World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Unit Inspection Services
WHO PUBLIC INSPECTION REPORT

Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	Zhejiang Jiuzhou Pharmaceutical Co, Ltd
Corporate address of manufacturer	99 Waisha Road, Jiaojiang District Taizhou Zhejiang, 318000 PR of China
Inspected site	
Name & address of manufacturing site	Zhejiang Jiuzhou Pharmaceutical Co, Ltd 99 Waisha Road, Jiaojiang District Taizhou Zhejiang, 318000 PR of China Phone No.: 86-576-88827681, 86-576-88827549 DUNS : 654682061.
Synthetic Unit/Block/Workshop	N/A
Desk assessment details	
Date desk assessment completed	23 August 2022
APIs covered by this desk assessment	WHOAPI-458, APIMF458
List of documents submitted	a) A list of all regulatory inspections performed in the last 5 years and their outcomes, including inspections with "non-compliant" outcomes; b) Current full inspection report(s), including deficiency letters, for inspections performed by a competent stringent regulatory authority in the past three years with a certified translated copy where this is not in English; c) Proof of CAPA implementation and final decision by the competent stringent regulatory authority related to observations or deficiencies noted in the latest inspection report or to any warning letter or equivalent regulatory action (production-line specific); d) A copy of the manufacturing authorization and GMP certificate

	granted by the local national authority together with a certified translation, where this is not in English; e) A site master file whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format; f) The list of all the products and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary Names (INN), including all types of chemicals and products (e.g., pesticides, herbal medicines, chemicals or veterinary products, etc.); g) The most recent product quality review(s) (PQR)(s) of the concerned product(s); PQR(s) or equivalent documentation covering all required subsections and trend results, including statistical evaluation; h) The completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s); i) The list of any recalls in the past three years related to any product manufactured on site with quality defects; j) A confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with; k) Master batch manufacturing and packaging record(s) of the WHO product(s) of interest; l) 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; m) Description of any recent or foreseen out-of-stock situations; n) A list of notifications of upcoming inspections by competent national regulatory authorities in the next 6 months; o) A table to specify which parts of the manufacturing process for the concerned product(s) were covered by the inspection of the competent SRA authorities performed in the last 3 years	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last) and comments**	
USA FDA	Dates of inspection:	10 to 13 September 2018
	Type of inspection:	GMP for APIs
	Block/Unit/Workshop:	N/A
	APIs covered:	Non sterile APIs
	Final conclusion of the inspection report:	Accepted – compliance with GMP
	Comments/observations on the scope and	Acceptable

	comprehensiveness of the inspection report and on the appropriateness of the CAPAs in lieu of an onsite inspection by WHO:	
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	No WHO PQT inspection has been performed at this site	
Brief summary of manufacturing activities	N/A	
General information about the company and manufacturing site	N/A	
Focus of the last WHO inspection	N/A	
Areas inspected	N/A	
Out of scope and restrictions (last WHO inspection)	N/A	
WHO APIs covered by the last WHO inspection	N/A	
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 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:
A valid GMP certificate was provided.

b) Site master file (SMF):
A SMF dated April 2022 was submitted and reviewed.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:
A full list of APIs was provided and reviewed.

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

No.	Inspection Date	Audit Agency	Product related	Outcome
1.	September 13~15, 2017	CFDA*	Gliclazide	Compliant
2.	October 11~13, 2017	PMDA	Sulfasalazine	Compliant
3.	April 09~13, 2018	ANVISA	Carbamazepine	Compliant
4.	May 28~June 01, 2018	Cofepris	Tenofovir Disoproxil Succinate & Abacavir	Compliant
5.	September 10~13, 2018	USFDA	Sulfadimethoxine, Sulfadimethoxine Sodium, Imatinib Mesylate	Compliant

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):
The PQR for Nirmaltrelvir was submitted. The review period was January to August 2022. Four batches were produced during this period. There were no complaints, reworks, reprocessed batches, recalls – but 2 OOS results were reported.

The company summary:
Nirmatrelvir (COE) was commercial manufactured in Waisha site. During review period, there were 4 batches final produced, according to review the critical process parameter, yield and product quality, all parameter and yield were within required range, the specification of intermediate and final product were qualified, manufacturing process was under control and process was stable.
During review period, raw material used for Nirmatrelvir production were supplied by qualified suppliers on Approved Supplier List. Documents of Nirmatrelvir were newly established and well maintained. There was no deviation, no reprocess, return, recall or ADR. There were 14 changes initiated, and 2 OOS happened on holding time study for raw material. The stability study of Nirmatrelvir is ongoing. Equipment qualification, process validation and cleaning validation were reviewed.

Conclusion: according to the current production in 2022, the production process conforms to the GMP, the production was under control, the process was stable. According to current process and control strategy, product can be produced continuous to meet intend usage and registered specification.

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

Batch records for Nirmaltrelvir (Batch 357101A220503; Batch 357102A220504, Batch 357103A220504, Batch 357104A220601 and Batch 357100A220604) were submitted. No significant observations were made. The Batch record of the process (synthetic area, translated copy) could not be opened for review). Test records were submitted (including translated copies).

g) Master batch manufacturing and packaging record(s) of the API(s) of interest:

Master documentation were submitted. No significant observations were made:
COE- B100, COE- B130, COE- B140, COE- B150, Batch record for processing in the clean area and Packaging record for Nirmaltrelvir.

h) Recalls in the past three years related to APIs with quality defects:

The company declared that there had been no recalls in the last three years

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:

The company declared that self-inspections were done and that CAPAs were taken. Only minor deficiencies were identified during the self-inspection

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 warning letter was issued by the USA FDA in 2014

k) Out-of-stock situations:

The declaration could not be downloaded

l) Additional documents submitted:
N/A

Part 5	Conclusion – Desk assessment outcome

Based on the GMP evidence received and reviewed, it is considered that a desk assessment may be performed in lieu of a WHO Inspection. The site ***Zhejiang Jiuzhou Pharmaceutical Co, Ltd***, located at ***99 Waisha Road, Jiaojiang District, Taizhou, Zhejiang, 318000, PR of China,*** 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 or 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-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://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)