

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

Part 1: General information

Name of Manufacturer	Cipla Ltd.
Unit number	Unit IX
Production Block	Unit IX
Physical address	M-61, M62 and M-63, Verna Industrial Estate, Verna, Salcette, Goa - 403722, India
Contact person and email address.	Mr. Davinder Singh Technical Director Cipla Ltd Mumbai Central Mumbai 400008 India e-mail: dsingh@cipla.com Phone : 91 22 23094319
Date of inspection	21, 22, 25 and 26 November 2013
Type of inspection	Routine inspection
Dosage forms(s) included in the inspection	Solution for injection (Filled on a production line with capability for lyophilised powders – Aseptic lyophilisation was not inspected) Powder for oral solution
WHO product numbers covered by the inspection	TB217 Amikacin (as sulfate) 500 mg/2 ml, sterile injection HA367 Stavudine 1mg/ml (200 mg), powder for oral solution
Summary of the activities performed by the manufacturer	Production and quality control
Inspector(s)	Mr. Ian Richard THRUSSELL, (WHO) Ms. Xingyu Chen (WHO)

Part 2: Summary

General information about the company and site

The manufacturing site of Cipla Ltd, Plot No: M-61, M62 and M-63 (hereafter referred to as Unit IX) 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

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 and 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.

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. At the time of the inspection the Goa site had nine separate units dedicated to the manufacturing of bulk formulations and Finished Pharmaceutical Product (FPP). There was a further site (Unit X) under construction and nearing completion to be dedicated for cytotoxic OSDs. This site will move into the initial validation phase of the construction project in January 2014. 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.

Unit IX 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 IX was self-sufficient with respect to laboratories and utilities, such as water purification and distillation, industrial and pure steam, compressed air and backup electricity. The backup generator set was rarely used as there was a special supply agreement with a private electricity supply company that has proved reliable. In addition, critical zones, such as Class A uniform velocity air flow cabinets (LAFs) were supplied with an Uninterruptable power supply (UPS) that provides instantaneous power in the event of a failure, and the generator set was said to come into action within 20-30 seconds.

History of WHO and/or regulatory agency inspections

The vast majority (Approximately 80%) of products manufactured at Cipla Goa are exported, with the major portion being to markets under the supervision of SRAs.

As a result the overall site and particularly the OSD units have a long history of SRA inspections, including those of several EU member NMRAs, USFDA and Australian TGA.

Inspections specifically concerning Unit IX included:

- US FDA - last inspected in May 2013 (Unit I, III, IV, V, VIII and IX)
- Germany - last inspected in September 2013 (Unit V and IX)
- UK MHRA last inspected in 2012 (Whole Verna site including Unit IX)

The last WHO inspection of Unit IX for the products in scope was held in September 2010. The most recent USFDA inspection was held in May 2013; however the product scope was different to those herein i.e. the two WHO PQ products were not covered by the USFDA's inspection.

Focus of the inspection

The inspection focused primarily on the production and control of the sterile solution for injection Amikacin (as sulfate) 500 mg/2 ml. 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. The production of Stavudine 1mg/ml (200 mg) powder for oral administration was inspected briefly. Both specific WHO products were not in manufacture at the time of inspection but other similar representative products were being manufactured, allowing effective sampling of the GMP operations by the inspectors.

Inspected Areas

The programme of which this report forms part, involved a series of inspections of the various operations relevant to WHO Prequalification across the whole Goa Campus. Site inspections were also performed of Units I, II, IV, VII, and VIII as well as Unit IX reported herein. Over the entire two weeks on the Goa site the following systems were examined across the various units sampling operations in several but not every block so as to obtain a representative sample of the consistency of systems and their approach.

Inspection of QMS

- Product Quality Reviews
 - SOP for PQR for products under inspection
- 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 system
- Validation master plan and that for Cleaning validation

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
- 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

After introductions in the opening meeting with the concerned staff specifically involved in the inspection of Unit IX, the company made a brief presentation about the activities performed in Unit IX. This presentation provided details of:

- High level description of manufacturing and sterile product range in Unit IX
- Changes since last inspection and proposed changes.
- Confirmation of the relevant PQ Product list and pipeline
- Unit IX Organization charts (production, QA – issued on 14 and 12 September 2011) and job descriptions
- The index list of SOPs specific to the Unit

The inspectors confirmed of scope of inspection and inspection plan for this Unit during this meeting.

Subsequently at the beginning of each day, 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.

Staff 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 members of staff met were well trained and experienced in their areas of expertise and responsibility. In many areas there were examples of “visual factory” concepts in place.

Production and QC labs inspected specifically in Unit IX 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.
- Engineering & Services:
 - Preventive Maintenance
 - Calibration

Documents reviewed included but were not limited to:

- Facility layouts
- Training
- Change control
- Deviation control
- OOS procedure

- Specifications and testing procedures including critical components and product contact materials
- Supplier's Approval
- Water system
- Complaints log 2013
- BMR V30097
- SOP on operation steam sterilizer and media fill
- SOP on operation tunnel sterilizer
- SOP on specification, ordering, receipt, inspection, storage, issue, replacement and disposal of air filters
- SOP on Fumigation and defumigation through BMS
- SOP on Integrity checking of HEPA Filter for tunnel sterilizer and the last test certificate did by external institute QA-tech in May 2013.
- Microbiological data of environment monitoring
- Technical agreement with API manufacturer

2.1 QUALITY ASSURANCE

The 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 good knowledge of, and working familiarity with, the implementation of WHO GMP and SRA requirements generally.

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 these units were identical to those for Unit 8 inspected earlier in this inspection cycle. The output of these key systems specific to Unit IX examined during this part of the inspection were

- Product Quality Reviews for the products in focus.
- Deviations
 - System, log and requested reports for Unit IX
- Customer complaints
 - System, log and requested reports for Units Unit IX
- Recalls
- Change Control and Management
 - Log and requested reports System, log and requested reports for Unit IX
- Contract agreements
- Supplier approval system and requested examples
- Document Control
- Self-inspection records
- Validation master plan and that for Cleaning validation System, log and requested reports for Unit IX

Based on the specific aspects reviewed in this inspection and the corporate procedures used throughout the site seen earlier in Unit IX, it was considered that the system of quality assurance in the manufacturing units was appropriate to the manufacture of sterile pharmaceutical products.

2.2 GOOD MANUFACTURING PRACTICES (GMPs) 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.

2.3 SANITATION AND HYGIENE

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

Clean areas were cleaned frequently in accordance with an approved written programme. It was the practice to rotate the disinfectants used in the critical clean rooms. Monitoring of the microbial status of in use disinfectants was included in the environmental monitoring programme and was regularly undertaken. Disinfectants used in Grade A and B areas were sterilized before use.

2.4 QUALIFICATION AND VALIDATION

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

During the inspection procedures and most recent validations were reviewed for

- Media process simulations
- Dry heat tunnel validation
- Validation of the sterilization of stoppers by steam
- Validation of the sterilization of equipment for filling machine set up

Media process simulations

The most recent media process simulation studies were reviewed in detail. The overall general programme involved an initial validation consisting of 3 consecutive runs of each actual presentation and then this to be followed with routine revalidations of each line on a 6 monthly basis using worst case presentations. The relevant SOP required that more than 5000 vials to be filled in each specific run. In addition, requalification was designed to include one run using each actual vial and stopper presentation within the overall production programme, such that all vial sizes and suppliers were covered over 2-3 year period.

The media simulation study protocol was comprehensive and provided for a reasonable set of routine and exceptional interventions and the BMRs for the media simulations reviewed were well completed and comprehensive.

The most recent validation to support the manufacturing configuration of Amikacin sulfate injection with the exact configuration was the filling of one lot of typtone soya broth (TSB) filled in January 2013. This run involved filling approximately 8000 vials filled as a worst case exposure. The vials used in this study were to the same specification as those for the WHO injection product.

Every operator participates in at least one study every 12 months. The acceptance criteria and number of interventions and simulated worst case issues were reviewed and found acceptable. The vials were incubated at 20-25C for 7 days, then 30-35 for 7 days. Inspection for growth was carried out at a qualified inspection table by a trained operator. Reconciliation was performed each time the vials were transferred.

There have been no media fill positives to date in the studies performed however the media simulation procedure gave appropriate guidance on the actions to be taken in the event of a positive being found.

Overall, the media simulation of the aseptic filling operation was considered acceptable.

Steam Sterilization Studies

The validation of the washer-sterilizer for rubber closures was reviewed. The most recent revalidation was performed on 22 March 2013.

This equipment dates from 2006 when the equipment was first validated.

The validation protocol was reasonably comprehensive but a number of observations were made concerning a lack of clarity on several points. In particular there was some confusion in the reviewed documents on the requirements for the number of working sensors to be used and the calibration before and after use. The company uses both wired probes and wireless probes and there was confusion as to exactly what the requirements for each were. In practice however there were an adequate number of probes in the studies reviewed and this point does not affect in any way the outcome of the studies reviewed but does need to be clarified for future studies. The company response clarified and rectified these issues to the satisfaction of the inspectors.

Tunnel sterilizer validation

The Groninger tunnel sterilizer had been appropriately validated and procedures for the operation of the tunnel were reviewed and considered to be acceptable. Testing of the tunnel HEPAs were reviewed. Risks of oil burn and resultant particulate matter problems were considered during the qualification and adequate mitigation was in place.

2.5 COMPLAINTS

A procedure for handling of product complaints was available for review. The complaint log book of 2013 was reviewed. A complaint regarding a batch where two cartons of the Amikacin product that had been externally labeled with the incorrect batch number was reviewed. The investigation and corrective action had been made as part of the CAPA and were considered satisfactory.

2.6 PRODUCT RECALLS

The written procedure to recall products from the market was available for review. There was no recall for the inspected products.

2.7 CONTRACT PRODUCTION AND ANALYSIS

Production or quality control operations were generally performed in house except for the rabbit pyrogen test, which was contracted out.

2.8 SELF INSPECTION AND QUALITY AUDIT

This was not covered by this part of the overall Goa site inspection.

2.9 PERSONNEL

The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience. Specific roles and 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. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. An organization chart was available and showed appropriate reporting arrangements.

There was a tracking record in place to ensure that the appropriate staff had been covered by their involvement in the routine media fills being performed.

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.

2.11 PERSONAL HYGIENE

All personnel employed received initial and regular training in disciplines relevant to the correct manufacture of sterile products.

No notable concerns were identified during the inspection. Overall there was an excellent approach to sanitation and hygiene. Aseptic production personnel hygiene was routinely monitored by taking swabs from operators' hands. The results of this testing that was reviewed was satisfactory.

All changing rooms were provided with SOPs with clear photographs which pictorially described the gowning procedures. Adequate hand sanitation was practiced in all areas using automated hand disinfectant dispensing systems. Monitoring was performed after every exit from controlled clean rooms with an extensive number of Rodac plates. 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.

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.

The construction standard of the core aseptic clean area and the supporting operational areas were of a high standard. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and of materials that permitted the repeated application of cleaning agents and disinfectants, where used. Changing rooms were flushed with filtered air. Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were equipped with mirrors. It was confirmed that airlock doors could not opened simultaneously.

The aseptic fill line used for Amikacin injection was designed to be usable both for aseptic filling of liquid sterile FPPs and also had the option of filling solution to be subsequently lyophilized prior to capping. Currently the only approved WHO PQ products from this site are sterile solutions. The associated lyophilization facilities were not inspected in detail other than for their potential impact on liquid filling operations.

Storage areas

This was not covered in detail during the inspection. The design and standards of construction and the systems in operation were similar to those inspected in other facilities on the campus and reported elsewhere. A new ERP system for material management is to be introduced and the company plans for this to be completely implemented and validated by the end of 2014. This should be targeted for inspection in future visits.

Quality control areas

QC laboratories including the microbiological laboratory were on the first floor of the production unit. They were well 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.

2.13 EQUIPMENT

The equipment installed was of an acceptable standard. The facility was well designed and the equipment appeared to be running well.

The manufacturing vessels and filter systems relevant to the products in focus were not designed to be automatically cleaned and sterilized in place. Detailed manual procedures (together with pictures) were well documented.

All fixed pipework was clearly labelled to indicate the contents and the direction of flow.

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

All critical equipment such as sterilizers, air-handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems were subject to planned maintenance.

2.14 MATERIALS

Incoming materials were purchased from approved suppliers, sampled and tested according to written formal specifications and testing procedures. Printed packaging materials were stored in secured conditions.

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

Rejected, recovered, reprocessed and reworked materials

Rejected materials and products were required to be marked as such and stored separately. Finished product was not reworked and could be reprocessed according to the procedure.

2.15 DOCUMENTATION

In general documents were well designed, comprehensive, and prepared, reviewed and distributed with care. 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

There had been no commercial batch produced of any WHO PQ product since the last inspection. At the time of the inspection of the filling step, manufacture of Azithromycin Injection was in operation and its related filling procedures and practices inspected. Other aseptic injections were also in process and spot checked at key points in their process over the other days allocated to this inspection and the inspection of these injections' preparation and filling, sealing inspection and labelling provided adequate coverage of general and specific processes that were essentially similar to those used for the PQ products in scope.

The general design of the facilities was appropriate. Processes were generally under control.

Manufacture of Sterile preparations (Aseptic processing and sterilization by filtration)

Clean areas for the manufacture of sterile products were classified according to the required GMP grades of environment. Classification and routine monitoring was acceptable. Clean rooms and clean-air devices were routinely monitored while in operation. For Grade A and B zones, continuous particle monitoring was undertaken for the full duration of critical processing, including equipment assembly. To control the microbiological cleanliness of Grades A–D in operation the clean areas were monitored using a variety of applicable microbiological techniques according to documented procedures and sampling plans. Appropriate alert and action limits were in place for the results of particulate and microbiological monitoring.

Components were sterilized after washing. The preparation of solutions which were to be sterile-filtered during the process was carried out in a Grade C or better environment. The filling of the aseptically prepared products was carried out within a Grade A environment.

The process for Amikacin sulfate injection required that the prepared solution be filtered through a sterilized filter of 0.22 micron pore size. A second filtration through a further sterilized microorganism-retaining filter immediately prior to filling was also part of the standard process. The integrity of both of the two critical sterilized filters was verified before use and immediately after use.

Examination of the records including the monthly trend reports for the grade A and B zones were acceptable and appropriate limits were in place.

The results of WFI monitoring were also noted to be satisfactory with no significant trends present.

Finishing of sterile products

Containers were closed by validated methods. Crimping of the caps was performed after filling. Filled containers were inspected individually. Inspection was carried out visually in a qualified and adequately maintained light inspection station, to ensure proper illumination and background of matt black and white panels. Operators doing the inspection were qualified by periodic practical testing.

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. The line clearance was performed and recorded in BPR. Production records were reviewed as part of the approval process of batch release before transfer to the authorized person.

2.17 GOOD PRACTICES IN QUALITY CONTROL

Quality Control and Quality Assurance were together concerned with the sampling, setting and maintenance of specifications, and performing and monitoring testing operations.

The QA organization performed independent documentation and test review and performed the release procedure so as to ensure that all necessary and relevant production steps and 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 reviewed and judged to be satisfactory.

The QC function was independent of other departments. Quality control activity was not confined to laboratory operations but was also involved in all decisions concerning the quality of the product by giving expert technical advice.

It was considered that adequate QC and QA resources were available to ensure that all the QC arrangements are effectively and reliably carried out.

The laboratory operates according to general Cipla corporate and site wide systems that were reviewed in other inspections before and after the inspection of Unit IX. The following documents were specifically reviewed in Unit IX QC

- SOP on OOS procedure.
- SOP on Investigation of sterility test positives. This was discussed in detail. Recommendations were discussed as to how the company might make it clearer in the procedure how to proceed with investigation should the case of a sterility test positive arise.
- EM results for all key production areas with an emphasis on those for aseptic filling.

Specifications of Amikacin sulfate API and the standard testing procedure in place in the laboratory were reviewed. It was noted that the specification for impurities and the in house testing method had not yet been up dated to meet the current pharmacopeal version i.e. BP 2014. The company explained that as per EP 7.5, a specific and unique Chromatographic system i.e. Liquid chromatography with an EC (Electro chemical) detector having a polymeric mixing coil was required for analysis. It was explained that this had not been available within/across Cipla at the time E.P 7.5 became effective. Hence the stability testing to date was being temporarily performed alongside the current methods on samples done by suitably equipped external laboratory. The analytical test reports of the same were shown to the inspectors during the inspection and satisfactory. The results of Amikacin Sulfate were found to comply with the requirements of E.P 7.5 and BP 2013 (the monographs in effect during the period of the audit). The company reconfirmed that no commercial lots had been produced during this period and that prior to their production the necessary equipment would be acquired and method transfer validated.

The Microbiology Laboratory and Microbiology QC test areas were segregated from the Chemistry Laboratory and were located on the second level of the facility with their own AHU. Walling of the critical clean rooms was constructed from all stainless steel panels. Major equipment included De Lama Dry heat sterilizer and Autoclaves. These were validated and subject to an annual revalidation.

Sterility testing

The sterility test was carried out by closed Millipore Steritest units. Media was Fluid Thioglycollate and Soya Casein Digest broth, pre-incubated for 5 days for a contamination check. Growth promotion testing was with 6 pharmacopoeia organisms and one in-house isolate. Acceptance criteria were visible growth for bacteria in 3 days and 5 days for yeasts

and moulds were regularly performed. 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.

LAL testing

Commercially available imported kits were being used for endotoxin testing. Kits and analysts were validated using the LAL competency check. Lambda, ½ lamb and ¼ lamba samples were always run with the negative controls provided by the kit manufacturer. Equipment used for sample preparation and for the testing was either depyrogenated at 250° C or were certified pyrogen free disposables from a qualified commercial source.

Stability Testing

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

No specific comments were made other than those discussed above regarding the pending updating from the BP 2013 pharmacopeal methodology utilized for Amikacin API to new methodology with the introduction of BP 2014.

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 9 of Cipla Ltd. located in M-61, M62 and M-63, Verna Industrial Estate, Verna, Salcette, Goa - 403722, 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.