

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

**Part 1: General information**

Name of Manufacturer	Cipla Ltd
Unit number	<u>Unit 8</u>
Production Block	N/A
Physical address	Plot No: L-139, S-103 & M-62 Verna Industrial Estate, Verna – Salcette - Goa, 403722 Goa India
Contact person .	Mr T Datta
Date of inspection	21 – 24 September 2011
Type of inspection	Routine GMP
Dosage forms(s) included in the inspection	Tablets (film and sugar coated – blister pack)
WHO product numbers covered by the inspection	RH030 (Ethinylestradiol + levonorgestrel + placebo 0.03/0.15mg tablets)
Summary of the activities performed by the manufacturer	Production and control

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Contact: prequalinspection@who.int

## **Part 2: Summary**

### ***General information about the company and site***

The manufacturing site of Cipla Ltd, Plot No: L-139, S-103 & M-62 (hereafter referred to as Unit VIII) located in Verna Industrial Estate, Verna – Salcette - Goa was inspected by a WHO prequalification inspection team on the above mentioned dates.

Cipla Ltd is a public limited company, founded in 1935. The company has several manufacturing sites in India e.g.:

- Bangalore - Pharmaceutical formulations and APIs
- Patalganga - Pharmaceutical formulations and APIs
- Kurkumbh - Pharmaceutical formulations and APIs
- Goa - Pharmaceutical formulations
- Baddi - Pharmaceutical formulations
- Sikkim - Pharmaceutical formulations
- Bommasandra - APIs
- Indore - Pharmaceutical formulations

There are 9 separate Units located on site. Operations at Unit VIII are dedicated to hormone products and some steroids.

Dosage forms include tablets, capsules, nasal preparations and topical preparations. The unit is physically separated from the other Goa units and has its own HVAC and water system as well as QC laboratory.

After introductions in the opening meeting, the company made a brief presentation about the activities on site, and Unit 8. About 2753 people were working at the site at the time of the inspection.

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

Cipla had been inspected by many DRAs – and Unit VIII was previously inspected by several stringent regulatory authorities and PIC/S inspectorate members e.g. US FDA, UK MHRA.

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

The inspection focused on the production and control of reproductive health products. The inspection covered several sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

### ***Inspected Areas***

The inspection plan was presented to the company  
After the opening meeting, the following documents were inspected:

- Product list
- Organization charts (production, QA)
- Job descriptions
  - Head QA, and other QA staff
  - Head QC

- Unit Head Production
- Lab QA Head
- Employee responsible for dispensing
- SOP for batch release -
- Training programme for 2011 (production and QA)
- Training record Head Unit QC and new employee
- SOP for training
- List of contract workers Unit VIII
- List of attendees for training in dissolution and water sampling
- SOP on risk assessment
- Risk assessment plan
- Dispatch records for released batches
- Training record for a selected contract worker
- FP release for identified products and batches
- Training program for microbiology laboratory staff
- Training records for water sampling and analysis and dissolution
- Product quality review
- SOP for complaints and records (complaint investigations)
- SOP for recall and mock recall record
- PQR for a selected product
- PQR schedule for products against product list

Members of staff were interviewed and procedures were explained to the inspectors. APIs were released / rejected by lab QA and Finished Product release was done by Unit QA.

On the second day of the inspection, the inspectors gave feedback on the observations made on the first day. They then reviewed the unit layout, pressure cascading, material and personnel flow – and then proceeded to Unit VIII and did an on-site inspection. They followed the flow of the materials from receiving, through production and packaging to the finished goods warehouse. In all areas, SOPs and records were checked and personnel were interviewed.. In general, all areas were clean and appropriately maintained.

Documents reviewed in the afternoon included:

- Annual plan for preventive maintenance
- Records for PPM of a compression machine and coating a machine in Unit VIII
- Procedure for maintenance
- Maintenance
- Schematic drawing for a selected AHU
- Qualification documentation for a selected AHU
- Schematic drawing for the water purification system
- Trend results for water testing (Phase I, II and III – selected points)
- Qualification documentation for the water purification system
- Results for water samples –identified points
- Change control for the water system
- SOP for calibration
- Annual calibration schedule
- Procedure and schedule for balance calibrations
- Calibration record for a pressure gauge
- Calibration certificate

- Validation (qualification) of an AHU (annual – after initial installation); selected documents and records e.g. installed filter leakage, air changes

On the third day, the inspectors presented the observations made during the second day of the inspection. They then proceeded to inspect documentation, and inspection of the HVAC and water system on site. Documents inspected included:

- Validation Master Plan
- Qualification of the coating machine
- Annual review of the coating machine (for purposes of re-qualification)
- Qualification of the primary packaging line
- Qualification of QC instruments
- Qualification of the camera (packaging line)
- Three sets of batch manufacturing records (validation batches)
- Process validation protocol and report with results (e.g. lubrication, blend, friability, disintegration, dissolution, compression)

The inspectors also inspected the service area where AHUs and wet scrubbers were located, and checked selected ones. They observed the monitoring of the BMS and checked records for the monitoring of conditions and alarms reported.

On day four, the inspectors gave feedback on the findings of the previous day. They then proceeded to inspect the receiving and storage of packaging materials and components. They inspected the QC lab for packaging materials. They reviewed the SOP for sampling, specifications, release reports, for selected materials (e.g. printed Al foil) and calibration records for selected instruments. They then inspected the QC laboratory and reviewed instruments, records, storage of HPLC columns, cuvettes, raw data (HPLC analysis chromatogram for a dissolution test in progress), test reports, work sheets, reference material control, instrument logs, audit trail (HPLC), dissolution tester and test kit, and interviewed analysts. They briefly looked at the microbiology laboratory (from the outside) and interviewed one microbiologist.

Documents inspected included:

- SOP sampling of packaging materials
- Calibration records (UV spectrophotometer)
- Test report for Al foil for a selected product
- Specification Al foil for a selected product
- Qualification of the UV spectrophotometer
- Qualification of the dissolution apparatus
- Stability testing SOP, protocol and schedule for a selected product
- Stability testing results (accelerated and real time at 6 months and 24 months respectively) – including assay and degradation products (raw data, chromatograms, calculations verified)
- Stability chamber records for monitoring of conditions
- SOP for Batch failure investigation
- SOP for Out of specification investigation and resolution procedure

At the end of the day, feedback was given on the findings of day 4, after which a closing meeting was held.

There were no critical or major deficiencies identified during the inspection.

## **2.1 QUALITY ASSURANCE**

A quality assurance system existed and consisted of various procedures, protocols, records, training and related activities.

Risk assessment was done for the product.

Procedures were in place for deviation management, change control, recalls, complaints, training, product quality review etc.

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

Good manufacturing practices were implemented and generally maintained.

Necessary resources were generally provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, laboratories and equipment for in-process and other controls. Manufacturing steps were recorded in batch manufacturing and packaging records. Instructions and procedures were generally written in clear and unambiguous language. Qualification and validation were performed.

## **2.3 SANITATION AND HYGIENE**

Procedures and records were maintained for the cleaning and sanitation of areas. The areas were clean. Personal hygiene was maintained

## **2.4 QUALIFICATION AND VALIDATION**

Protocols and reports were in place for qualification and validation. A Validation Master Plan existed. Protocols and reports inspected were generally acceptable and evidence of improvement over the years was evident. For cleaning validation - a worst case approach was followed (cleaning and calculation (dose criterion – 10ppm and visually clean)). The documentation in relation to the establishment of the worst case, sampling, recovery and cleaning validation report for the vibro sifter were reviewed

## **2.5 COMPLAINTS**

An SOP and register were maintained for complaints. Selected complaint investigations were reviewed.

## **2.6 PRODUCT RECALLS**

A corporate SOP was in place for recalls. No recall was initiated in the last 18 months. A mock recall was done. (All distribution is done from Mumbai, for all manufacturing sites – therefore a mock recall is done from Mumbai rotating between sites of manufacture).

## **2.7 CONTRACT PRODUCTION AND ANALYSIS**

No activity was contracted out for the production or control of this product. Contract laundry facility was utilised.

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

This was not inspected during this inspection.

## **2.9 PERSONNEL**

The company employed over 2000 members of staff on site. Job descriptions for selected positions as well as training records were reviewed. A large number of key people had extensive experience and had been working at the company for a long time. They had appropriate qualifications.

## **2.10 TRAINING**

An SOP for training was in place. A training program was established for the year – covering different topics. Each section had its own training plan e.g. QC, QA and Engineering. Training records for selected staff were requested and inspected.

## **2.11 PERSONAL HYGIENE**

Clean garments were used, and all areas including change rooms, personal hygiene, procedures for gowning were meeting GMP requirements.

## **2.12 PREMISES**

The layout, design, finishing, maintenance and cleanliness of the areas inspected were acceptable.

## **2.13 EQUIPMENT**

All equipment inspected was qualified, calibrated, cleaned, and maintained. Records were in place.

## **2.14 MATERIALS**

Materials were sourced from approved suppliers, appropriately stored, sampled and tested according to procedures and specifications. Stock was controlled through an IMS system (excluding finished goods) and status was controlled.

## **2.15 DOCUMENTATION**

Documents were suitably designed, and distributed. Copies were clear and controlled. Records were maintained.

## **2.16 GOOD PRACTICES IN PRODUCTION**

Good practices were followed in all areas of production. Production operations followed clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

## 2.17 GOOD PRACTICES IN QUALITY CONTROL

Quality control was concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensured that the necessary and relevant tests were actually carried out and that materials were not released for use, nor products released for sale or supply, until their quality had been judged to be satisfactory. Quality control was not confined to laboratory operations but was involved in all decisions concerning the quality of the product. Quality control was independent from production.

### 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, Unit VIII, Verna, Goa, India - was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

The minor deficiencies identified during the inspection have been addressed by the company.

### Part 4: References

1. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report.* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 3 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf)
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 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_929\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf)
3. WHO guidelines for sampling of pharmaceutical products and related materials. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report.* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_929\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf)
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. Forty-fifth Report.* Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf)
5. Supplementary guidelines on good manufacturing practices: validation. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report.* Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_937\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf)
6. Good Practices for National Pharmaceutical Control Laboratories. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth Report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 3. [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_902.pdf#page=37](http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page=37)

## ***DEFINITIONS***

### **Critical Observation**

An observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.

### **Major Observation**

A non-critical observation that:

- has produced or may produce a product which does not comply with its prequalification application (including variations); and/or
- indicates a major deviation from the GMP guide; and/or
- indicates a failure to carry out satisfactory procedures for release of batches; and/or
- indicates a failure of the person responsible for QA/QC to fulfil his/her duties; and/or
- consists of several other deficiencies, none of which on its own may be major, but which may together represent a major deficiency and should be explained and reported as such.

### **Other Observation**

An observation that cannot be classified as either critical or major, but indicates a departure from good manufacturing practice.

A deficiency may be “other” either because it is judged as minor, or because there is insufficient information to classify it as major or critical.

### **Notes:**

1. Classification of an observation is based on the assessed risk level and may vary depending on the nature of products manufactured, e.g. in some circumstances an example of another deficiency may be categorized as major.
2. A deficiency that was reported at a previous inspection and not corrected may be reported in a higher classification.
3. One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer during the inspection.