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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Guilin Pharmaceutical Co. Ltd**
Corporate address of manufacturer	Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd., Building A, No.1289, Yishan Road, Shanghai 200233, P.R. China
Name & address of inspected manufacturing site if different from that given above	Guilin Pharmaceutical Co. Ltd – API No 43, Qilidian Road, Guilin, Guangxi, 541 004, China North latitude: N25º14'42.31", East longitude: E110 º 20'22.58"
Synthetic unit /Block/ Workshop	1. API workshop I (API-I) for Artesunate, Artemether and Dihydroartemisinin 2. API workshop II (API-II) for Sulfadoxine and Pyrimethamine
Inspection details	
Dates of inspection	22-26 September 2021
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	Manufacturing and quality control of APIs, sterile and non-sterile APIs, sterile powders for injections, small-volume parenteral (SVP) injections, tablets, soft capsules and hard capsules. This inspection specifically focused on the API manufacturing of sterile and non-sterile powders.
General information about the company and site	Guilin Pharmaceutical Co Ltd is a member enterprise of Shanghai Fosun Pharmaceutical (Group) Co Ltd since 2003. From the site master file, the manufacturer is engaged in the following manufacturing activities:

Name of manufacturing center	Workshop name	Production line	Abbreviation
API manufacturing center	Multi-purpose workshop	Production line of artemisinin-derived APIs	API- I
		Multi-purpose production line	API- II
	Levamisole hydrochloride workshop	Levamisole hydrochloride production line	API- III
OSD manufacturing center	OSD- I workshop	General production line for dosage forms/ preparations	OSD- I
	OSD- II workshop	Lactasin production line	OSD- II
	OSD- III workshop	Soft capsules production line	OSD- III
INJ manufacturing center	INJ- I workshop	Production line for Artesunate for injection	INJ- I
	INJ- II workshop	SVP production line (New)	INJ- II
	INJ- VI workshop	SVP production line (Old, named as Workshop 7)	INJ- VI
	INJ packaging workshop	Co-package center for Artesunate for injection (named as Workshop 8 and INJ-V formerly)	INJ-PA1
		INJ-VI packaging line	INJ-PA2

History	During the past ten years, the site has been inspected several times by WHO for API, OSD and sterile injections. The last WHO inspection of the APIs was performed in October 2018. The site has been regularly inspected by the local provincial drug regulatory authority as noted from the opening meeting presentation
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Quality management Personnel Building 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 controls Rejection and re-use of materials Complaints and recalls Contract manufacturing (and analysis)
Restrictions	None
Out of scope	The API site inspection was limited to WHO Prequalified APIs manufactured in API-I and API-II workshops.
WHO APIs covered by the inspection	1. WHOAPI-181 (APIMF181, Artemether) 2. WHOAPI-278 (APIMF278, Pyrimethamine) 3. WHOAPI-279 (APIMF279, Sulfadoxine) 4. WHOAPI-355 (APIMF355, Artesunate)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product

FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high-performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MR	Management review
NC	Nonconformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
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
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	Summary of the findings and comments

1. Quality management

The quality management system was generally established, documented and implemented. The quality management system is common to sterile and non-sterile active pharmaceutical ingredients and finished pharmaceutical products operations. The site organizational structure was presented and was generally acceptable. Quality-related activities were defined and documented generally. The Quality Assurance department was independent of production.

Annual product quality review (APQR)

The SMP for annual product quality review was recently revised for trend analysis and added notes for statistical graphs and analysis. The procedure stated that APQR protocol should be prepared in January every year but not necessarily based on the calendar year. The procedure stated that the review should be completed within 3 months. The company had taken appropriate action to revise the procedure in accordance with WHO GMP requirements.

Deviations: The deviations were handled in accordance with the approved procedure. A timeline of 30 working days was set for closing of deviations.

CAPA: The corrective actions and preventive actions were handled in accordance with the approved procedure. A robust tracking mechanism would help company to ensure CAPAs are timely closed.

Quality risk management: The QRM was handled in accordance with the approved procedure. A number of QRMS were initiated in 2021. A holistic approach would help company to ensure risks had been adequately identified and assessed across the entire site.

Management review: Management review was performed quarterly by following the SOP. The QRM report for 2021 Q1 was discussed. No objectional findings were made.

Issues noted from this section have been addressed and will be verified during future inspections.

2. Personnel

An organization chart was available. Quality and production departments were separate. The manufacturer had an adequate number of personnel with the necessary qualifications and practical experience.

There were facilities to ensure personnel hygiene and appropriate clothing suitable for the manufacturing activities were provided in the API block inspected. The changing rooms for the clean areas were equipped with hand wash facilities. The gowning and changing procedures for entry into the manufacturing facilities were satisfactory and displayed on the walls.

GMP training was managed according to procedure. The procedure for personnel qualification of QC-Physical & Chemical Lab and training record of the QA staff were reviewed. The training effectiveness was checked when interviewed the personnel during the inspection.

Issues noted from this section have been addressed and will be verified during future inspections.

3. Buildings and facilities

The premises for manufacturing, storage and quality control of the inspected API products were generally of a satisfactory standard. The inspected production blocks API-I and API-II are multipurpose plants. The plants and the facilities inspected were seen to be in good condition.

Premises were designed to have a logical flow of materials and personnel. The production areas had adequate space for the placement of equipment and materials to prevent mix-ups and contamination. The company claimed that there are no highly active products or non-pharmaceutical products manufactured on the premises.

Issues noted from this section have been addressed and will be verified during future inspections.

4. Process equipment

Process equipment was installed and maintained in a way to minimize the risk of contamination and cross-contamination. The SMP for periodic calibration of measuring instrument was discussed. The procedure described metrology management work and ensured the accuracy of measuring equipment. The SMP for periodic review and validation described the frequency for requalification of the area once every 6 months (Grade A/B) and 12-month (Grade C/D). Another SOP for requalification for cleanroom and HVAC was in place describing test parameters to be performed.

A routine cleaning was applied between batches. Thorough cleaning is performed for product changeover or every 20 batches during continuous production, which usually takes not than one month.

Issues noted from this section have been addressed and will be verified during future inspections.

5. Documentation and records

Documentation was controlled according to a documented procedure which was reviewed during the inspection. A system was in place for document management.

Batch production records and batch testing records were kept and available. They were reviewed and results were considered during batch release. The BMRs were in process during the inspection and reflected the stage of production that was ongoing at the time of the inspection. The following documents were reviewed:

- Logbook of BMR review and release for Artesunate in 2021.
- The completed BMR and BPR for Artesunate.
- SOP for material code conversion application form.

Issues noted from this section have been addressed and will be verified during future inspections.

6. Materials management

The receipt, identification, quarantine, storage, sampling, testing and approval or rejection was conducted according to approved documented procedures. An automated warehouse was used for solid material and finished API and FPP products.

The warehouse activities were spread over several warehouses (solid materials, reagents, gases and storage of liquids). The key starting materials (KSM) used for API manufacturing were stored in separate warehouses. A separate warehouse was used for the storage of primary packaging materials. For KSM warehouse, a manual inventory system was in use. An automated warehouse was used to store finished APIs, sterile FPPs, non-sterile FPPs, raw materials and excipients. For the automated warehouse, SAP and manual system were used in parallel. The SAP was owned by Fosun Pharma not by Guilin Pharma.

Issues noted from this section have been addressed and will be verified during future inspections.

7. Production and in-process controls

The production process was guided by documented procedures and instructions. Production processes including synthesis, purification, crystallization, drying etc. were conducted in the specified facilities and equipment. Clean areas were available for the final steps of the API's manufacture and were maintained at a satisfactory level. The manufacturing of APIs in API block I and API block II was inspected including chemical area and clean rooms. Production took place on three floors with the clean rooms on the ground floor.

Issues noted from this section have been addressed and will be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

In the area where packaging operations were performed the material flow of API, personnel and packaging materials were controlled. A brief inspection of the API I and API II workshop packaging area was undertaken.

Issues noted from this section have been addressed and will be verified during future inspections.

9. Storage and distribution

Incoming materials, quarantine and acceptance/rejection in the warehouse was controlled by a computer system. The material status was saved in the computer system and controlled by a code reader. A brief inspection of the (electronically controlled material) warehouse was undertaken. Issues noted from this section have been addressed and will be verified during future inspections.

10. Laboratory controls

The QC laboratories were responsible for physical, chemical and microbiological testing of starting materials, packaging materials, products (API's), environmental monitoring samples, purified water samples. The laboratory was spread over 5 floors as follows:

- 1st floor for receipt of incoming materials and samples, change room, QA archive and stability study chambers
- 2nd floor for testing of incoming materials and samples using physical, chemical and instrumentation analysis. The Quality Research (QR) Centre located on the 2nd floor is also responsible for method development, method validation and stability studies for WHO markets
- 3rd floor for microbiology testing (covered during the inspection of sterile site).
- The 4th floor had an R&D office and was used for the analysis of R&D samples including testing of pilot-scale batches (APIs and FPPs). The 4th floor also had an archive room (claimed to be for the domestic market).
- 5th floor was used for the synthesis of small scale and lab-scale experiments (both for APIs and FPPs).

The quality control laboratory uses a manual system for receiving and recording incoming materials and samples for testing (on the 1st floor).

Issues noted from this section have been addressed and will be verified during future inspections.

11. Validation

The company has the validation policy and approach to validation activities as laid down in the validation master plan. The validation protocol and reports for some of the APIs including intermediates were reviewed.

Method validation report for the determination of NDMA in Sulfadoxine using the GC-MS/MS method was available. No consideration was given to test other impurities.

Issues noted from this section have been addressed and will be verified during future inspections.

12. Change control

The change controls were handled according to the approved procedure. The company should consider implementing a tracking system to ensure changes were closed on time.

Issues noted from this section have been addressed and will be verified during future inspections.

13. Rejection and re-use of materials

Reprocessing and reworking

Reprocessing and reworking were managed according to SMP.

Recovery of materials and solvents

Recovered solvents and mother liquid were used at the site according to the production process. The recovered materials are reused within the same process.

Issues noted from this section have been addressed and will be verified during future inspections.

14. Complaints and recalls

The company had separate procedures to manage complaints and recalls respectively. The recall register 2020 was checked. There were no API batches recalled.

Issues noted from this section have been addressed and will be verified during future inspections.

15. Contract manufacturers (including laboratories)

External contract laboratory testing was used for a limited number of specialist analytical procedures e.g. Artesunate API polymorphism test.

Part 3	Conclusion – Inspection outcome

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, ***Guilin Pharmaceutical Co. Ltd-API***, ,located at ***No 43, Qilidian Road, Guilin, Guangxi, 541 004, China*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR

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

Part 4	List of GMP Guidelines referenced in the 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