

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Finished Product Manufacturer

Part 1: General information

Name of Manufacturer	Cipla Ltd.
Unit number	Unit VIII
Production Block	Unit VIII
Physical address	L-147, L-147/1, L147/2, L147/3, L147/4 and L-138, Verna Industrial Estate, Verna Goa. India.
Contact person and email address.	Mr. Davinder Singh Technical Director Cipla Ltd Mumbai Central Mumbai 400008 India e-mail: dsingh@cipla.com
Date of inspection	18 to 20 November 2013
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Oral Solid Dosage Forms (OSD)
WHO product numbers covered by the inspection	RH030 Ethinylestradio/Levonogestrel + Placebo 0.03/0.15mg Tablet RH039 Misoprostol 200mcg Tablet
Summary of the activities performed by the manufacturer	Production and quality control of Reproductive Health (RH) Finished Pharmaceutical Products (FPPs)

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. 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

Experience from previous WHO inspections has shown that the company has a strong unified approach to unit manufacturing operations, particularly in its OSD (Oral Solid Dose) operations, utilising standardised equipment and procedures wherever possible. This has led to a high standardisation of processing and interchangeability between sites utilising platform technologies. This is appropriately supported by strong corporate technical leadership. WHO has accepted the Cipla interchangeability approach when dealing with variations and applications for several OSD products.

The Goa site has nine separate units dedicated to the manufacturing of Finished and bulk Pharmaceutical formulations (FPP). There is a further site (Unit X) under construction and nearing completion which will be dedicated for cytotoxic OSDs. This site will move into the initial validation phase of the construction project in January 2014. At Goa, Salcette the manufacturing operations operate across several physical plots on the industrial estate with the majority being contiguous. Each block has its own internal management but operate under overall site leads for production, quality and QA. The total workforce is about 2945 employees for the whole Verna site Goa site at the time of inspection. There are 1345 people working in QA and QC and 1245 people working in Production.

The detailed physical location of Unit 8 is plots L-147, L-147/1, L147/2, L147/3, L147/4 and L-138, Verna Industrial Estate, Verna Goa, India. These designations refer to the land plots on the Industrial estate.

Operations at Unit VIII are dedicated to hormone products and other potent products. Dosage forms include tablets, capsules, nasal preparations and topical preparations currently. The unit is physically separated from the other Goa units and has its own HVAC and water system as well as QC laboratory.

The specific products under WHO PQ were not in production at the time of inspection however other hormonal products utilizing the same equipment were being manufactured and this allowed a full review of operations of the manufacturing in the unit.

The company stated that currently Cipla Goa has no injectable or implantable RH contraceptive products in its portfolio. The majority of the APIs used in Goa originate from Cipla Kurkumbh and Bangalore facilities. Unit VIII utilizes a number of hormones manufactured by SRA suppliers.

A new fully automated Korsch press is in the process of being installed.

History of WHO and/or regulatory agency inspections

The vast majority of product manufactured in Goa is exported with the major portion being to markets under the supervision of SRAs. Approximately 80% of all product manufactured at Goa is exported with 100% of that from UNIT VIII being exported primarily to Japan, UK and Germany being the major markets.

As a result of the supply to SRA territories, the overall site has a long history of inspections. Many NMRAs including those from several EU member NMRAs, USFDA and Australian TGA over a period of the last 12 years.

Unit VIII has been specifically inspected and approved by ANVISA, MHRA, TGA and USFDA.)

Unit VIII was previously inspected by WHO in September 2011 and USFDA in November 2011.

Focus of the inspection

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

Inspected Areas

- After introductions in the opening meeting, the company made a brief presentation about the activities on site, and Unit VIII specifically. This provided detail together with subsequent discussion and Introductions and Attendance Record
- Confirmation of scope of inspection and inspection plan
- Company presentation, and overview of activities on site
- High level description of manufacturing and product range
- Changes since last inspection and proposed changes.
- Product list
- Organization charts (production, QA – issued on 14 and 12 September 2011)
- Job descriptions
- SOP list

Inspection of QMS

- Product Quality Reviews
 - SOP CQA 97, PQR for product under inspection (2012 PQR)
- Deviations
 - System, log and requested reports
- Customer complaints
 - System, log and requested reports
- Recalls

- System
- Change Control and Management
 - System, log and requested reports
- Contract agreements
- Supplier approval system and requested examples
- Document Control
- Self-inspection
- Master BMR of ~~Misoprostol 200mcg~~ Tablet
- Validation master plan and that for Cleaning validation
-

Site visit:

Inspection of Production Operations & Facilities

- Batch document preparation
- Finished product release and batch record review
- Site layout
- Personnel and material flow
- Warehousing and storage
- Starting and packaging materials
- Sampling
- Changing Facilities
- Dispensaries
- Status control
- Temperature (and humidity) monitoring
- Finished Products and distribution
- Tablet manufacture
- In-process controls

Packaging operations

- Component testing
- Primary packaging
- Secondary packaging

Engineering & Services:

- Preventive Maintenance
- Calibration

HVAC

- Design & construction including documentation
- Operation and maintenance
- IQ/OQ/PQ
- Monitoring and testing
- BMS

Water

- Design & construction including documentation
- Operation and maintenance
- IQ/OQ/PQ
- Monitoring and testing

Quality Control Laboratory

Organization and management

- Quality management system
- Personnel, training and assessment
- Premises
- Sampling and sample handling
- Work allocation

Materials

- Chemicals and reagents
- Reference standards
- Retention samples

Environmental monitoring

- Environmental monitoring results
- Purified water

Quality Control

Documentation:

- Specifications and test methods
- SOPs, logbooks, records
- Worksheets and test reports
- Contract testing
- OOS result system
- Analytical method validation
- Evaluation of results, release and rejection procedures
- Trending of results
- Traceability
- Retention Samples
- Change control
- Validation and qualification

Stability testing

- Protocol and schedule, results
- Bulk tablets, finished product
- Chambers
- Hold time studies

Equipment, instruments and devices

- Operation and maintenance
- Calibration and qualification

At the beginning of each day of the inspection, the inspectors gave feedback on the observations made on the previous day. In the factory the inspection followed the general workflow of the materials from receiving, through production and packaging to the finished goods warehouse. In all areas, SOPs and records were spot checked and personnel were interviewed. In general, all areas were clean and appropriately maintained.

Staffs were interviewed and procedures were explained as necessary to the inspectors. In general documents and staff were readily available for inspection as requested. Overall the SOPs reviewed were comprehensive and in place and the staff met well trained and experienced in their areas of expertise and responsibility. In many areas there were examples of “visual factory” concepts in place.

2.1 QUALITY ASSURANCE

A system of quality assurance was generally well established with comprehensive procedures for all expected key quality elements. In general the procedures reviewed were a very good standard reflecting a good level of input from personnel with a good knowledge of WHO GMP and SRA requirements. It was also clear that many of the procedures were very mature in their preparation with several key SOPs such as those for Change Management, Deviations and Investigation and CAPA and OOS with revision numbers in the 10 – 20 range suggesting multiple improvements over very many years and the impact of many audits by both internal groups, Corporate and NMRA inspections by SRAs.

Most of these key procedures are corporate procedures standardized across all production sites and therefore reflect considerable maturity. Any observations made were therefore, as might be expected, of a relatively minor nature.

The company is performing quarterly management reviews and OOT reviews also quarterly in addition to the APQR programme.

The APR for RH30 was reviewed and covered the period Feb 2012 to Jan 2013. Only 4 batches of RH30 had been produced and these were all made in July 2012 and all were commercial lot validation batches.

In summary:

- The production and control operations of hormone and other potent products were designed in a way that takes account of the requirements of GMP and these were clearly specified in written procedures.
- There was a relatively mature system for Quality Risk Management (QRM), with the first Risk assessments for the product in focus being performed in May 2011.
- Quality reviews were conducted and generally comprehensive and critique of the process and follow up generally good.
- There were procedures for effective and well used change control and deviations procedures with the number and level of examples being typical for a site of this size.

The company is in the process of implementing an updated computer based CAPA and deviation management system which will be fully integrated with the SAP ERP and IMS system during 2014. It utilizes the US based Pilgrim software.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) FOR PHARMACEUTICAL PRODUCTS

Good manufacturing practices generally were well implemented. Necessary resources were generally well provided for, 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.

2.3 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.

2.4 QUALIFICATION AND VALIDATION

Protocols and reports were in place for qualification and validation selected for review. 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 with the most stringent of the calculation of 0.1% of dose criterion – 10ppm and visually clean). The documentation in relation to the establishment of the worst case, sampling, recovery and cleaning validation were satisfactory. As might be expected due to the nature of the potent materials handled the worst cases were based the dose criteria

The company had identified what qualification and validation work was required. Documentary evidence was available that the premises, supporting utilities, equipment and processes have been designed, installed, operated in accordance with their design specifications.

2.5 COMPLAINTS

The procedure for handling product complaints was available for inspection. There were no complaints reported for the specific products inspected during the review periods selected for review.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was available for inspection. There had been no recall reported for the products inspected.

A corporate SOP was in place for recalls. Mock recall reviews are performed. (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

Production and quality control operations were not contracted out except the testing for particle size of APIs.

Contract laundry facility was utilised.

2.8 SELF INSPECTION AND QUALITY AUDIT

This was not covered by this inspection.

2.9 PERSONNEL

The company employed almost 3000 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.

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience working in Unit VIII. The specific duties of responsible staff 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.

2.10 TRAINING

Training was provided in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories. Training records were kept. Records for Analyst qualification and verification were in place for review. 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

Entry changing and washing/hand sanitization followed a written procedure. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The only area that was exceptionally was in the blistering operations where a level of interaction at the tablet blistering stage occurred with operators' gloved hands.

2.12 PREMISES

Construction of Unit VIII was started in 2003 and production was started in 2004. See SMF for details. The premises used for production and quality control were designed, constructed and maintained to suit the operation to be carry out. Measures were taken to minimise the risk of contamination/cross-contamination and took full account of the potent API materials or product stage being processed.

QC laboratories were situated on the first floor of the production unit. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents.

2.13 EQUIPMENT

The equipment installed was of a high standard and mainly supplied by well-known manufacturers. The facility was well designed and the equipment appeared to be running well.

Equipment inspected was qualified, calibrated, cleaned, and maintained. Records were kept in place. All equipment specifically inspected was found to be appropriately qualified, calibrated, cleaned, and maintained. Records were in place.

2.14 MATERIALS

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedure. Printed packaging materials were stored in secured conditions. Generally the system of checks were robust however several comments were made during the inspection concerning improving and making clearer and more unambiguous the connections between vendor addresses, manufacturing site addresses and that on various in house documents such as specifications, inspection documents and verifying how these related to Vendor supplied documentation.

Finished products were held in quarantine until their final release according to the procedure.

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were marked as such and stored separately. Finished product was not reworked and could be reprocessed according to the procedure. They were also status controlled by their status in the IMS system.

Waste materials

This was not inspected.

2.15 DOCUMENTATION

Documents were well designed, comprehensive, and prepared, reviewed and distributed with care in general. Documents were approved, signed and dated by the appropriate responsible persons. Documents were regularly reviewed and kept up to date.

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.

Deviation instructions and procedures were comprehensive and the examples chosen for review by the inspectors adequately handled and had been performed in accordance with the approved procedure. Computer software was used to manage the deviations but this is in the process of being updated (see above section on QA). Minor batch related deviations which had occurred during the production were required to be recorded in the BMR and to be reviewed at the batch release, currently how and by whom this manually recorded deviations to be transferred to the computer data base was considered to be not sufficiently detailed in the written procedure.

Packaging operations

Before packaging operations begun, steps were taken to ensure that the work area, packaging line, printing machine and other equipment were clean and free from any products, materials or documents used previously according to the procedure. The line clearance was performed

and recorded in BPR. Production records were reviewed as part of the approval process of batch release.

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.

The QC function was independent of other departments. Adequate resources were available to ensure that all the QC arrangements are effectively carried out.

A written programme for stability study was implemented. Stability and on-going stability samples were stored properly. Temperature in the incubators was continuously monitored. Incubators were equipped with alarm system.

Sampling and testing procedure of potent materials were inspected and considered satisfactory.

Reference standards

Official reference standards were used as well as working reference standards prepared by the manufacturer. Reference standards were properly labeled and stored.

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, as well as the corrective actions taken and planned, Unit 8, Cipla Ltd located in L-147, L-147/1, L147/2, L147/3, L147/4 and L-138, Verna Industrial Estate, Verna Goa, India was considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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 this WHOPIR

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.