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Prequalification Unit Inspection services
WHO INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Zhejiang Apeloa Kangyu Pharmaceutical Co Ltd
Corporate address of manufacturer	333, Jiangnan Road, Hengdian, Dongyang, Zhejiang 322118, China
Inspected site	
Name & address of manufacturing site	Zhejiang Apeloa Kangyu Pharmaceutical Co Ltd 333 Jiangnan Road, Hengdian, Dongyang, Zhejiang Province, 322 118, China (People's Republic of) 120.29°E,29.15°N DUNS: 420823163 FEI: 3003744129
Synthetic Unit/Block/Workshop	Site No 1, Workshop No 3 • Section II (Building 18) • Section III (Building 17)
Manufacturing license number	No Zhe 20000362, expiry date December 30, 2020
Desk assessment details	
Start and end dates of review	07 – 10 September 2020
APIs covered by this desk assessment	APIMF 099 Levofloxacin hemihydrate
List of documents submitted	1. A list of all regulatory inspections performed in the last 5 years and their outcomes 2. FDA US Establishment inspection report December 3-7, 2018 3. CAPA to FDA US Establishment inspection December 3-7, 2018 4. PMDA, Japan inspection report October 23-25, 2017 5. CAPA to PMDA, Japan inspection October 23-25, 2017 6. Manufacturing authorization: No Zhe 20000362, expiry date December 30, 2020 7. GMP certificate: No ZJ20190145, valid until 11/29/2024 8. SMF and lay-outs of water treatment and air-handling systems 9. The list of all the products and dosage forms manufactured on-site 10. PQR Levofloxacin Hemihydrate 11. BMR/BPR and analytical raw data Levofloxacin Batch XX 12. Master BMR/BPR Levofloxacin 13. Declaration: self-inspection 14. Declaration: warning letter 15. Declaration: out of stock situations 16. Declaration: notifications of upcoming inspections by competent national regulatory

	authorities in the next 6 months 17. Declaration: recalls	
Any documents missing?	N/A	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
US FDA	Dates of inspection:	3 – 7 December 2018
	Type of inspection:	Surveillance inspection
	Block/Unit/Workshop:	• Site 1, Workshop 11 • Site 2, Workshop 1 • Site 2, Workshop 16 • Site 2, Workshop 18
	APIs covered:	• Dextromethorphan Hydrobromide • Pseudoephedrine HCl • Amantadine HCl • Fenbendazole WHO API under PQ was not specifically covered
PMDA Japan	Dates of inspection:	24 – 26 October 2017
	Type of inspection:	GMP compliance inspection
	Block/Unit/Workshop:	Site 1, Workshop 3
	API covered:	• Levofloxacin Hemihydrate for Levofloxacin Eye Drops 0.5% ("Nissin")
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	27 – 30 January 2015 Routine inspection 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, a decision on the compliance of Zhejiang Apeloa Kangyu Pharmaceutical Co. Ltd. with WHO GMP guidelines will be made after the manufacturer's response to all of the observations has been assessed". Inspection was closed 4 December 2015 as following: "The actions taken or proposed were considered acceptable and their satisfactory implementation will be verified during future inspections".	
Brief summary of manufacturing activities as of January 2015	Production, quality control of non-β-lactam APIs. Manufacturer of Cephalosporin API and FPP in separate blocks on the site (not inspected)	
General information about the company and manufacturing site as of January 2015	Zhejiang Apeloa Kangyu Pharmaceutical Co. Ltd. was established in 1993 and is a member of the Hengdian Group. The site inspected is located in Dongyang, Hengdian, P.R.C. and started operation in 1995. Key intermediates, APIs and some finished pharmaceutical products are manufactured at this site. The company has been licensed by the SFDA for the manufacturing of Active Pharmaceutical Ingredients (APIs) as well as Finished Pharmaceutical Products (FPP). Zhejiang Apeloa Kangyu Pharmaceutical Co., Ltd. has two manufacturing sites. One is located at the 333 Jiangnan Road, Hengdian Town and another is located at the 333	

	Second Jiangnan Road, Hengdian Town. Only the 333 Jiangnan Road of Hengdian Town site was inspected, where Levofloxacin hemihydrate is manufactured in Synthesis Workshop No. 3 and Ofloxacin is manufactured in Synthesis Workshop No.2. These workshops are dedicated to Levofloxacin (various salts) and Ofloxacin, respectively.
Focus of the last WHO inspection	The inspection focused on the production and control of Ofloxacin and Levofloxacin hemihydrate. The inspection covered most of the sections of WHO GMP for Active Pharmaceutical Ingredients and was conducted, with modification as necessary, according to a tentative inspection plan sent to the company in advance.
Areas inspected	Personnel • Organization Chart • Job descriptions for key personnel • Training procedures and records Quality Management • Product Quality Review • Quality Risk Management • Deviation control and change control • Complaints and Recalls • OOS and investigation • Supplier approval • Product release • Rejection and reuse of materials • Contract agreements • Document Control • Self-inspection Buildings and Facilities • Site layout • Design and construction • Utilities Warehouse(s) • Storage – quarantine, release, reject • Materials • Receipt, handling and storage • Identification • Sampling • Status Control • Temperature (and humidity) monitoring • Packaging materials Production (Documentation and site visit) • Batch document preparation • Production area • IPC sampling and testing • Contamination Control • Reprocessing and Reworking • Packaging • Cleaning • API testing and release • Batch record review

	Validation and qualification: • Validation Master Plan • Validation and qualification status (matrix) and schedule • Equipment qualification • Process validation Quality Control Laboratory (documentation and site visit) • Quality management system • Premises • Sampling and sample handling • Work allocation • Documentation: • Specifications and test methods • SOPs, logbooks, records • Worksheets and test reports • Contract testing • Stability program • OOS results • Analytical method validation • Evaluation of results, release and rejection procedures • Trending of results • Traceability • Materials • Chemicals and reagents • Reference standards • Retention samples • Equipment, instruments and devices Purified water system • Design & construction including documentation • Operation and maintenance • IQ/OQ/PQ • Monitoring and testing Engineering & Services: • SOPs, registers and records including: • Preventive Maintenance • Calibration
Out of scope and restrictions (last WHO inspection)	API not submitted to WHO for Prequalification
WHO APIs covered by the last WHO inspection	APIMF 099 Levofloxacin hemihydrate Ofloxacin
Additional products to be covered by this desk assessment:	N/A

Abbreviations	Meaning
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change controls
CoA	Certificate of analysis
GMP	Good manufacturing practices
PQR	Product quality review
APQR	Annual product quality review
SOP	Standard operating procedure
OOS	Out of specifications
OOT	Out of trends

Part 4	Summary of the assessment of supporting documentation

a) Manufacturing authorization and GMP certificate granted by the local authority:
Manufacturing authorization: No Zhe 20000362, expiry date December 30, 2020
GMP certificate: No ZJ20190145, valid until 11/29/2024

b) Site master file (SMF):
SMF submitted and reviewed. SMF written according to the WHO TRS No. 961, Annex 14

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
21 APIs are manufactured at site – therapeutic groups:

- Immune Modulator Agent
- Antineoplastic Agent
- Quinolone Antibacterial Agent
- Central Antitussives Agent
- β-lactam antibiotics
- Cephalosporins
- Antiviral Agent
- Anti-Parkinson's Agent
- Gastrointestinal Spasmolytic Agent
- Adrenergic Agonist Agent
- Antipyretic analgesic, non - steroidal anti - inflammatory Agent
- Anti-Alzheimer's Agent
- Anti-inflammatory and Antirheumatic Agent
- Disinfectants and Antiseptics
- Broad-spectrum Benzimidazole Anthelmintic Agent
- Broad-spectrum Antibacterial

23 FPPs are manufactured at site – therapeutic groups:

- β-lactam antibiotics, Cephalosporins
- Quinolone Antibacterial
- Antihypertensive Drug
- Antiviral Agent
- Antiepileptics
- Immune Modulator, Antineoplastic
- Macrolide Antibiotics
- H2 Receptor Antagonist
- Treatment of Angina Pectoris and Congestive Heart Failure
- Hemostatic
- Treatment of Digestive System Disease
- Disinfectants and Antiseptics
- Prevention and Treatment of Type A (including H1N1, H2N2, H3N2) Influenza Virus Infection
- Treatment of cold symptoms

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

Name of Authority	Dates	Scope product and process covered	Outcome
WHO PQ	January 27-30, 2015	API (Ofloxacin, Levofloxacin)	Approved
FDA USA	December 12-16, 2016	API (Dextromethorphan Hydrobromide, Pseudoephedrine HCl, Amantadine HCl)	VAI
PMDA, Japan	October 23-25, 2017	API (Levofloxacin)	Approved
NMPA, China	September 4-6, 2018	Tablets, Capsules	Approved
FDA, USA	December 3-7, 2018	API (Dextromethorphan Hydrobromide, Pseudoephedrine HCl, Amantadine HCl, Fenbendazole)	VAI
NMPA, China	January 3-5, 2019	Lyophilized powder for injection	Approved
NMPA, China	April 1-4, 2019	API (Amantadine HCl, Ephedrine HCl, Pseudoephedrine HCl)	Approved
MARA, China	June 5-6, 2019	API for veterinary use (Fenbendazole, Marbofloxacin)	Approved
NMPA, China	July 17-19, 2019	API (Dextromethorphan Hydrobromide)	Approved
NMPA, China	September 19-21, 2019	Tablets, Capsules, Powder for Suspension, Oral Solutions, Solutions (Topical Use) and API (Povidone-iodine and Cefetamet Pivoxil HCl)	Approved
NMPA, China	November 1-4, 2019	API (Ofloxacin, Levofloxacin, Levofloxacin HCl, Levofloxacin Mesylate, Rimantadine HCl and Ubenimex)	Approved

e) Most recent product quality reviews of the concerned WHO APIs:
Submitted and reviewed:
PQR Levofloxacin Hemihydrate 2019
PQR Levofloxacin Hemihydrate 2019 (Japanese market)

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant API:
Submitted and reviewed
- BMR Levofloxacin carboxylic acid synthesis Batch XX
- BMR Levofloxacin crude synthesis Batch XX
- BMR Levofloxacin Hemihydrate purification Batch XX
- BMR Levofloxacin Hemihydrate synthesis Batch XX
- BMR/BPR for blending and packaging of Levofloxacin Hemihydrate Batch XX
- CoA Levofloxacin Batch XX
- Batch analysis record Batch XX (raw data)

g) Master batch manufacturing and packaging records of the API of interest:
Submitted and reviewed
- BMR Levofloxacin carboxylic acid synthesis
- BMR Levofloxacin crude synthesis
- BMR Levofloxacin purification
- BMR Levofloxacin Hemihydrate synthesis
- BMR Levofloxacin Hemihydrate purification
- BMR/BPR for blending and packaging of Levofloxacin Hemihydrate

h) Recalls in the past three years related to APIs with quality defects:
Declaration submitted: no recalls in the past three years

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API has been performed and all matters dealt with:
Declaration submitted: a full self-inspection or external audit dedicated to the API has been performed and all matters dealt with

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):
Declaration submitted: no warning letter, or equivalent regulatory action, issued

k) Out-of-stock situations:
Declaration submitted: no out-of-stock situations

l) Additional documents submitted:
N/A

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* ***Zhejiang Apeloa Kangyu Pharmaceutical Co Ltd (site No 1, workshop No 3)***, located at ***333 Jiangnan Road, Hengdian, Dongyang, Zhejiang Province, 322 118, China (People's Republic of)*** 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 WHO TRS No. 957, Annex 2**
   http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf

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 TRS No. 986, Annex 2**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2.
   Short name: WHO TRS 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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. 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**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.
Short name: WHO TRS No. 961, 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. **Short name: WHO TRS 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. **Short name: WHO TRS 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. **Short name: WHO TRS 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. **Short name: WHO TRS 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.
Short name: WHO TRS 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. **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

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. **Short name: WHO TRS 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 production 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

21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5.
Short name: WHO GDRMP guidance or WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

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 Multisource guidance or WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

23. 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

24. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1015), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

25. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

26. 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
https://www.who.int/publications-detail/978-92-4-000182-4

27. 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://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1