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Prequalification Unit Inspection Services
WHO INSPECTION REPORT
(WHOPIR)
Desk Assessment of Finished Product Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	Zhejiang Huahai Pharmaceutical Co. Ltd.	
Corporate address of manufacturer	Xunqiao, Linhai, Zhejiang 317024, China Tel: 86 576 85010288 Fax: 86 576 85016013 http://www.huahaipharm.com	
Contact person	Linda Lin Head of Regulatory Affairs Tel: +86-576-85016200, +86-13958570355 regulatory_affairs@huahaipharm.com lindalin@huahaipharm.com	
Inspected site		
Name & address of manufacturing site	Zhejiang Huahai Pharmaceutical Co. Ltd. Xunqiao, Linhai, 317024 Zhejiang, China DUNS No.: 530 732 460 GPS: 28°48'18.64"N 121°09'58.87"E FEI: 3003999190	
Production Block/Unit	Building F2, Workshop V	
Manufacturing license number	Zhe20000311, issued by NMPA on 24 April 2023, is valid until 12 January 2025 for tablets, oral suspensions, granules, API, freeze-dried powder injections (including anti-tumor), small-volume injections (including anti-tumor), hard capsules, and soft capsules.	
Desk assessment details		
Start and end dates of review	18th December – 19th December 2023	
Inspection record number	INS-FPP-2018-0026	
Products covered by this desk assessment	CV016 Nirmatrelvir Tablet, film-coated + Ritonavir Tablet, film-coated 150mg + 100mg	
Any documents missing?	N/A	
Part 2	**Summary of SRA/NRA inspection evidence considered**	
Landesamt Für Soziales, Jugend und Versorgung (Germany)	Dates of inspection:	04 – 08 September 2023
	Type of inspection:	A distant assessment within the frame of a product-related routine GMP inspection referring to GMP Guideline Part I

	Block/Unit:	Building F2, Workshop V, Dispensing and Granulation Center, Unit B, and Unit C for tablets (Bulk-production); Packaging Center (Primary packaging and Secondary packaging)
	Type of products/Dosage forms covered:	1. VIRAMUNE, Immediate Release Tablets Nevirapine Tablets, 200mg, 14/ 60/ 120 Tab. in Alu-PVC – Blister 2. VIRAMUNE XR, Extended Release Tablets Nevirapine Tablets, 400 mg, 30 / 90 Tab. in Alu-PVC – Blister 3. RIVAROXABAN Tablets Rivaroxaban tablets 10 mg, 15 mg, and 20 mg in a drum, blister, and bottle SITAGLIPTINE / METFORMINE Tablets Sitagliptin + Metformin Hydrochloride tablets, 50 mg + 850 mg/ 50 mg + 1000 mg
JAZMP Agency for Medicines and Medical Devices of the Republic of Slovenia	Dates of inspection:	5 – 8 July 2023
	Type of inspection:	GMP inspection
	Block/Unit:	Bulk tablets, Building F2
	Type of products/Dosage forms covered:	1. Quetiapine hemifumarate film coated tablets 2. Gliclazide film-coated tablets
US FDA	Dates of inspection:	28 June – 2 July 2021
	Type of inspection:	Pre-announced mission-critical for cause compliance follow-up cGMP inspection
	Block/Unit:	1. API workshop 3 2. API workshop 8 3. API workshop 13 4. API workshop 14 5. FDF (finished dosage forms) Building F1, workshop 6
	Type of products/Dosage forms covered:	1. APIs 2. Solution for injections
Landesamt Für Soziales, Jugend und Versorgung (Germany)	Dates of inspection:	26 – 30 August 2019
	Type of inspection:	General GMP inspection of the finished dosage form Viramune, immediate-release tablets 200 mg and Viramune XR extended-release tablets 400 mg
	Block/Unit:	Workshop V, line C for tablets (bulk production, primary packaging blister and secondary packaging)
	Type of products/Dosage forms covered:	1. Viramune, immediate release tablets 200 mg 2. Viramune XR extended release tablets 400 mg
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	The last WHO inspection of Zhejiang Huahai Pharmaceutical Co. Ltd., located at Xunqiao, Linhai, 317024 Zhejiang, China (building F1, workshop I) was performed by from 25 to 28 July 2017.	

Summary of manufacturing activities	Production and Quality control of oral solid dosage forms
General Information about the company and manufacturing site	The site included the production of API and OSD. An R&D facility was located on the same site, in the building C2. Efavirenz film coated tablet 600 mg and Raltegravir film coated tablet 400 mg were manufactured in Workshop 1, building F1. There were four different production lines in Workshop 1, of which three were wet granulation lines and one dry granulation line. It was non-dedicated workshop with up to 33 different products produced.
Focus of the last WHO inspection	Production and Quality control of: 1. HA 337 Efavirenz film-coated tablet 600 mg 2. HA 673 Raltegravir film-coated tablet 400 mg
Areas inspected	1. Starting materials, packaging components, intermediates and finished products warehouses, including sampling areas 2. Production facilities in Building F1, Workshop 1 3. QC facilities Building C1 and C2 4. Purified water system 5. HVAC system
Out of scope and restrictions (last WHO inspection)	Products out of PQ scope
WHO products covered by the last WHO inspection	HA 337 Efavirenz film-coated tablet 600 mg HA 673 Raltegravir film-coated tablet 400 mg
Abbreviations	**Meaning**
AHU	Air handling unit
API	Active pharmaceutical ingredient
BMR	Batch manufacturing record
BPR	Batch production record
CAPA	Corrective and preventive action
CC	Change control
FPP	Finished pharmaceutical product
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
SMF	Site master file
SOP	Standard operating procedure

Part 4	Summary of the assessment of supporting documentation

a) List of all regulatory inspections performed in the last 5 years and their outcomes:

Dates of inspections	Type of inspection	Authority	Result	Scope (workshop)
25 Feb. 2019 – 01 Mar. 2019	Pre-approval Inspection	ANVISA/Brazil	Pass	Capsules &Tablets (Workshop I, V)
20 – 31 May 2019	For-cause Inspection	FDA/US	OAI	All products for the US
17 – 19 Jun. 2019	General inspection	NMPA/China	Pass	Tablets (Workshop II)
24 – 28 Jun. 2019	Pre-approval Inspection	FDA/US	Pass	Injections (Workshop VI)
26 – 29 Aug. 2019	Pre-approval Inspection	LSJV/Germany	Pass	Tablets (Workshop V)
21 – 24 Oct. 2019	Pre-approval Inspection	JAZMP /Slovenia	Pass	Tablets (Workshop V)
25 – 27 Nov. 2019	General Inspection	NMPA/China	Pass	Tablets (Workshop IX)
18 – 20 May 2020	General Inspection	NMPA/China	Pass	Tablets (Workshop I, IX)
13 – 15 Jan 2021	General Inspection & Pre-approval Inspection	NMPA/China	Pass	Tablets (Workshop I, II, III, V)
28 Jun. – 2 Jul. 2021	For-cause Follow-up Inspection	FDA/US	NAI	All products for the US
7 – 10 Sep 2021	General Inspection & Pre-approval Inspection	NMPA China	Pass	Hard capsules (Workshop V)
27 – 30 Jun. 2022	General Inspection & Pre-approval Inspection	NMPA/China	Pass	Freeze-dried powder injection (Workshop VII)
28 – 30 Jun. 2023	General Inspection	NMPA/China	Pass	Tablets (Workshop II, III, IV)
28 – 30 Jun. 2023	General Inspection & Pre-approval Inspection	NMPA/China	Pass	Tablets (Workshop I, IX)
5 – 8 Jul. 2023	General Inspection	JAZMP /Slovenia	Pass	Tablets (Workshop V)
9 – 11 Aug 2023	General Inspection	NMPA/China	Pass	Hard capsules (Workshop IX, V)
4 – 8 Sep. 2023	General Inspection	LSJV/Germany	Pass	Tablets (Workshop V)

b) Manufacturing authorization granted by national authorities:
Manufacturing authorization number Zhe20000311, issued by NMPA on 24 April 2023, valid until 12 January 2025 for tablets, oral suspensions, granules, API, freeze-dried powder injections (including anti-tumor), small-volume injections (including anti-tumor), hard capsules and soft capsules.

c) Site master file:
The site master file and its Annexes were reviewed. The SMF was written according to the 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.

d) List of all the products and dosage forms manufactured on-site:
The list has been provided and reviewed as part of this desk assessment.

e) Most recent product quality reviews (PQR) of the concerned WHO product:
The PQR for Nirmatrelvir Tablets co-packaged with Ritonavir Tablets, review period June 21, 2022 – November 23, 2023, was submitted and checked:

- Three (3) validation batches manufactured:
- OOT – 3
- Deviations - 3

Taking into account that only validation batches of Nirmatrelvir Tablets co-packaged with Ritonavir Tablets were manufactured, the PQR for Escitalopram tablets 5 mg, 10 mg, and 20 mg, USP, review period August 28, 2022 – August 27, 2023, was requested, reviewed and found to be acceptable:

- Complaints and adverse reactions – 12
- Change Control – 8
  - ✓ Production – 5
  - ✓ Specification – 1
  - ✓ Engineering - 2
- Deviations – 2
- No returns and recalls, OOS/OOT

f) Batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant products:

The following records were reviewed and found to be acceptable:

1. Batch manufacturing record of batch 0000043711 of Nirmatrelvir tablets (150,000 tablets)
2. Batch packaging record of batch 0000045551 of Nirmatrelvir Tablets co-packaged with Ritonavir Tablets 150mg/100mg
3. Analytical report (CoA) of the packaged product, batch 0000045551-ROA (Initial)
4. Analytical report (CoA) of the packaged product, batch 0000045551-ROA (current specification)
5. Analytical part of Nirmatrelvir Tablets, batch 0000043711
6. Analytical part of Ritonavir Tablets, batch 0000045555
7. Analytical part of co-packaged drug product, batch 0000045551 (Nirmatrelvir tablets)
8. Analytical part of co-packaged drug product, batch 0000045551 (Ritonavir tablets)

g) Master batch manufacturing and packaging records of the product of interest:

The following master records were reviewed and found to be acceptable:

1. Master batch manufacturing record of Nirmatrelvir Tablets 150mg (150,000 tablets)
2. Master batch manufacturing record of Nirmatrelvir Tablets 150mg (800,000 tablets)
3. Master batch packaging record of Nirmatrelvir Tablets co-packaged with Ritonavir Tablets 150mg/100mg

h) If any of the products are sterile, the completed batch records for the most recent media fill validation that is relevant to the product of interest and report on its outcome:

Not applicable

i) Recalls in the past three years related to products with quality defects:

Zhejiang Huahai submitted a statement that no recalls were executed in the past three years.

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

Zhejiang Huahai submitted a statement that a full self-inspection or external audit dedicated to the product had been performed, and all matters dealt with.

k) Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:

Zhejiang Huahai submitted a statement that no warning letters, or equivalent regulatory action, were issued by any authority for the concerned site.

l) Out-of-stock situations:

Zhejiang Huahai submitted a statement that no out-of-stock situations are foreseen.

m) Additional documents submitted:
Product Quality Review of Escitalopram Tablets USP.

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 Huahai Pharmaceutical Co. Ltd.,** located at **Xunqiao, Linhai, 317024 Zhejiang, China**, namely Building F2, Workshop V, is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

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

Part 6	List of guidelines referenced in this inspection report

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.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

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.
   Short name: WHO TRS No. 957, Annex 2
   https://www.who.int/publications/m/item/annex-2-trs-957

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/publications/m/item/trs1010-annex9

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
   https://www.who.int/publications/m/item/annex-3-trs-1033

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://www.who.int/publications/m/item/annex-4-trs-929

6. 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
   https://www.who.int/publications/m/item/trs957-annex1

7. 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://www.who.int/publications/m/item/trs957-annex3

8. 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://www.who.int/publications/m/item/Annex-8-trs-1010

9. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditionning 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://www.who.int/publications/m/item/trs1019-annex2

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 4
    https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 2
    https://www.who.int/publications/m/item/trs1044-annex2

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***
    https://www.who.int/publications/m/item/trs943-annex3

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

https://www.who.int/publications/m/item/trs961-annex2

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
https://www.who.int/publications/m/item/trs981-annex2

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
https://www.who.int/publications/m/item/annex-3-trs-981

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
https://www.who.int/publications/m/item/tr961-annex14

17. 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://www.who.int/publications/m/item/trs1019-annex3

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
https://www.who.int/publications/m/item/trs992-annex4

19. 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://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

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
https://www.who.int/publications/m/item/trs992-annex5

21. WHO Recommendations for quality requirements when plant – derived artemisinin 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

https://www.who.int/publications/m/item/trs-992-annex-6

22. 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
https://www.who.int/publications/m/item/annex-4-trs-1033

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.
Short name: WHO TRS No. 996, Annex 10
https://www.who.int/publications/m/item/trs966-annex10
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***
https://www.who.int/publications/m/item/trs1010-annex10

25. 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
https://www.who.int/publications/m/item/annex-2-trs-1033

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/m/item/trs-1025-annex-6

27. 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. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

27. 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/m/item/trs1025-annex4