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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**Cipla Ltd**
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 <u>Products under assessment:</u> 1. RH060: Mifepristone Tablet 200mg 2. RH059 Oxytocin Solution for injection 10IU

Abbreviations

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

QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2	Brief summary of the findings and comments (where applicable)

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 30^0C.

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

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. http://www.who.int/medicines/publications/44threport/en/
3. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. 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?ua=1
5. WHO 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?ua=1
6. 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?ua=1
7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1 http://www.who.int/medicines/publications/44threport/en/
8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2 http://www.who.int/medicines/publications/44threport/en/
9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3 http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1
13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf
20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the prosecution of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6 http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf
22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf
23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf
24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf