

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Finished Product Manufacturer

Part 1: General information about the inspection

Name of manufacturer	Cipla Ltd. Goa Unit IX
Physical address	Plot No: L-139, S-103 & M-62 Verna Industrial Estate, Verna – Salcette - Goa, 403722 Goa India
Postal address	As above
Telephone number	+91 832 2782581/2782582/2889000
Fax number	+91 832 2782479/2782598/2782805
Summary of all the activities performed by the manufacturer Dosage forms and type of products	Unit IX Manufacture and distribution of : <ul style="list-style-type: none"> • Sterile products - small/large volume liquid injectables, lyophilized injectables, pre filled syringes, liposome injectables • Non-sterile products - dry syrup (for oral suspension), dry powder
Scope and type of inspection	Routine GMP inspection
Pharmaceutical dosage forms	Sterile products, aseptically filled
Focus of inspection - products in WHO PQ program covered in the scope at the time of inspection with the WHO reference number	Product under assessment
Date of inspection:	September 6 - 9, 2010
Programme	Prequalification of Medicines Programme

Part 2: Summary

Background information

The manufacturing site of Cipla Ltd, Plot No: L-139, S-103 & M-62 (hereafter referred to as Unit 9) 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 eight manufacturing sites in India:

- 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

Goa site has 9 separate production Units. Operations at this Goa site Unit 9 commenced in 2004.

Unit 9 manufactures sterile and non-sterile products - dry syrup (for oral suspension) and dry powder. It is physically separated from the other Goa units and is about 1km distant from them. Unit 9 was self sufficient with respect to laboratories and utilities, such as water purification and distillation, industrial and pure steam, compressed air and backup electricity.

History of WHO or regulatory agencies inspections

The Goa site Unit 9 has never been inspected by WHO prequalification team but has been inspected by other agencies:

- DFDA, Goa, India
- NDA, Uganda
- MHRA, UK
- MOH, Iran
- PPB, Kenya
- USFDA, USA
- PMPB, Malawi
- MOH, Egypt
- JFDA, Jordan
- MOH, Indonesia
- TGA, Australia
- ANVISA, Brazil
- SIDC, Slovak Republic

- INVIMA, Colombia
- MOH, Ukraine
- MOH, Oman

Focus of the inspection

The purpose of the inspection was to ascertain the level of GMP compliance for the manufacture of the product under assessment.

The areas inspected included:

- Receiving areas (raw materials and packaging materials)
- Storage areas for starting and packaging materials
- Sampling and dispensing areas
- Production areas related to the WHO product, including support areas such as washing, vial washing and sterilization, solution preparation, vial filling, vial crimping, labeling and inspection, cartoning, and finished product storage
- Quality control laboratory (chemical, stability testing, microbiological laboratory, printed material QC laboratory)
- Quality assurance and documentation
- HVAC, water, compressed air, nitrogen cylinders and nitrogen lines, pure steam, boilers, back up electricity generators and other support utility areas.

Documents reviewed included (but not limited to):

- Quality Risk Management
- Batch records
- Deviations
- Complaints
- Product Quality Review
- Validation protocols and validation reports
- Qualification protocols and qualification reports
- Training plans and records, medical records
- Various SOPs and related training records
- Calibration and qualification procedures and records
- Stability testing
- List of documents and SOPs reviewed

General information

Cipla had many corporate documents, for example raw material sampling and inspection, recalls, complaints, training etc.

2.1. Quality Assurance (QA)

A quality assurance system generally was implemented and maintained.

Product release was the responsibility of Authorized person, hierarchically independent from production.

Change Control

Change control was described in a written SOP and flow chart. Changes were classified.

Deviation management

Deviation management was described in a written SOP and flow chart. Deviations were classified.

A number of deviation reports were reviewed and found to be acceptably managed:

Product Quality Review (PQR)

The PQR for the 3 registration batches was reviewed. It followed the corporate PQR SOP which was acceptable.

Quality risk management (ORM)

There was a Quality Risk Policy for the site, and a corporate approach to risk management in the validation master plan.

The FMEA SOP was applicable to equipment, facilities and manufacturing operations which were likely to affect the product of process and for investigating the root causes of product complaints, OOS, deviations or problems.

QRM approach flow charts for process and equipment were available. QRM was found to be appropriately performed.

2.2. Good manufacturing Practices for Pharmaceutical products

Good manufacturing practices were implemented and generally maintained.

Necessary resources were generally provided, including qualified and trained personnel, adequate premises and space, suitable equipment and services, appropriate materials, containers and labels, approved procedures and instructions, suitable storage, adequate personnel, laboratories and equipment for in-process controls.

Manufacturing steps were recorded in batch manufacturing and packaging records; records were made during manufacture.

Instructions and procedures were generally written in clear and unambiguous language.

Qualification and validation were performed.

Inspected product batch documentation for a number of batches was reviewed.

2.3 Sanitation and Hygiene

The topic was covered during the inspection; no notable concerns were identified during the inspection. Overall there was an excellent approach to sanitation and hygiene.

2.4 Qualification and Validation

The key elements of the qualification and validation program were defined and documented in Validation Master Plan (VMP). Re-validation/re-qualification periods were specified.

Process validation

Process validation protocol and report were reviewed and found to be acceptable. The media simulation and sterilization validation reports for autoclaves and the dry heat tunnel also were reviewed.

Compressed air validation

Validation studies were performed annually for all user points.

Cleaning validation

Cleaning validation was covered for all product contact surfaces. A worst case approach using 2 molecules selected for toxicity and solubility was followed. The approach used both rinse solution and swabs testing. Equipment drawings indicating the sampling positions were available. All equipment parts which were in direct contact with the product were taken into account for total area calculations. Cleaning re-validation was carried out once in 5 years, if no changes occurred. Cleaning verification was carried out annually.

2.5. Complaints

Complaints were handled properly. Complaints register was available for inspectors. Complaints were trended.

2.6 Product Recalls

The responsible person for the recall was designated. Recalls were classified.

A mock recall was carried out once in two years on the corporate level.

2.7 Contract production and analysis

Manufacturing activities were not contracted out. Based on the contracts, some products were manufactured for other companies.

Six outside analytical laboratories were used for a few specific tests than can not be carried out at the site. Contract laboratories were audited regularly.

2.8 Self inspection and Quality Audits

This topic was not covered during the inspection.

Vendor qualification

SOP and flow chart was available for inspection. SOP was applicable for starting material (raw material, packaging material) manufacturers. Approved suppliers lists were available.

2.9 Personnel

In general, the personnel met and interviewed during the inspection were experienced, skilled and conscientious.

2.10 Training

Training files and related information for several staff members were checked:

2.11 Personal Hygiene

Direct contact was avoided between operators' hands and starting materials, primary packaging materials and intermediate or bulk product. All changing rooms were provided with photographs which described the gowning procedures. Adequate hand sanitation was practiced in all areas using automated hand disinfectant dispensing systems. Operators, including inspectors who wanted to enter clean room were required to pass the microbiological sampling program to verify clean room garment change and hygiene practices in the clean rooms.

2.12 Premises

Generally premises were located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of premises minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination. Premises were designed and constructed to facilitate good sanitation.

Storage areas were of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation.

Production premises were laid out to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

2.13 Equipment

Production equipment was in good condition. Production equipment was cleaned on a scheduled basis.

Laboratory equipment and instruments were suited to the testing procedures undertaken.

2.14 Materials

Materials were managed in the electronic Inventory Management System IMS.

Upon receipt, materials were checked against purchase orders. Starting materials were sampled 100% for identity tests and labeled with "sampled" labels.

Packaging materials sampling was carried out in accordance with Acceptable Quality Level (AQL).

2.15 Documentation

In general, the documentation system was established and maintained; documents were approved, signed and dated by appropriate responsible persons, regularly reviewed and kept up to date. Alterations made to documents were signed and dated. Specifications and testing procedures were available.

2.16 Good practices in production

At the time of inspection there was no production of the product under assessment, but other injections preparation and filling were checked.

The general design of the facilities was appropriate. However, equipment washing was deficient see observations below.

Processes were generally under control.

Manufacturing area audit

On the 07.09.2010 one member of the WHO team visited and entered all classified clean rooms after following the clean room entry procedures, and checked the situation regarding the manufacture of injections.

There was no negative observations regarding aseptic operations.

2.17 Good practice in Quality Control

Adequate facilities, personnel and approved procedures were available. Records of analysis were checked. During inspection particular attention was paid to the all the methods and instruments used the product under assessment API and finished product specifications and test methods, by following the method to the instrument, such as FTIR, Polarimeter, and HPLC apparatus etc. Then calibration records were checked, as well as analyst training and qualification and Out of Specification (OOS) investigations.

HPLC

Mobile phases were freshly prepared and not reused. Mobile phase was sonicated for 2-3 minutes and filtered under vacuum. HPLC columns were dedicated for each product/material and for each different type of test. Columns were not regenerated. Disposable vials were used for analysis.

OOS

OOS investigation and resolution procedure and flow chart SOPs were available for inspection, as well as SOP for Microbiological OOS investigations and flow charts. A number of OOS investigation reports were reviewed.

Analyst certification and qualification

Analysts competency list was available.

Stability studies

There have only been three registration batches made, which were still under stability studies, checked the incubators and found acceptable.

Reference substances

Reference and working standards were managed appropriately and stored under controlled conditions. One person was assigned as custodian for all primary and working standards.

Microbiology

The Microbiology Laboratory was segregated from the Chemistry Laboratory and had with its own AHU. Laboratory was made with all stainless steel panel. Major equipment were validated and revalidated annually.

Bacterial Endotoxin Testing

Only Commercially available imported kits were used. Kits and analysts were validated using the LAL competency check. Samples were always run with negative controls provided by the kit manufacturer.

The WHO team observed technician conducting a bacterial endotoxin test for a routine water test sample. The water bath temperature was checked by a calibrated digital display, and temperature 37±1°C was checked with calibrated thermometer. No negative observations were made.

Sterility testing

The sterility test was carried out by closed Millipore Steritest units using a Sartorius peristaltic pump, in a horizontal flow Class A LAF in a Grade B cleanroom, which was all stainless steel panel. Media was Fluid Thioglycollate and Soya Casein Digest broth. Growth promotion testing was with 6 pharmacopoeia organisms and one in-house isolate. The WHO team observed technician conduct a sterility test. No negative observations were made.

Negative control samples were always run for every sterility test sessions. The negative control samples were drawn from media that had been produced during media simulation trials. This was considered acceptable.

The sterility test was validated.

Media sterilization, growth promotion checks, water monitoring and microorganism identification was inspected. No negative observations were made.

Routine monitoring of water for injection and purified water included sampling points in the production and water supply areas – No negative observations were made.

Media simulation tests

There were more than 5000 vials filled for 3 consecutive runs, conducted every 6 months, with every operator participating every 12 months. Each vial size was checked on a 2 yearly cycle. The acceptance criteria and number of interventions and simulated worst case issues were checked and found acceptable. Overall, the media simulation of the aseptic filling operation was considered acceptable.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, reflected in the observations listed in the inspection report, Plot No: L-139, S-103 & M-62 Verna Industrial Estate, Verna – Salcette - Goa, 403722 Goa India, Unit IX, was considered to be operating at an acceptable level of compliance with WHO GMP.

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.