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

Part 1	**General information**
Company information	
Name of Manufacturer	Zhejiang Langhua Pharmaceutical Co. Ltd.
Corporate address of manufacturer	No.7, Donghai 3rd Avenue, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai, Zhejiang, China GPS (Lat N28°42′00″ Lon E121°32′34″.)
Inspected site	
Name & address of manufacturing site	Zhejiang Langhua Pharmaceutical Co., Ltd. (Langhua) No.7, Donghai 3rd Avenue, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai, Zhejiang, China GPS (Lat N28°42′00″ Lon E121°32′34″.)
Synthetic Unit/Block/Workshop	-Zidovudine: B # 11, Workshop 113 B # 14 (also named 15A) -Levofloxacin hemihydrate: B #11, Workshop (110), B # 16, Workshop (161), B #03, Workshop (034). -Darunavir: B #15, Workshop (151)
Desk assessment details	
Date of review	22 July 2019 – 10 October 2019
APIs covered by this desk assessment	Zidovudine [WHOAPI-167] Levofloxacin hemihydrate [WHOAPI-203] Levofloxacin hemihydrate (Intermediate) [APIMF275] Darunavir (Intermediate) [WHOAPI-378]
List of documents submitted	-Drug manufacturing license -A list of Products Manufactured -Recent APQR of Zidovudine (AT00N) -Blank BMR of DR02N -GMP certificate -Levofloxacin (Bulk drug) Re-registration approval -Zidovudine (Bulk drug) Re-registration approval -Last FDA EIR -Last EDQM Inspection report.

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Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US FDA	Dates of inspection:	19 – 23/03/2018
	Type of inspection:	CDER surveillance inspection
	Block/Unit/Workshop:	-Building # 15, Workshop # 5 [Darunavir & Ibrutinib] -Building # 10, Workshop # 103 [Levofloxacin API & Enrofloxacin API] -Building # 11, Workshop # 110 [Levofloxacin API & Enrofloxacin API] -Building # 16, Workshop # 161 [Levofloxacin API] Building # 3, Workshop # 31 [Enrofloxacin API], Workshop #34 [Levofloxacin API]
	Type of APIs covered:	Darunavir Intermediate, Ibrutinib intermediate, Levofloxacin API & Enrofloxacin API.
EDQM	Dates of inspection:	1-3 November 2017
	Type of inspection:	Full Routine inspection for Spironolactone & Follow up of CAPAs for EDQM's last inspection dated 2014 on Zidovudine.
	Block/Unit/Workshop:	T05 (workshop for spironolactone)
	Type of APIs covered:	Spironolactone
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	-Date of inspection: 16-18 /05/2016 -Type of inspection: Routine *Based on inspection findings and subsequent responses, the inspectors recommended that the APIs Levofloxacin (APIMF 203) & Zidovudine (APIMF167) are considered to be manufactured in compliance with WHO GMPs for API published by WHO.*	
Brief description of manufacturing activities	The company manufactures 4 types of APIs at this site: Quinolones antibiotics including (Levofloxacin), Antivirus (Zidovudine), Cardiovascular and Antidepressant APIs. Penicillins APIs & FPPs were no longer produced on site. Activities done on site are: Production, QC, Packaging, storage and distribution of APIs.	
General information about the company and manufacturing	Zhejiang Langhua Pharmaceutical Co., Ltd. is a comprehensive manufacturing Enterprises focusing on APIs, Pharmaceutical Intermediates and CDMO projects. It was founded in 1986, formerly as Xinhua Pharma Chemical Co., Ltd. Huangyan Zhejiang, and it was named as Zhejiang Xinhua Pharmaceutical	

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site	Co., Ltd. in 2005, and then it was named as Zhejiang Langhua Pharmaceutical Co., Ltd. from 2013 Feb. It has about 467 employees. Total area of Langhua plant is 189,278 m2 Building area: 35,168 m2 Storage area: 9515 m2 Quality control area: 1880 m2
Focus of the last WHO inspection	The inspection focused on the production and control of Levofloxacin and Zidovudine APIs. It covered all the sections of WHO GMP for API including premises, equipment, documentation, materials, validation, sanitation & hygiene, production, QC and utilities, Validation, CC, Recalls & complaints, production & IPC, Storage & distribution, packaging & labelling.
Areas inspected	All production areas were inspected including: Areas where production of Levofloxacin and Zidovudine APIs took place, namely: -B#11, workshop 110 -B#16, workshop 161 [dedicated to levofloxacin] -B#3, workshop 034 (purification, drying & packaging) [Levofloxacin production] -B#14, all workshops. [dedicated to Zidovudine] -B#11, workshop 113 (purification, drying & packaging) [dedicated to Zidovudine]
Out of scope and restrictions (last WHO inspection)	Other production areas that were used for APIs other than Levofloxacin and Zidovudine.
WHO APIs covered by the last WHO inspection	- Levofloxacin (APIMF 203) - Zidovudine (APIMF167)
Additional products covered by this desk assessment:	- Levofloxacin hemihydrate (Intermediate) [APIMF275] - Darunavir (Intermediate) [WHOAPI-378]
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

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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:

- Drug manufacturing license NO.: Zhe 20000303, issued by: Zhejiang Food & Drug Administration (Seal), valid until: 20/10/2020.
- GMP certificate No.: ZJ20150047, issued by: Chinese FDA, valid until: 19/3/2020.
  - Scope: Bulk Drug (Zidovudine, Levofloxacin, Levofloxacin Lactate, Levofloxacin Mesylate, Levofloxacin Hydrochloride)
- Levofloxacin (Bulk drug) Re-registration approval by CFDA No.: GYZZH20094174, valid until: 30/11/2019.
- Zidovudine (Bulk drug) Re-registration approval by CFDA No.: GYZZH20094076, valid until: 9/11/2019.

b) Site master file (SMF):

- SMF Doc. No. SMP-AD033 Ver.21, issued on 29/6/2018 was reviewed and found acceptable in line with WHO guidance on drafting a SMF.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:

Serial No.	Proprietary Name	International Nonproprietary Name
1	Ciprofloxacin Hydrochloride	Ciprofloxacin Hydrochloride
2	Ciprofloxacin	Ciprofloxacin
3	Enrofloxacin	Enrofloxacin
4	Levofloxacin	Levofloxacin
5	Levofloxacin Hydrochloride	Levofloxacin Hydrochloride
6	Levofloxacin Lactate	Levofloxacin Lactate
7	Levofloxacin Mesylate	Levofloxacin Mesylate
8	Zidovudine	Zidovudine
9	Spironolactone	Spironolactone
10	Olanzapine	Olanzapine
11	IB05K (CASNo.:330786-24-8, English name:4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidine)	Ibrutinib intermediate
12	DR02N (CAS No.:156928-09-5,	Darunavir intermediate

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Serial No.	Proprietary Name	International Nonproprietary Name
	English name: (3R,3aS,6aR)-Hexahydrofuro [2,3-b] furan-3-ol)	

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

Date	Product/name	Authorities	Outcome
16-18/5/2016	Levofloxacin-Zidovudine	WHO	GMP Compliant
1-3/11/2017	Spironolactone	EDQM(EU)	GMP Compliant
7-10/12/2017	Ciprofloxacin Hydrochloride Olanzapine	CFDA	GMP Compliant
19-23/3/2018	General GMP inspection (including Levofloxacin, Darunavir, intermediate (DR02N), IB05K)	FDA (USA)	GMP Compliant

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):

- APQR for Levofloxacin issued on 29/3/2019 was reviewed, it contains summary for all the number of batches produced (63 batches) with total quantity 9808.14 kg, included critical process parameters & specifications trends, also trends for raw materials, yield of each stage, stability study data, 5 OOS review,3 deviations, 25 CC &. 1 reprocessed batch.

- APQR of DR02N issued on 29/3/2019 was reviewed, it contains summary for all the number of batches produced (39 batches) with average batch size 707 kg, included critical process parameters & specifications trends, also trends for raw materials, yield of each stage, stability study data, OOS review, deviations, CC &.no reprocessed or rework batch.

- APQR of DR02N issued on 29/3/2019 was reviewed, it contains summary for all the number of batches produced (39 batches) with average batch size 707 kg, included critical process parameters & specifications trends, also trends for raw materials, yield of each stage, stability study data, OOS review, deviations, CC &.no reprocessed or rework batch.

- Recent APQR of Zidovudine (AT00N) issued on 29/3/2019 was reviewed, it contains summary for all the number of batches produced (58 batches) with total quantity 14626.52 kg, including critical process parameters & specifications trends, also trends for raw materials, yield of each stage, stability study data, 5 OOS review, 2 deviations, 4 CC & one reprocessed batch.

- Note: There was no statistical measure to process capability in all PQRs.

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

-Complete BMR of Levofloxacin, Zidovudine & DR02N were submitted & reviewed.

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g) Master batch manufacturing and packaging record(s) of the API(s) of interest:
- Blank BMR & packaging of Levofloxacin, Zidovudine & Darunavir intermediate were reviewed and found acceptable with detailed information on production process, IPC, product specifications & equipment

h) Recalls in the past three years related to APIs with quality defects:
- A statement letter signed by QA manger declared that no recalls in the past three years related to APIs manufactured at their 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:
-Two external audit reports were conducted on the site:
1- The first audit focused on the activities and systems involved in the storage, production, testing and control of active pharmaceutical products especially; Zidovudine.
2- The second audit focused on the assessment of the quality system with respect to the manufacturing, control and testing of Levofloxacin.
-A confirmation letter signed by head of quality declared that full self-inspection or extremal audit dedicated to the API(s) has been performed and all matters dealt with for Darunavir intermediate and levofloxacin hemihydrate intermediates.

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):
-A statement letter signed by QA manger declared that no warning letter, or equivalent regulatory action, was issued by any authority, to which the site provides or has applied to provide any API(s) manufactured at their site.

k) Out-of-stock situations:
-A statement letter signed by QA manger declared that no out of stock situations have taken place in the last 3 years and no existing foreseen situations in the nest year.

l) Additional documents submitted:
-APQR of Zidovudine 2016 & 2017.

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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 Langhua Pharmaceutical Co., Ltd. (Langhua) No.7, Donghai 3rd Avenue, Zhejiang Provincial Chemical and Medical Materials Base Linhai Zone, Linhai, Zhejiang, China, GPS (Lat N28°42'00" Lon E121°32'34")*** 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***
   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 GMP Guidelines*** or ***WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

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

4. WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fourty-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/

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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
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. 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, 2019 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

7. 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://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

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. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

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
http://www.who.int/medicines/publications/44threport/en/

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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

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
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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. 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

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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***
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 TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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

23. 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

24. 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