# WHO PUBLIC INSPECTION REPORT

## (WHOPIR)

### Active Pharmaceutical Ingredient Manufacturer

**Part 1**  
**General information**

<table>
<thead>
<tr>
<th>Manufacturers details</th>
</tr>
</thead>
</table>
| 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 | 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:  

<table>
<thead>
<tr>
<th>Name of manufacturing center</th>
<th>Workshop name</th>
<th>Production line</th>
<th>Abbreviation</th>
</tr>
</thead>
</table>
| API manufacturing center | Multi-purpose workshop | Production line of artemisinin-derived APIs | API-I  
| | Levamisole hydrochloride workshop | Levamisole hydrochloride production line | API-II  
| OSD manufacturing center | OSD- I workshop | General production line for dosage forms/preparations | OSD-I  
| | OSD- II workshop | Lactacid 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 ?) | INJ-VI  
| | INJ packaging workshop | Co-package center for Artesunate for injection (named as Workshop 8 and INJ-VI formerly) | INJ-PA1  
| | | INJ-VI packaging line | INJ-PA2  

---

Prequalification Team Inspection services  
WHO PUBLIC INSPECTION REPORT  
(20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT)  
Guilin Pharmaceutical Co. Ltd, - API site-China  
22-26 September 2021  
This inspection report is the property of the WHO  
Contact: prequalinspection@who.int
### 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

<table>
<thead>
<tr>
<th>Areas inspected</th>
<th>Quality management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Personnel</td>
</tr>
<tr>
<td></td>
<td>Building and facilities</td>
</tr>
<tr>
<td></td>
<td>Process equipment</td>
</tr>
<tr>
<td></td>
<td>Documentation and records</td>
</tr>
<tr>
<td></td>
<td>Materials management</td>
</tr>
<tr>
<td></td>
<td>Production and in-process controls</td>
</tr>
<tr>
<td></td>
<td>Packaging and identification labelling of APIs and intermediates</td>
</tr>
<tr>
<td></td>
<td>Storage and distribution</td>
</tr>
<tr>
<td></td>
<td>Laboratory controls</td>
</tr>
<tr>
<td></td>
<td>Validation</td>
</tr>
<tr>
<td></td>
<td>Change controls</td>
</tr>
<tr>
<td></td>
<td>Rejection and re-use of materials</td>
</tr>
<tr>
<td></td>
<td>Complaints and recalls</td>
</tr>
<tr>
<td></td>
<td>Contract manufacturing (and analysis)</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHU</td>
<td>Air handling unit</td>
</tr>
<tr>
<td>ALCOA</td>
<td>Attributable, legible, contemporaneous, original and accurate</td>
</tr>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>APR</td>
<td>Annual product review</td>
</tr>
<tr>
<td>BMR</td>
<td>Batch manufacturing record</td>
</tr>
<tr>
<td>BPR</td>
<td>Batch production record</td>
</tr>
<tr>
<td>CC</td>
<td>Change control</td>
</tr>
<tr>
<td>CIP</td>
<td>Cleaning in place</td>
</tr>
<tr>
<td>CoA</td>
<td>Certificate of analysis</td>
</tr>
<tr>
<td>CpK</td>
<td>Process capability</td>
</tr>
<tr>
<td>DQ</td>
<td>Design qualification</td>
</tr>
<tr>
<td>EDI</td>
<td>Electronic deionization</td>
</tr>
<tr>
<td>EM</td>
<td>Environmental monitoring</td>
</tr>
<tr>
<td>FMEA</td>
<td>Failure modes and effects analysis</td>
</tr>
<tr>
<td>FPP</td>
<td>Finished pharmaceutical product</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>FTA</td>
<td>Fault tree analysis</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>HEPA</td>
<td>High efficiency particulate air</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography (or high-performance liquid chromatography equipment)</td>
</tr>
<tr>
<td>HVAC</td>
<td>Heating, ventilation and air conditioning</td>
</tr>
<tr>
<td>IQ</td>
<td>Installation qualification</td>
</tr>
<tr>
<td>KF</td>
<td>Karl Fisher</td>
</tr>
<tr>
<td>LAF</td>
<td>Laminar air flow</td>
</tr>
<tr>
<td>LIMS</td>
<td>Laboratory information management system</td>
</tr>
<tr>
<td>MB</td>
<td>Microbiology</td>
</tr>
<tr>
<td>MBL</td>
<td>Microbiology laboratory</td>
</tr>
<tr>
<td>MR</td>
<td>Management review</td>
</tr>
<tr>
<td>NC</td>
<td>Nonconformity</td>
</tr>
<tr>
<td>NRA</td>
<td>National regulatory agency</td>
</tr>
<tr>
<td>OQ</td>
<td>Operational qualification</td>
</tr>
<tr>
<td>PHA</td>
<td>Process hazard analysis</td>
</tr>
<tr>
<td>PLC</td>
<td>Programmable logic controller</td>
</tr>
<tr>
<td>PM</td>
<td>Preventive maintenance</td>
</tr>
<tr>
<td>PQ</td>
<td>Performance qualification</td>
</tr>
<tr>
<td>PQR</td>
<td>Product quality review</td>
</tr>
<tr>
<td>PQS</td>
<td>Pharmaceutical quality system</td>
</tr>
<tr>
<td>PW</td>
<td>Purified water</td>
</tr>
<tr>
<td>QA</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality control</td>
</tr>
<tr>
<td>QCL</td>
<td>Quality control laboratory</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality management system</td>
</tr>
<tr>
<td>QRM</td>
<td>Quality risk management</td>
</tr>
<tr>
<td>RA</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>RCA</td>
<td>Root cause analysis</td>
</tr>
<tr>
<td>RO</td>
<td>Reverse osmosis</td>
</tr>
<tr>
<td>SMF</td>
<td>Site master file</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>URS</td>
<td>User requirements specifications</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet-visible spectrophotometer</td>
</tr>
</tbody>
</table>
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


   [http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1)
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1


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

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

http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
  
**Short name:** WHO TRS No. 943, Annex 3
  
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

  
**Short name:** WHO TRS No. 961, Annex 2
  
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

  
**Short name:** WHO TRS No. 981, Annex 2
  
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en

  
**Short name:** WHO TRS No. 981, Annex 3
  
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en

  
**Short name:** WHO TRS No. 961, Annex 14
  
http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

  
**Short name:** WHO TRS No. 992, Annex 3
  

  
**Short name:** WHO TRS No. 992, Annex 4
  

Short name: WHO TRS No. 992, Annex 6

Short name: WHO GDRMP guidance or WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

Short name: WHO Multisource guidance or WHO TRS No. 996, Annex 10

Short name: WHO TRS No. 1010, Annex 10

Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications-detail/978-92-4-000182-4

Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications-detail/978-92-4-000182-4

*Short name: WHO TRS No. 1025, Annex 6*

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