressure cascading and related documentation. This included:  
 -Floor plans showing classification of each area, material movement, personnel movement, air pressure mapping for the ground floors, 1<sup>st</sup> and 2<sup>nd</sup> floors of Unit IV. HVAC systems, water systems were also examined for Unit IV.

It was noted that there were three floors in unit IV. Warehouses, sampling and dispensing areas, canteen facilities, change rooms and offices were located on the ground floor. Production (including packaging) took place on the first floor and quality control and technical area with provision for packaging were located on the second floor.

There were three sampling areas (2 for excipients, one for active pharmaceutical ingredients), and 4 dispensing areas (one dedicated for APIs). One sampling area and one dispensing area were not in use.

In many cases, the pressure differentials were not monitored. When asked why, the company stated that this is because manometers simply had not been installed. Company representatives claimed that adequate studies were performed using smoke tests. This was not an acceptable explanation because it only insures air flow direction. The change room 218 connected directly to airlock 217 and this was the only change room for some of the manufacturing areas, hence posed an issue.

The company was asked how ingress was prevented and if any pressure gage was showing the pressure of the facility relative to the atmosphere. No clear answer could be provided at the time. (It was later explained that this was monitored on the service floor).

They then inspected the protocol and report for qualification (e.g. DQ, IQ and PQ) of AHU 37 servicing the granulation area (granulation 3) which further included sifting, granulation and drying. They verified data relating to particle counting, air volume and air exchange rate and verified the schematic drawing of the AHU, and selected component installation verification, calibration and some calculations.

After lunch, they inspected the warehouse including SOPs, records and related documents for receiving of materials, staging, cleaning, environmental monitoring, sampling, quarantine area, released material area, and the dispensing area. The usage and cleaning logs for areas were inspected including balances and other equipment / instrument calibration records.

The following areas were inspected:

-Receiving: the unloading bay was examined from room PT002 (receipt). Company representatives and operators were asked if different shipments were ever received at the same time and loaded on the same pallets at the same time. They replied that this was not the case, mainly because the plant was not producing at full capacity but that if this was ever to happen, a physical separation would be used to reduce the risk of any mix-up. The SOP CQA/517 (issued 16.06.2010) was examined and the operator was found to be knowledgeable on that SOP. The cleanliness of the area was found to be acceptable and was maintained for 7 days. The pallets used inside as well as outside were initially said to be cleaned across the facility, which could pose a contamination risk as this would mean bringing the dirty/contaminated pallets across a corridor adjacent to other areas. It was later explained that pallets used outside were cleaned by "mopping" (not inside the facility). The SOP has been provided and fund which is accepted after review.

Operators present described the procedure used for cleaning the room and for use/cleaning of the vacuum cleaner. The SOP and associated logbook (CQA86, version 09) were examined and found to be up to date, but the earliest record dated only from July 2010. The cleanliness status of the vacuum cleaner was clearly identified and was verified by opening and examining the filter and pipes.

-Warehouse: The approved and quarantine stores were examined (with an emphasis on excipients and active pharmaceutical ingredients that were stored in sections F7/F8). Temperature mapping results were requested.

-Sampling: Operators present stated that the ULAF was turned on 30 min prior to sampling. Procedure for sampling was examined. An operator was asked to confirm how the sample size and containers to be sampled were determined. The n plan was used for excipients (not in WHO products) but not for APIs.

-Dispensing Area: The cleaning status was found to be maintained for 7 days, as cleaning was performed every 7 days on a regular basis. Reading on the S015 balance was examined and appeared to be unstable when the ULAF system was turned on. A missing screw was visible on the adjacent panel. Butterfly screws were used to maintain the panel in place, which was not considered to be an acceptable practice because this could lead to the accumulation of dust and particles. The operator was interviewed and adequate training on SOP's was verified. The set of calibrated standard weights that was used to calibrate the 20g-120 kg capacity balance was also verified to be readily available, complete and in good condition.

Documents requested for the next day included:

- schematic diagram for the FBD & air handler
- water system documents (SOP for the sampling of water, etc...)

The day was ended by giving feed back on the observation made during the course of the day.

The tentative inspection plan for day 3 was as follows:

<b>Day 3</b>		
Morning	<b>Validation and qualification:</b> <ul style="list-style-type: none"> <li>• Validation Master Plan</li> <li>• Validation and qualification status (matrix) and schedule</li> <li>• Equipment qualification</li> <li>• Process validation</li> <li>• Cleaning validation</li> <li>• Computer validation</li> </ul>	
	Lunch	
Afternoon	<b>Production</b> (On site inspection continues) <ul style="list-style-type: none"> <li>• Production (tablets and capsules)</li> </ul> <b>Documentation review</b> <ul style="list-style-type: none"> <li>• Transfer of Technology</li> <li>• Finished product release and distribution</li> <li>• Batch record review</li> </ul>	
	Summary of observations for the day	

On the third day, the inspectors started the inspection by reviewing the water purification system documentation. This included the:

- Schematic diagram
- Slope diagram and calculations
- Trend results for Phase I and II of loop 1 user point 12 and 14
- Matrix for qualification and validation
- IQ of FBD T/036 (December 2010)
- Cleaning validation -unit IV including the determination of the worst case, cleaning validation protocol and report for the sifter
  - SOP for cleaning
  - Recovery study
  - Limits for micro contamination on contact surfaces
  - Calculation of equipment surface area for cleaning validation purposes
  - Verification of the equipment use and clean log versus the BMR FD0011
  - Sampling procedures
  - Template
  - Detergent used
  - LOQ

The inspectors then inspected the stores area for packaging materials. This included an inspection of the premises, sampling area, dispensing area, primary and secondary packaging storage, quarantine, under test and released material areas. Some related SOPs and records were inspected on site. During the on site inspection, the knowledge and experience of some operators were challenged on the tasks they were responsible for.

After a lunch break, they reviewed some documents requested in the morning (further to the cleaning validation) such as the chromatograms, and sample preparation. The inspectors then went to Unit IV again to inspect the production area. The focus was put mainly on the areas related to the production of tablets. In general, the following was checked and verified:

- SOPs,
- Records e.g. cleaning and use,
- the layout and design;
- finishing (premises and equipment),
- equipment status,
- calibration,
- preventive maintenance labels,
- area status,
- container labels,
- materials,
- air flow patterns,
- pressure cascades
- BMRs

Areas included in the inspection were:

- Sieving of materials;
- Granulation area (manufacturing 3);
- Tool room (punches and dies)
- Sieves, screens and FBD bag storage;
- Compression areas;
- IPQC;
- In process storage;
- Change rooms;

The day was ended by giving feed back on the observation made during the course of the day.

The tentative inspection plan for day 4 was as follows:

<b>Day 4</b>		
Morning	<b>Quality Control Laboratory</b> <ul style="list-style-type: none"> <li>Organization and management               <ul style="list-style-type: none"> <li>• Quality management system</li> <li>• Personnel, training and assessment</li> <li>• Premises</li> <li>• Sampling and sample handling</li> <li>• Work allocation</li> </ul> </li> <li>Documentation:               <ul style="list-style-type: none"> <li>• Specifications and test methods</li> <li>• SOPs, logbooks, records</li> <li>• Worksheets and test reports</li> <li>• Contract testing</li> <li>• Stability program</li> <li>• OOS results</li> <li>• Analytical method validation</li> <li>• Evaluation of results, release and rejection procedures</li> <li>• Trending of results</li> <li>• Traceability</li> </ul> </li> <li>Materials               <ul style="list-style-type: none"> <li>• Chemicals and reagents</li> <li>• Reference standards</li> <li>• Retention samples</li> </ul> </li> <li>Equipment, instruments and devices               <ul style="list-style-type: none"> <li>• Operation and maintenance</li> <li>• Calibration and qualification</li> </ul> </li> </ul>	
	Lunch	
Afternoon	<b>Microbiology Laboratory</b> <ul style="list-style-type: none"> <li>• Personnel</li> <li>• Premises, environment</li> <li>• Equipment</li> <li>• Reagents and culture media, preparation and control</li> <li>• Reference materials and reference cultures</li> <li>• Sample handling</li> <li>• Purified Water monitoring</li> <li>• Environmental monitoring</li> <li>• Testing of materials and finished product</li> <li>• Disposal of waste</li> </ul>	
	Summary of observations for the day	
	Summary by inspectors (closed meeting)	
	Closing meeting with company representatives	

On the last day, the inspectors reviewed the following areas:

-Documentation: inspectors reviewed the cleaning validation data demonstrating recovery and calculation of the surface area of the sieves. A cleaning recovery average of 78% was obtained for the rinse and of 79% for the swab. Cipla representatives claimed that this factor was used in the calculations performed. Cipla also demonstrated that the correction that had been made in their calculations of the area of the sieves (which was previously erroneous), did not have a significant impact on results.

-Packaging for Unit IV: Packing line 2 was examined on site. It was noted that performance qualification was performed when packaging capsules, not tablets. The SOP for line clearance was consulted. Tablets were being manufactured at the time of inspection. Inspectors verified controls on the machine. The calibration of the camera that determined whether blisters are full was verified. Inspectors were informed that joints in the foil were recorded but not for the PVC. Set-up was verified as well as the number of in-process checks (12 per hour). Rejected tablets were visible in a bag but were not recorded, which was determined to be acceptable because reconciliation was performed only at the end of the run. On the reconciliation record, the number of tablets was changed from 2600 to 52000 without any written record of the reason for the change.

-Water purification system for Unit IV: The different components of 1 out of 2 systems were examined in detail. This system was in phase III of qualification. Inspectors confirmed that adequate measures were in place to ensure that the intensity of the UV light remained within acceptable limits. Verification of the flow rate, supply and return conductivity, as well as pH, was performed by inspectors. The potable feed water and the purified water were being tested every day by QC. The loop 1 storage tank was examined in order to confirm that a spray ball was indeed used. The absence of dead legs was also confirmed, along with the use of adequate valves (absence of ball valves). Sanitization records were verified for both loops.

-HVAC system in Unit IV: AHU-37 was examined. All of the filters that were described in the diagrams were verified to be present. Measuring of the pressure drop was performed only over the 1<sup>st</sup> set of filters, not the second set. Air leakage was noted in the ducting after the HEPA filters which could result in potential contamination. The procedure for restarting the AHU's, which were stopped during cleaning of filters was requested but was not brought in due time to the inspector's attention.

-Unit I - Related to HA053 variation (Lamivudine 50 mg / 5 ml oral solution)

This included:

- Receipt and handling area (examined only briefly and from a distance)
- Dispensing (very briefly)
- The active material storage area for steroids (Room 245) was not labelled for steroids.
- Raw material storage area: the area was examined in more detail. The applicant was requested to show a sugar consignment that had been used in the manufacture of the HA053, but this was not possible as the entire stock had been used.
- Some issues were identified with confusion regarding the passed/quarantine status of raw materials.
- Syrup production area: the different pieces of equipment were shown by the company. The packaging line used for the WHO HA053 product was examined. The company claimed that compressed air was used to pressurize water to clean product

bottles but it was unclear if the pressure was sufficiently high to ensure adequate cleaning.

#### -Quality Control Unit

This included:

- Documentation/specifications room.
- Stability rooms (the location of samples in the 30°C, 70% RH chamber was verified along with the ongoing stability study protocols). The manufacturer confirmed that there was 1 bottle for every planned timepoint and explained the numbering system used. Inspectors also enquired as to what measures were in place in case of a breakdown of the stability chamber. The company representatives present stated that there was a second generator which would take over in such situations.
- Retention sample storage room: this included an examination of the time during which retention samples were being kept, as well as the temperature and humidity conditions (the method for data logger for humidity conditions and the responsible person's adequate resetting after readings was verified). The reserve sample procedure was examined, with a focus on the dates (samples taken on 11.06.2010) vs. the actual date of manufacturing and the date where the analyses were actually performed. Inspectors also verified the amount of time between actual QC analyses and the removal of stability samples from incubation, which was of only 2 days in the specific example that was examined.
- Weighing room: the calibration and daily verification methods for analytical balance FA-041 was verified by asking one of the analysts present how this was performed. He showed us the set of calibrated weights that were used as well as his method, which was generally acceptable.
- Main laboratory: included working standards, and dissolution apparatus (calibration and preventive maintenance, as well as analyst training on procedure that was used to measure the comparative dissolution profiles). The specifications and procedure for identity testing of Lamivudine was also examined. The SOP for qualification of working standards was examined concomitantly.
- HPLC (instrumental) laboratory: included verification of the qualification of the HPLC that was used to perform analyses on tablets. This included maintenance and storage of columns with emphasis on column PDHM 001/01 which was used to perform dissolution studies (brief overview). An examination of the original chromatograms for the dissolution profiles that were obtained was done. The audit trail was examined on the Chromeleon chromatography program for that particular run.

At the end of the day, the team reviewed progress of the activities of the day and the entire inspection, gave feedback and wrap up for the inspection and received reactions from the management of the company.

There was consensus on all of the observations made with the exception of identity testing.

## **2.1 QUALITY ASSURANCE**

The company had quality systems in place to address possible risks associated with the production and control of pharmaceutical products. Organization charts, job descriptions, SOPs, protocols and reports were in place.

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

Systems were in place and in general, the site was considered to be operating in compliance with GMP.

## **2.3 SANITATION AND HYGIENE**

Acceptable

## **2.4 QUALIFICATION AND VALIDATION**

In general, the qualification and validation was acceptable. The company had to further address the issue of cleaning validation. Corrective and preventive action submitted for review by the inspectors was accepted, and this will be checked again at the next inspection.

## **2.5 COMPLAINTS**

Acceptable. No complaints had been received to date as the site was new.

## **2.6 PRODUCT RECALLS**

Acceptable. No recalls had been initiated to date as the site was new.

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

Contracts were reviewed (contract analysis). See observations below.

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

Not inspected in detail.

## **2.9 PERSONNEL**

This was not inspected in detail. Personnel interviewed and questioned during the inspection were trained and could answer most of the questions.

## **2.10 TRAINING**

Not inspected in detail

## **2.11 PERSONAL HYGIENE**

Acceptable

## **2.12 PREMISES**

The inspection was done of unit I and IV and focussed mainly on unit IV. The location, cleanliness, design, maintenance etc were mainly acceptable. The change rooms required attention in terms of design, cleanliness, control and its room classification.

## **2.13 EQUIPMENT**

In general, the design, maintenance, qualification and cleaning of equipment was acceptable.

## **2.14 MATERIALS**

Starting materials and packaging materials, receiving and storage flow was generally acceptable. Exclusions were that material was not always labelled adequately for example, the transfer of materials from site and material in sieving staging area (magnesium stearate and silicon dioxide - in one container labelled as silicon dioxide).

## **2.15 DOCUMENTATION**

Documentation: we looked at SOPs, registers, protocols, reports and in general these were appropriate.

## **2.16 GOOD PRACTICES IN PRODUCTION**

Acceptable

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

Acceptable

### **Part 3: Conclusion**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, Cipla Ltd India, Indore SEZ (Unit I and IV) was 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 one year.

#### **Part 4: References**

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