## Prequalification Team Inspection services

### WHO PUBLIC INSPECTION REPORT (WHOPIR)

#### Finished Product Manufacturer

<table>
<thead>
<tr>
<th>Part 1</th>
<th>General information</th>
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<tbody>
<tr>
<td><strong>Manufacturers details</strong></td>
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<tr>
<td>Company information</td>
<td></td>
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<tr>
<td>Name of manufacturer</td>
<td>Cipla Ltd</td>
</tr>
</tbody>
</table>
| Corporate address of manufacturer | Cipla Limited  
Cipla House  
Peninsula Business Park  
Ganpatrao Kadam Marg  
Lower Parel, Mumbai – 400 013  
India  
Telephone: 91 22 24826000  
Facsimile : 91 22 24826120  
24 hours contact Telephone No. : +91 832 2889000 / 2889199 / 2889101 |
| **Inspected site** |  |
| Address of inspected manufacturing site if different from that given above | Plot No: L-139, S-103 & M-62,  
Verna Industrial Estate, Salcette,  
Goa 403722, India |
| Unit / block / workshop number | Unit-VIII (Unit-8) |
| Manufacturing license number, (delete if not applicable) | 611 |
| **Inspection details** |  |
| Dates of inspection | 13 to 17 June 2016 |
| Type of inspection | Routine GMP Inspection |
| **Introduction** |  |
| Brief summary of the manufacturing activities | Manufacture, blending / granulation, compression, coating, capsule filling and packaging of solid unit dosage forms including tablets, and hard gelatin capsules. (Reproductive health products.) |
### 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 /8**) is located in Verna Industrial Estate, Verna – Salcette - Goa and was inspected by a WHO prequalification inspection team on the above mentioned dates.

Cipla Ltd is a public limited company. The company has several manufacturing sites in India with that at Goa being its largest complex. Other sites in India are located at:

- 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

A common site presentation covering all non-sterile manufacturing units taking part in WHO prequalification process was given on day 1. There are 11 manufacturing blocks producing various dosage forms; however, the scope of this presentation was limited to Unit III, IV, VII (including PD II) and VIII which are under scope of WHO inspection. The inspection report for Unit-III, IV and VII was prepared separately.

### History

**Brief report of inspection activities undertaken**

**Scope and limitations**

**Areas inspected**

*The inspection focused on the production and control of the oral solid dosage form for Unit-VIII. The inspection covered most of the sections of the WHO GMP text, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.*

**Restrictions**

None

**Out of scope**

None

**WHO product numbers covered by the inspection**

1. RH030: Ethinylestradiol/Levonorgestrel tablets +Placebo tablet 0.03mg/0.150mg+0mg
2. RH039: Misoprostol tablet 200mcg
3. RH040: Levonorgestrel tablet 0.75mg
4. RH046: Levonorgestrel tablet 1.5mg

**Products under assessment:**

1. RH060: Mifepristone Tablet 200mg
2. RH059 Oxytocin Solution for injection 10IU

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Contact: prequalinspection@who.int

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<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHU</td>
<td>air handling unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>attributable, legible, contemporaneous, original and accurate</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
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<tr>
<td>APQR</td>
<td>annual product quality review</td>
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<tr>
<td>BDL</td>
<td>below detection limit</td>
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<tr>
<td>BMR</td>
<td>batch manufacturing record</td>
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<tr>
<td>BPR</td>
<td>batch packaging record</td>
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<tr>
<td>CAPA</td>
<td>corrective actions and preventive actions</td>
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<tr>
<td>CC</td>
<td>change control</td>
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<tr>
<td>CFU</td>
<td>colony-forming unit</td>
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<td>CoA</td>
<td>certificate of analysis</td>
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<td>CpK</td>
<td>process capability index</td>
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<tr>
<td>DQ</td>
<td>design qualification</td>
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<tr>
<td>EM</td>
<td>environmental monitoring</td>
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<td>FAT</td>
<td>factory acceptance test</td>
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<td>FBD</td>
<td>fluid bed dryer</td>
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<td>FMEA</td>
<td>failure modes and effects analysis</td>
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<td>FPP</td>
<td>finished pharmaceutical product</td>
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<td>FTA</td>
<td>fault tree analysis</td>
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<td>FTIR</td>
<td>Fourier transform infrared spectrometer</td>
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<td>GC</td>
<td>gas chromatograph</td>
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<td>GMP</td>
<td>good manufacturing practice</td>
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<td>HACCP</td>
<td>hazard analysis and critical control points</td>
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<td>HPLC</td>
<td>high-performance liquid chromatograph</td>
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<td>HVAC</td>
<td>heating, ventilation and air conditioning</td>
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<td>IR</td>
<td>infrared spectrophotometer</td>
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<td>IQ</td>
<td>installation qualification</td>
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<td>KF</td>
<td>Karl Fisher</td>
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<td>LAF</td>
<td>laminar air flow</td>
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<td>LIMS</td>
<td>laboratory information management system</td>
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<tr>
<td>LoD</td>
<td>limit of detection</td>
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<tr>
<td>LOD</td>
<td>loss on drying</td>
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<td>MB</td>
<td>microbiology</td>
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<tr>
<td>MBL</td>
<td>microbiology laboratory</td>
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<td>MF</td>
<td>master formulae</td>
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<td>MR</td>
<td>management review</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
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<td>NRA</td>
<td>national regulatory agency</td>
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<tr>
<td>OQ</td>
<td>operational qualification</td>
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<tr>
<td>PHA</td>
<td>process hazard analysis</td>
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<tr>
<td>PM</td>
<td>preventive maintenance</td>
</tr>
<tr>
<td>PpK</td>
<td>process performance index</td>
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<tr>
<td>PQ</td>
<td>performance qualification</td>
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<tr>
<td>PQR</td>
<td>product quality review</td>
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<td>PQS</td>
<td>pharmaceutical quality system</td>
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<td>QA</td>
<td>quality assurance</td>
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<td>QC</td>
<td>quality control</td>
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<td>QCL</td>
<td>quality control laboratory</td>
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**Brief summary of the findings and comments**

1. **Pharmaceutical quality system**

A system for quality assurance was well established with procedures for all key quality elements. In general the procedures reviewed were of a good standard reflecting a good level of input from personnel with a good knowledge of WHO GMP requirements.

Cipla had a well-established documentation infrastructure consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. The key QMS systems and procedures for Unit-VIII was identical to those for other Units (III, IV and VII) inspected earlier in this inspection cycle. The output of these key systems examined were PQR, deviations, change controls, quality risk management etc.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

2. **Good manufacturing practices for pharmaceutical products**

Good manufacturing practices generally were well implemented. 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. Manufacturing processes were clearly defined and systematically reviewed. Instructions and procedures were generally written in clear and unambiguous language. Qualification and validation were performed. Operators were trained to carry out procedures correctly, and records were made during manufacture.

3. **Sanitation and hygiene**

In general, premises and equipment were maintained at a satisfied 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.
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.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

5. Complaints

The procedure for handling product complaints was available for inspection. There were no complaints reported for the products inspected.

6. Product recalls

Not inspected due to time constraint.

7. Contract production, analysis and other activities

There was no contract manufacturing carried out for WHO prequalified products.

The SOP for selection, evaluation and approval of contract analysis was reviewed and noted that procedure does not specifically described how contracted laboratories will be selected and what standard or criteria will be used to evaluate before approving any contracted laboratories. The procedure uses a checklist which described responsibilities of contract giver and acceptor. The procedure stated that contracted laboratory will provide hard copies of test data sheet, chromatograms, histograms etc, and raw data shall be retained by the contracted laboratory for a period of 7 years. These contracted laboratories were re-audited by corporate QA every two year.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

8. Self-inspection, quality audits and suppliers’ audits and approval

The SOP for Self-inspection was reviewed. Site Inspections were required to be done twice a year while corporate audits were done once in a year. It was noted that the scope did not cover contract laboratory audits. The annual Self-inspection schedule for 2016 was reviewed. The self- inspection log, was also reviewed. The next self- inspection would be carried out in September. The previous self- inspection report carried out in March was not reviewed as inspectors were expected to be looking for compliance with the self- inspection SOP- not necessarily at actual deficiencies. Ad –hoc inspections were not usually carried out in preparation for external regulatory audits e.g. WHO audit. This was mainly because the site was always undergoing one form of external regulatory audit or the other within very short timelines.

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. An organization chart was available and was appropriate.

10. Training

There was system in place for the training of personnel on a regular basis. The trainings were periodically assessed to ensure their effectiveness.

11. Personal hygiene

The level of hygiene observed and the measures taken to maintain the facility were considered to be of a good standard. The approach to sanitation and hygiene was acceptable in general. Photos describing the gowning procedures were appended to the changing procedures and provided on the walls of changing rooms.

12. Premises

The premises for manufacturing, storage and quality control of products were generally of a satisfactory standard. The production facility of Unit-VIII is a multipurpose area. The equipment and the facilities inspected were generally in good condition. Layouts of the facilities were available and up-to-date.

Premises were designed to have a logical flow of materials and personnel except the access to toilets in the building. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. Hormone products were produced in Unit-VIII with adequate containment facility.

QC laboratories including the microbiology laboratory 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.

A quick inspection of water system was made in Unit-VIII. Potable water was used as a source for purified and purified was the source for water for injection.

13. Equipment

Process equipment was installed and maintained in a way to minimize the risk of contamination and cross contamination. Production equipment was identified as to its content or purpose and cleanliness status.

The SOP on cleaning of air filters was in place which was applicable to Unit-V, VI, VIII and X which produces hormone and cancerous products. The filters were cleaned using appropriate PPEs. It was noted that for critical processing areas, double HEPA filters were used, one at the terminal and another HEPA (BIBO) above return riser. The exhaust air was also passed through double HEPA filters. The primary and secondary filters were cleaned in the service floor of Unit-VIII using potable water and compressed air.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.
14. Materials

A brief inspection of the (electronically controlled material) warehouse was undertaken. Materials and finished products were stored in this store. The storage conditions (temperature and humidity) of the inspected products were controlled below 30°C.

15. Documentation

A paper system was in place for documentation management. Documents were designed, prepared, reviewed and distributed according to SOPs. Documents were approved, signed and dated by the appropriate responsible persons. However, several discrepancies were observed in the documents, records and logbooks. The quality of documentation needs to be improved.

Misoprostol 200mcg tablets and Levonorgestrel tablets BP 0.75mg were the current specifications and method of analysis which were being used by the laboratory.

16. Good practices in production

The inspected finished dosage form facilities of Unit-VIII were multi-product facilities. The temperature, relative humidity and air pressure differentials were monitored according to written procedures.

It was noted during inspection of Unit-VIII that green color uniform was used by the personnel working in Unit-VIII. The hormones and excipients were received through the same receiving bay, wherein excipients were sampled therein and actives moved to another area meant for sampling and dispensing of actives under containment cabinet. The batch size of actives received was smaller. In addition, cold storage was provided for the storage of Misoprostol.

Hormone materials were sampled and dispensed in containment cabinet (Henzaids) which was equipped with two balances and HMI. These were not interfaced as noted. The containment cabinet was equipped with wash in place. There was separate material and personnel airlock provided.

Separate change rooms were provided for the operators for entry and exit from and to the processing area. There was one manufacturing suite in Unit-VIII which was equipped with FBP, co-mill and high sheer mixer. As Misoprostol tablets was produced using direct compression material, there was no drying involved. The manufacturing suite was equipped with FBP, miller, sifter, steam kettle, vibratory sifter and IPC blender. The entire plant was maintained at negative pressure to the atmosphere wherein corridor was set to 1.5 against cubicles -0.5. The change rooms were designed in sink shape to retain air within change rooms. The personnel leave the manufacturing area through air shower. Although double gloves were worn in the core processing by the operators, it would have been useful to tape or sealed these gloves on to the protective suit sleeves to avoid potential retention of products.

Seven packing lines were available (one strip pack, one bottle pack, one topical and four blister lines). It was noted that the company had employed all male staff in the production and packaging area.

The injectable facility of Unit-VIII for hormone products was also briefly inspected. At the time of inspection, there was no activity i.e. preparation, filtration and or filling operation was being carried out. This new facility
has already produced few registration batches of Oxytocin injection for WHO submission, and will be used to produce other sterile products. It was noted that this sterile facility was not used for commercialization as yet but it targets to produce batches for domestic market sometime in 2016.

Currently, the BMS was under qualification and was being compared with manometer.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. Their satisfactory implementation will be verified during future inspections.

17. Good practices in quality control

The Unit-VIII does not have quality control laboratory. A dedicated microbiology laboratory for Unit-VIII was housed in Unit-VIII.

The laboratory located on the 2nd floor of QC-X building was being used for the testing of hormone products by physico-chemical and instrumentation methods. The laboratory was also responsible for the testing of stability studies for Unit-III, IV and VII.

As the quality system of Cipla across various units is the same, the laboratory used for the testing of Unit-VIII products was not inspected. Refer inspection report of other units (Unit-III, IV and VII) for laboratory details.

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, M/s Cipla Ltd. Unit-VIII Goa, India at was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPiR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPiR

This WHOPiR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.
PART 4
List of GMP guidelines referenced in the inspection


http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1


   http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf
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