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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-IX,
Manufacturing license number, (delete if not applicable)	704; 749; 655; 832
Inspection details	
Dates of inspection	6 - 10 June 2016
Type of inspection	Routine GMP Inspection
Introduction	
Brief summary of the manufacturing activities	Manufacture and packaging of small volume aseptically-processed sterile products and those sterilized by filtration, and manufacture and packaging of unit and multi-dose non-sterile liquid dosage forms for internal use (powders for oral liquid

	suspensions).
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-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, Goa, Unit-IX facility was operational from the year 2005. The total built up area of the facility is 11651 sq. meters, and quality control laboratory (chemical, instrumentation, microbiology and stability testing) was available to support Unit-IX.
History	The last WHO inspection to Unit-IX was held in November 2013. In addition, Unit-IX has a long history of inspections by the stringent regulatory authorities, including those of several EU member NMRAs, USFDA and Australian TGA.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Production and controls of solution for injection and powder for oral suspension
Restrictions	None
Out of scope	None
WHO product numbers covered by the inspection	TB 217 – Amikacin (Sulphate) Solution for Injection 500mg/2ml IN017- Oseltamivir (Phosphate) Powder for oral Suspension 6mg/ml

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 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 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.

Gowning for visitors and use of disinfectant was found satisfactory.

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.

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 SOP on Handling of Complaints was reviewed. The procedure provided for recording and investigating any product complaint received from customers (local and export), medical professionals, regulatory authorities and to ensure that appropriate corrective and preventive actions were taken. The scope covered drug substances and drug products manufactured both for local and export market. The procedure cross referenced other relevant written procedures and included definitions of key terms to provide clarity. These include market complaint; internal product complaint; critical complaint; non-critical complaint; complainant; confirmed compliant; non-confirmed complaint; counterfeit products; adverse drug reaction and lack of effect. The procedure was noted to be adequate.

6. Product recalls

An approved procedure for recall of products was reviewed. No recall had been carried out in Unit-IX since the last WHO inspection in November 2013. The scope covered all products manufactured by the company for both local market (sale and physician's sample) as well as for overseas/export. Relevant written procedures were cross referenced in the procedure. Recall was classified as class I, II and III depending on the relative degree of health hazard presented by the product being recalled.

7. Contract production, analysis and other activities

Production or quality control operations were generally not contracted out except some tests. In addition, calibration of equipment & instruments and qualification of facility was contracted out.

The quality agreement between Cipla and Calitech described roles and responsibilities of contract giver and contractor acceptor including use of standards, retention of records, calibration and qualification of area which will be qualified by Calitech.

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

Not inspected due to time constraint.

9. Personnel

The manufacturer had an adequate number of personnel with the necessary qualification and practical experience. Responsible staff, 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. Steps were taken to prevent unauthorized people from entering production, storage and QC areas. An organization chart was available - and was appropriate.

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.

10. Training

The timelines were defined for induction module in the training procedure.

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

11. Personal hygiene

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.

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 of core clean area and the operations were of the high standard. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and 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. Airlock doors did not opened simultaneously.

The fill lines are designed applicable both for aseptic filling and to be lyophilized sterile FPPs.

Ground floor Unit-9 (production and warehouse) U09/GF/02, first floor: reserve samples and stability section and technical area and second floor, QC (chemical, instrumentation and micro), water system and technical area.

13. Equipment

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

14. Materials

Merck Life Science Pvt Ltd provided a certification based on inspector's request that Soyabean Casein Digest Medium used in media fill test is validated using gamma irradiation does of 30, 40 & 50 KGy and checked the physical properties, sterility testing and GPT. Based on the study, 40 KGy has been set as an optimum dose of irradiation. Manufacturer Assessment Questionnaire was sent by the Corporate Cipla to Merck Specialist Pvt

Ltd, Goa using a checklist to provide requested information on QMS and other general aspects. The assessment report did not provide any information about the gamma irradiation. It is to be noted that supplier was not audited by Cipla as yet though.

15. Documentation

The SOP on control of documents and Legacy were reviewed. It was revealed that documents were categorised as level 1 (quality manual), level 2 (corporate master documents and level 3 (Unit master documents).The company had a hybrid system for document management. Document control was either manual or computerized. Company only started migration to electronic document management in July 2016. A schedule for the migration plan was seen. Since the migration was still on-going, some documents were still presented as manual hard copies while others were generated electronically.

Document Management procedure was one of the SOP cross referenced by the Control of Documents SOP. It stated that documents were printed only in three forms- either as *"DISPLAY COPY", "UNCONTROLLED COPY"* and *"CONTROLLED COPY"* and *"STATELESS PRINT"*. It was, however, not clear how multiple printouts would be controlled.

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.

16. Good practices in production

There was no commercial batch produced of WHO PQ product since last inspection. The filling step was in operation for product of at the time of inspection, but other aseptic injections were in process and spot checked during key parts of the process over the days allocated to the inspection but other injections preparation and filling were checked.

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

Differential pressure, temperature and humidity were managed through BMS, and respective alarms were provided inside production area. Four probes of particle counter used in vial filling area (filling nozzle, stoppering, near stopper and infeed).

Local display unit for relative humidity, temperature, differential pressure and FFU (managed through BMS) was available. Finger access system (biometric) for authorized personnel was provided, total of 61 personnel (QA, Production, Engineering and Microbiologist) were authorized to enter area, same uniform for all personnel from different departments. Air lock (Grade-B), Change room-1 (Grade-C), Change room-2 (Grade-B) and Change room-3 (Grade-B).

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

The Microbiology Laboratory and Microbiology QC test was segregated from the Chemistry Laboratory and was on the second level of the facility with its own AHU. It was made with all stainless steel panels. Major equipment includes De Lama Dry heat sterilizer and Autoclaves which were validated and revalidated annually.

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.

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-IX, 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