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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, Indore**
Corporate address of manufacturer	Cipla Limited, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013
Inspected site	
Address of inspected manufacturing site if different from that given above	Cipla Limited Plot No 9, 10 and 15, Indore Special Economic Zone, Phase II, Pithampur, District Dhar, Pin Code: 454775, Madhya Pradesh, India
Unit / block / workshop number	Unit-I and IV
Manufacturing license number, (delete if not applicable)	Licence No. 28/2/2010 granted on 26/02/2010 (valid until 25/2/2020)
Inspection details	
Dates of inspection	3-6 October 2017
Type of inspection	Routine GMP inspection

Introduction	
Brief summary of the manufacturing activities	Cipla Ltd, Indore is situated at Indore Special Economic Zone (SEZ) at Pithampur, Dist. Dhar, (Madhya Pradesh). It is at a distance of about 40 Kilometers from Indore city. The operations commenced in Year 2010. The total area of site (Plot no 9 & 10) is approximately 153,100 sq. m. Plot No. 9 consists of following Units: Unit-I: form fill seal and liquid oral Unit-II metered dose inhalers Unit-III nasal sprays, eye drops and pre-filled syringes Plot No. 10 consists of Unit-IV (tablets, capsules, pellets, sachets and multi-inhalers).
General information about the company and site	Cipla Limited is a public limited company established in 1935 by Dr. K.A. Hamied and managed by a professional board of directors. It has its own management control & operation and has no parent company. Cipla manufactures products of various range including prescription, animal health care, over the counter (OTC) and active pharmaceutical ingredients, which are supplied to over 150 countries located in the various regions including USA, Europe, Australia, South America, Brazil, Middle East Asia and Africa. The corporate headquarters including the corporate quality assurance is located in Mumbai. Senior personnel are available in Mumbai for providing support to the manufacturing units in the area of technology, R&D, manufacturing, quality assurance, quality control and regulatory affairs. Import, export and distribution activities are monitored from the corporate office. Research centers are located at Vikhroli, Patalganga, Kurkumbh and Bengaluru. Cipla has eight manufacturing facilities in India: ▪ Active Pharmaceutical Ingredients are manufactured at Bengaluru, Bommasandra, Patalganga and Kurkumbh. ▪ Pharmaceutical formulations are manufactured at Goa, Patalganga, Kurkumbh, Baddi, Sikkim, Bengaluru and Indore SEZ.
History	The manufacturing site has been regularly inspected by WHO-PQT since 2010. The site was last inspected by WHO-PQT in October 2014.
Brief report of inspection activities undertaken	

Scope and limitations	
Areas inspected	**Document reviewed including but not limited to** • Organization Chart • Job descriptions for key personnel • Product Quality Review • Quality Risk Management • Management Review • Responsibilities of the quality units and production • Complaints and Recalls • Deviation control and change control • OOS and investigation • CAPA procedure • Material release • Validation and qualification • Data integrity • Product release • Sampling and testing of materials • Batch processing records • Materials management system • Purified water system • Internal Audit **Site visited:** • Unit-I and Unit-IV. • Stability study QC laboratory and control system • Starting material and finished Goods warehouse
Restrictions	None
Out of scope	Products not submitted to WHO for Prequalification
WHO product numbers covered by the inspection	HA365 Lamivudine/Nevirapine/Zidovudine 150/200/300mg MA064 Artemether/Lumefantrine 20/120mg HA060 Lamivudine/Zidovudine 150/300mg TB321 Linezolid Tablets 600mg MA115 Artemether/Lumefantrine Dispersible Tablets 20/120mg HA052 Zidovudine 100mg capsules HA053 Lamivudine 50mg/5ml oral solution HA200 Nevirapine oral suspension 50mg/5ml HA382 Abacavir oral solution 20mg/ml HA054 Zidovudine oral solution 50mg/5ml HA680 Dolutegravir Tablets 50mg

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 quality assurance system was in general terms implemented and maintained. Quality Assurance (QA) and Quality Control (QC) departments were independent from production. Production and control operations were specified in written form and GMP requirements were generally followed. Managerial responsibilities were specified in job-descriptions. Product and processes were monitored and the results were taken into account in batch release. Regular reviews of the quality of pharmaceutical products were conducted.

Product quality reviews and batch release were adequately performed as per the respective procedures. Change controls, deviations and quality risk management were performed according to the approved procedures.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

In general, good manufacturing practices were implemented. The necessary resources were generally provided. Manufacturing processes and quality control test requirements were generally well defined in approved documents. Validations, qualifications were performed according to the site policy and documented procedures. Adequate premises and equipment were available for production, in-process quality control and storage.

Significant deviations were recorded and investigated, root causes were determined and CAPAs were implemented with some exception. Systems were in place for handling complaints and recalling any batch of product from sale or supply.

The production was performed in a multi-product facility and production equipment was not dedicated. WHO prequalified products were produced in Unit-I and Unit-IV.

3. Sanitation and hygiene

The facilities and procedures for sanitation and hygiene established on the site were found to be adequate to ensure that premises and equipment were properly cleaned. The gowning and changing procedures for entry into the manufacturing facilities were adequate and procedures were displayed where necessary.

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 in the validation master plan. The VMP described life cycle approach for process validation which consisted of three stages.

Process validation, cleaning validation, product transfer, analytical method and product assessment for the selected products were reviewed and these were found to be adequate.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

5. Complaints

Handling of product complaints procedure was discussed and noted that complaints were received by the corporate quality assurance (CQA) based in Mumbai, investigated at the manufacturing site/ Drug Safety Department (based on nature of complaint) and response was also given by the CQA to customers. The complaints were handled using a system. It was noted that there was no complaints received for WHO prequalified products since the last WHO inspection. There were no critical confirmed complaints received for other products.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

6. Product recalls

A recall procedure was available for review. Statutory recall was performed for one of the non-WHO prequalified product in 2016.

7. Contract production, analysis and other activities

Not inspected due to time constraints.

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

Self-inspection / internal audits procedure was discussed. Approx. 60-70 internal auditors were qualified for the entire site. The internal audits were performed once every 6 month by at least two auditors. The internal audit schedule for Unit-I for 2017 was available. The internal audits were performed using internal audit checkpoints. A checklist was prepared using these checkpoints. The audit findings were classified into critical, major and

minor and timeline for their action was also defined. All internal audits must be closed within 90 days from the day internal audit report was issued. In addition to internal audits, the site QA head recommend adhoc audits which were unannounced in the nature. Beside this, the CQA also performs audits using a risk based approach. Auditor certification program was also in place. New auditors were subjected to training before their qualification.

9. Personnel

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible.

10. Training

Personnel training were required according to company procedure. To support the knowledge of personnel, the company provided training. The training programs were arranged into a scheduled program. Training conducted according to the procedure of training for employee.

11. Personal hygiene

The level of hygiene observed and the measures taken to maintain the facility were considered to be of a good standard in Unit-I and Unit-IV.

The approach to sanitation and hygiene was acceptable in general. Photos describing the gowning procedures were appended to the changing procedures and provided on the walls of changing rooms in the Unit-I and Unit-IV.

12. Premises

The premises for manufacturing, storage and quality control of products were generally of a satisfactory standard.

Premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. The company indicated that there were no other highly active products or non-pharmaceutical products manufactured in the area.

Warehouses were situated in separate floors, materials and products were controlled by a computerized system.

QC laboratories including the microbiology laboratory were separated from production areas. Sufficient space was given to avoid mix ups and cross-contamination. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

13. Equipment

Fixed pipework was clearly labelled to indicate the contents and the direction of flow. Balances and other measuring equipment of an appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Balances were verified daily, full scale calibration was carried out monthly. Daily verification of balances was carried out using minimum, middle and maximum weights.

Production equipment was cleaned on a scheduled basis. Production equipment was installed and maintained in a way to minimize the risk of contamination and cross contamination. Production equipment was identified as to its content or purpose and cleanliness status. The majority of the equipment was of European and Asian origin. The maintenance and cleaning status appeared good.

14. Materials

A brief inspection of the (electronically controlled material) warehouse was undertaken. Materials and finished products were stored in this store. Incoming starting materials and finished products were quarantined after receipt until they were released for use or distribution. The storage conditions (temperature and humidity) of the inspected products were controlled between 15 and 25^0C.

Materials in the warehouses were stored in mobile racks (compactor storage). SAP system was used for materials management. SAP system was validated at the corporate level and implemented to all Cipla units as indicated by the company.

15. Documentation

In general documents were designed, prepared, reviewed and distributed with care. Documents were approved, signed and dated by the appropriate responsible persons. Records were made or completed when any action was taken.

The issues related to this section have been adequately addressed, and the same shall be verified during future inspections.

16. Good practices in production

The raw materials for manufacturing of oral liquids and tablet were dispensed, processed, packaged and distributed under appropriate conditions. Actual yields were compared with expected yields at designated steps in the production process. Processing status of operation room was labelled with product names and batch numbers. In-process controls were performed by QC analysts. Manufacturing areas were accessed through secondary change rooms.

All core manufacturing, sampling and dispensing areas were as per ISO 8 classification and with dedicated air handling units to maintain temperature, relative humidity and pressure differential with plenum HEPA filter.

Local display units were placed in the production areas for the monitoring of relative humidity, temperature and pressure differential. Temperature and relative humidity were maintained throughout the production areas.

The issues related to this section have been adequately addressed, and the same shall 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. QC personnel had access to production areas for sampling and investigation as appropriate.

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, API and FPP finished products, environmental monitoring samples, and purified water samples.

QC laboratory of Unit-I was occupied on the first floor and adequate resources were generally available to ensure that the QC arrangements are effectively and reliably carried out. The laboratory had sections on stability, raw materials, finished products, packaging materials, instrumentation, chromatography and laboratory quality assurance.

Quality control laboratory of Unit-IV was located on the third floor. The laboratory was equipped with 31 HPLC and 3 GC systems which were connected with software.

The issues related to this section have been adequately addressed, and the same shall 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, as well as the corrective actions taken and planned, Cipla Ltd., Unit I & Unit-IV, located at Plot No 09, 10 & 15, Pharma Zone, Phase II, Indore Special Economic Zone, Pithampur, M.P., India 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