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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	Cipla Limited	
Corporate address of manufacturer	Cipla House Peninsula Business Park Ganpatrao Kadam Marg Lower Parel, Mumbai 400013 India	
Inspected site		
Name & address of manufacturing site	Cipla limited Old Madras Rd Virgonagar District Bengaluru Karnataka, 560 049 India DUNS: 915154892	
Synthetic Unit/Block/Workshop	Synthetics I, Synthetics VII, API Finishing Area	
Desk assessment details		
Date of review	19 July 2022	
APIs covered by this desk assessment	Not specific – general review of GMP compliance as per EU inspection information including Zidovudine, Granisetron, Amlodipine besilate	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
Finnish Medicine Agency, on behalf of EMA	Dates of inspection:	27 to 31 January 2020
	Type of inspection:	General GMP
	Block/Unit/Workshop:	API Block III and V, Lab Production II and Finishing area
	APIs covered:	Amlodipine Granisetron Zidovudine
US FDA, USA	Dates of inspection:	15 to 19 July 2019
	Type of inspection:	cGMP
	Block/Unit/Workshop:	Included API Block III / IV
	APIs covered:	Synthetic small molecule

Part 3	Summary of the last WHO inspection
Date and conclusion of most recent WHO inspection	Cipla Bangalore was considered to be operating at an acceptable level of compliance with WHO GMP guidelines: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. The inspection was closed out on 20th April 2014. A desk review was also done in 2020.
Brief summary of manufacturing activities	Production operations in buildings API-I, API-III and Synthetics-VII were covered. Production and packaging of Vinblastin Sulphate took place in block API-I. Levofloxacin Hemihydrate and Ritonavir were manufactured in block API-III and finishing and packaging steps were carried out in block Sysnthetics VII.
General information about the company and manufacturing site	Cipla was established in 1935 and it is managed by a board of directors. It manufactures and distributes a wide range of FPPs and APIs which are registered in several countries around the world. The headquarters are located at Mumbai and there are several manufacturing and R&D sites established in India. The site in Virgonagar was first licensed in 1978 and it is authorized to manufacture APIs for FPPs intended for human use. The manufacturing facilities are located approximately 45Km from Bangalore airport. The campus consists of separate blocks for the manufacture of APIs and intermediates. Anticancer APIs are manufactured in dedicated areas. According to the company antineoplastics are handled with sufficient operational controls and change over procedures. Finishing areas are located in separate blocks: Synthetics-I, Synthetics-VII, API Block-III, API Block-IV, Lab production and API Block-V. All APIs are manufactured in campaigns.
Focus of the last WHO inspection	The 2014 WHO PQ inspection covered the production and control of Levofloxacin, Ritonavir and Vinblastine. The inspection reviewed most of the sections of WHO GMP for APIs, including Quality Management; Personnel; Buildings and Facilities; Process Equipment; Documentation and Records; Materials Management; Production and In-Process Controls; Packaging and Identification Labelling of APIs and Intermediates; Storage and Distribution; Laboratory Controls; Validation; Change Control; Rejection and Reuse of Materials and Complaints and Recalls A desk review was done in 2020.
Areas inspected	The 2014 WHO PQ inspection focused on manufacturing, quality control and packaging activities of: APIMF156 Vinblastin Sulphate (production and packaging in workshop API-I) APIMF088 Levofloxacin Hemihydrate (production excluding finishing in workshop API-III and finishing and packaging in workshop Sysnthetics VII) APIMF 215 Ritonavir (production excluding finishing in workshop API-III and finishing and packaging workshop Synthetics VII)

Out of scope and restrictions (last WHO inspection)	N/A
WHO APIs covered by the last WHO inspection	APIMF 156 Vinblastine Sulphate (production and packaging in workshop API-I) APIMF 088 Levofloxacin Hemihydrate (production excluding finishing in workshop API-III and finishing and packaging in workshop Sysnthetics VII) APIMF 215 Ritonavir (production excluding finishing in workshop API-III and finishing and packaging workshop Sysnthetics VII)
Additional products to be covered by this desk assessment:	

PQT Number	API	Prequalification status
APIMF088	Levofloxacin hemihydrate	Accepted
APIMF004b	Artesunate	Accepted

Note: Artesunate is no longer manufactured

Abbreviations	Meaning
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
GMP	Good manufacturing practices
NC	Non conformity
NRA	National regulatory agency
PQR	Product quality review
PQS	Pharmaceutical quality system
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis
SOP	Standard operating procedure

Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
The manufacturing license and GMP compliance documentation were submitted. Valid until 31/12/2026.

b) Site master file (SMF):
A detailed SMF dated 12 July 2022 was submitted and found acceptable.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
Reviewed. No issues of concern were found.

d) List of all regulatory inspections performed in the last 3 years and their outcomes:

List of Regulatory Inspections

List of all regulatory inspections performed in the last 5 years with outcomes

Name of the competent authority	Inspection dates	Scope of Inspection	Inspection outcome
CDSCO (Central Drugs Standard Control Organization)	June 7-8, 2022	Written Confirmation inspection	Written Confirmation Certification received
State Licensing Authority	April 8, 2021	Routine Inspection	Facility Approved
FMA (Finnish Medicines Agency)	January 27-31, 2020	cGMP Inspection	Facility Approved
USFDA	July 15-19, 2019	cGMP Inspection	Facility Approved
State & CDSCO-India (Joint inspection)	July 04-05, 2019	cGMP Inspection	Facility Approved
ANVISA-Brazil	September 11-15, 2017	cGMP Inspection	Facility Approved.

Inspections from April 2017, considered for past 5 years inspection.

TGA-EDQM joint physical inspection was in June 9-11,2009, validity extended part of desktop review of USFDA inspection until January' 2023.

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
APQR (Annual product quality review) of Levofloxacin hemihydrate attached was submitted.

Ten (10) batches were produced and included in ~~I~~the PQR. There were no reprocessed batches, no returns, recalls or complaints. There was one OOS result reported and investigated. Results were trended and PpK calculated. Generally, the PQR was acceptable.

Artesunate batches FWA190004, FWA190005, FWA190006 were micronized in the period of 2019 and thereafter no other batches have been manufactured.

f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):

Levofloxacin - Batch: FDC 210447 production and analytical record submitted, manufactured in September 2021
Levofloxacin USP - Batch FDP210263 submitted, manufactured November 2021
LVF 4, Batch Manufacturing Record: Batch FDC210555 Analytical report

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
Levofloxacin Hemihydrate MBMR and MBPR submitted.
LVF-4 (Intermediate of Levofloxacin) MBMR submitted.
Generally, the BMR was acceptable.
Artesunate: Obsolete since 2019.

h) Recalls in the past three years related to APIs with quality defects:
There was no recall in the past three years related to any product manufactured on site with quality defects.

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:
A letter was submitted stating that self-inspections are conducted and CAPAs are implemented.

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):
Not applicable

k) Out-of-stock situations:
No out-of-stock situation is foreseen

l) Additional documents submitted:
None

m) The following information regarding waste management practices (As per WHO points to consider for manufactures and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance", Technical report series 1025, Annex 6):

Disposal procedure of Levofloxacin Hemihydrate product waste (Liquid and solid) - All waste generated at site are evaluated by External agency M/S ERM (Environmental Resource Management). The collected waste from Levofloxacin Hemihydrate are segregated separately and sent to authorized 3rd party E-NANO, Bangalore for thermal destruction through regulatory requirements as per Hazardous waste rule 2016. After the destruction, destruction certificate from vendor are received to ensure incineration.

Disposal of the liquid and solid waste, that contain residues of Levofloxacin Hemihydrate API and of its intermediates, generated during the Levofloxacin Hemihydrate manufacturing process: For the disposal of Levofloxacin Hemihydrate API and of its intermediates, generated during the Levofloxacin Hemihydrate manufacturing process following procedure is followed. All the liquid and solid waste from levofloxacin hemihydrate product are collected separately. Collected waste liquid and solid are sent to KSPCB (Karnataka State pollution Control Board) authorized incinerator with manifest Form 10. Post completion of incineration, certificate is received as evidence. This process is carried out by an external agency M/S ERM. Decontamination methods are not used for waste management of liquid waste as the liquid waste is not released to sewers/streams or into the municipality water.

Note: In general, these were found acceptable. Due to time constraints, documents were briefly reviewed and an in-depth inspection was not done.

Part 5	Conclusion – Desk assessment outcome

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site Cipla Ltd, located at Old Madras Rd, Virgonagar, District - -Bengaluru, Karnataka, 560 049, India is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

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

Part 6	List of guidelines referenced in this inspection report

1. 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. ***Short name: WHO GMP for APIs*** or ***TRS No. 957, Annex 2***
   untitled (digicollections.net)

2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report. Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO GMP Guidelines o***r ***WHO TRS No. 986, Annex 2***
   https://digicollections.net/medicinedocs/documents/s21467en/s21467en.pdf

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. ***Short name: WHO TRS 1010, Annex 9***
   https://digicollections.net/medicinedocs/documents/s23457en/s23457en.pdf

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   9789240020900-eng.pdf (who.int)

5. 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.
   Short name: WHO TRS No. 929, Annex 4
   https://digicollections.net/medicinedocs/documents/s21440en/s21440en.pdf

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
https://digicollections.net/medicinedocs/documents/s23455en/s23455en.pdf

7. 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.
Short name: WHO TRS No. 937, Annex 4
https://digicollections.net/medicinedocs/documents/s20108en/s20108en.pdf

8. 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.
Short name: WHO TRS No. 961, 957), Annex 1
https://digicollections.net/medicinedocs/documents/s18681en/s18681en.pdf

9. 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 3.
Short name: WHO TRS No. 957, Annex 3
https://digicollections.net/medicinedocs/documents/s22358en/s22358en.pdf

10. 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.
Short name: WHO TRS No. 961, Annex 6
https://digicollections.net/medicinedocs/documents/s19959en/s19959en.pdf

11. 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.
Short name: WHO TRS No. 961, Annex 7
https://digicollections.net/medicinedocs/documents/s18677en/s18677en.pdf

12. 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. ***Short name: WHO TRS No. 961, Annex 9***
https://digicollections.net/medicinedocs/documents/s18683en/s18683en.pdf

13. 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. ***Short name: WHO TRS No. 943, Annex 3***
https://digicollections.net/medicinedocs/#d/s21438en

14. 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.
Short name: WHO TRS No. 961, Annex 2
https://digicollections.net/medicinedocs/documents/s18682en/s18682en.pdf

15. 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.
Short name: WHO TRS No. 981, Annex 2
https://digicollections.net/medicinedocs/#d/s20177en/

16. 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.
Short name: WHO TRS No. 981, Annex 3
https://digicollections.net/medicinedocs/#d/s20175en/

17. 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.
Short name: WHO TRS No. 961, Annex 14
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

18. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3. ***Short name: WHO TRS No. 1019, Annex 3***
https://digicollections.net/medicinedocs/documents/s23697en/s23697en.pdf

19. 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. ***Short name: WHO TRS No. 992, Annex 4***
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. 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. ***Short name: WHO TRS No. 992, Annex 5***
Essential Medicines and Health Products Information Portal (digicollections.net)

21. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4. ***Short name: WHO TRS No. 1033, Annex 4***
9789240020900-eng.pdf (who.int)

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. 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
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

24. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.
Short name: WHO TRS No. 1010, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

25. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://digicollections.net/medicinedocs/documents/s23699en/s23699en.pdf

26. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2. **Short name: WHO TRS No. 1033, Annex 2**
9789240020900-eng.pdf (who.int)

27. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6. **Short name: WHO TRS No. 1025, Annex 6** 9789240001824-eng.pdf (who.int)