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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product 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
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Guilin Pharmaceutical Co Ltd. No 43 Qilidian Road, Guilin, Guangxi, 541 004, China
Unit / block / workshop number	INJ- I, INJ- II, INJ- VI and Co-package center for Artesunate for Injections
Inspection details	
Dates of inspection	15 -19 September 2021
Type of inspection	Routine reinspection
Introduction	
Brief description of the manufacturing activities	Manufacturing and quality control of APIs, OSDs and sterile powders for injections and small-volume parenteral (SVP) injections.
General information about the company and site	Guilin Pharmaceutical Co., Ltd. is a subsidiary company affiliated with Shanghai Fosun Pharmaceutical (Group) Co., Ltd. Several anti-malaria APIs and FPPs have been qualified by the WHO PQ programme and are manufactured on the site.
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 sterile FPPs was performed 6 to10 January 2020. The site has been regularly inspected by the local provincial drug regulatory authority. The company's FPP facilities have not been inspected by any PIC/s member inspectorate.

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	▪ Quality management system ▪ Sterile assurance ▪ Media fill, process validation ▪ CAPA verification from the last inspection. ▪ Changes made since the last inspection. Site areas visited: ▪ Production block: Injection-I, II and VI ▪ Quality control laboratories ▪ Water system ▪ Penicillin FPP production block
Restrictions	The inspection was restricted to the production of the products listed in the inspection scope.
Out of scope	All other products were outside of the inspection scope.
WHO products covered by the inspection	**MA089** Artesunate – 30mg – Powder for injection – Artesunate for Injection+ Sodium Bicarbonate Injection + Sodium Chloride Injection – (Vial + Ampoule); 30mg/vial + 25mg/0.5ml + 22.5mg/2.5ml **MA090** Artesunate – 120mg – Powder for injection – Artesunate for Injection+ Sodium Bicarbonate Injection + Sodium Chloride Injection – (Vial + Ampoule); 120mg/vial + 100mg/2ml + 90mg/10ml **MA051** Artesunate – 60mg – Powder for injection – Artesunate for Injection+ Sodium Bicarbonate Injection + Sodium Chloride Injection – (Vial + Ampoule); 60mg/vial + 50mg/1ml and 45mg/5ml **MA168** Arginine/Sodium Bicarbonate Injection+ Artesunate for Injection; 20mg/ml/8.4mg/ml+60mg
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original, and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
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
GPT	Growth promotion test
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
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
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
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	Summary of the findings and comments

1. Pharmaceutical quality system

A documented system for quality assurance was established, with procedures covering key quality elements in place. The Quality Department was divided into QA and QC and were separate from the production department. Operations were specified in written form and critical GMP requirements were essentially being met. The procedures reviewed and discussed during the inspection were generally of an acceptable standard.

Product quality review (PQR):

The preparation, review and approval of PQRs were managed according to a Standard Management Procedure (SMP) for annual product quality review (APQR).

PQR of Artesunate for injection of 2020 and PQR of co-packaged artesunate for injection of 2020 were reviewed. This APQR covered the period January to December 2020. Some deficiencies observed during the inspection that was listed in the full report regarding PQR were addressed by the manufacturer to a satisfactory level.

Quality risk management:

A risk assessment report on nitrosamine impurity for Arginine and Arginine/Sodium Bicarbonate Injection was available and discussed during the inspection.

Change control (CC)

Change control procedures were described in an SMP. The following CCs were reviewed during the inspection.

- The proposed change control to increase the batch size by filling Artesunate (AS) injection in three continuous days by several shifts as a single batch.
- A permanent change control for compounding of Arginine/Sodium Bicarbonate injection and the automated visual inspection system.
- Change control for removal of Penicillin FPP production block.

Some deficiencies observed during the inspection that was listed in the full report regarding CC were addressed by the manufacturer to an acceptable level.

Deviation and CAPA management

Deviation and CAPA were managed according to written SMPs. The CAPAs implemented to the deficiencies made during the last inspection were verified. In general, they had been implemented in accordance with the written submissions to PQT.

2. Good manufacturing practices for pharmaceutical products

Production of Artesunate sterile powder for injection was performed in a dedicated production block with the line and related production equipment dedicated to the filling of sterile Artesunate powders into vials. All process operations were performed under grade A LAF in a class B background area. The critical operating equipment's vials washing, dehydrogenation tunnel, vials filling, bunging and cap sealing are synchronized. Labelling and packaging operations are carried out separately. Artesunate API and FPP manufacture were operational during the inspection.

Proposed changes to the manufacturing processes of the powder for injection was verified during the inspection. The manufacturing process proposed to fill the vials in three continuous days by several shifts as a single batch. Several aspects reviewed e.g., media fill, smoke tests in the critical area were inspected in the inspection.

Sterile Artesunate API used to produce Artesunate sterile powder for injection was manufactured on the site. The media simulation process and final drying and filling process of sterile Artesunate API were reviewed.

Some deficiencies observed during the inspection that was listed in the full report regarding media fill were addressed by the manufacturer to an acceptable level.

3. Sanitation and hygiene

The facilities and procedures for sanitation and hygiene established on site were found to be adequate with the relevant SOP's meeting GMP requirements. Sanitation of clean areas is performed frequently in accordance with an SOP.

4. Qualification and validation

Process validation

The media simulation and process validation of AS injection were performed as CAPA implementation to the observations made in previous WHO inspection. The relevant process validation documentation was reviewed. Improvements on sterile product validation were noted.

The injection production block VI of ampule line equipped an inspection machine for leak detection was inspected. The performance qualification of the inspection machine was reviewed.

Process validation protocol on Arginine/ Sodium Bicarbonate Injection was discussed. Three batches of Arginine + Sodium Bicarbonate injection were taken as part of validating the manufacturing process. In general, the reviewed validation documents appeared adequate.

Media fill test (MFT)

SMPs for media fill test were in place. Several MFT protocol and reports for aseptically processed injection products were reviewed and discussed during the inspection.

Cleaning validation

The following procedures were reviewed during the inspection.

- SMP for clean validation or qualification which applied to APIs, OSDs, and injectables.
- SOP for cleaning of pipes, tools and containers directly contacting product.
- SOP for dynamic (in operation) environmental monitoring of INJ-II
- Cleaning validation report for MFT in INJ-II

Some observations noted during the inspection that was listed in the full report regarding cleaning validation were addressed by the manufacturer to an acceptable level.

5. Complaints

Customer complaints handling procedure SMP, complaint register for 2020 and several complaints related to WHO Prequalified products were reviewed and considered acceptable generally.

6. Product recalls

A product recall was managed according to an SMP. The recall was classified into three levels with specified time requirements. A mock recall was required to be performed once every two years if no actual product recall occurred. The recall register for 2019 and 2020 was checked. Some observations were noted during the inspection regarding complaint and recall management were addressed by the manufacturer to an acceptable level.

7. Contract production, analysis and other activities

No external contracts were applicable for production and routine testing operations relating to the inspection scope.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections (internal audits) were performed annually according to an SMP. A self-inspection report 2020 for an internal audit to injection production was reviewed as acceptable generally.

Suppliers are required to be qualified before materials are sourced and a list of qualified suppliers was available and reviewed. Some observations noted during the inspection that was listed in the full report regarding Supplier qualification were addressed by the manufacturer to an acceptable level.

9. Personnel

Organization charts were in place. Responsibilities for production and QC/QA were separated. In general, personnel met during the inspection appeared knowledgeable on the principles of GMP.

10. Training

Training was managed according to an SMP. The training records of a QA person responsible for drafting APQR was spot checked during the inspection.

11. Personal hygiene

Changing and washing before entry to production areas followed written procedures. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk products. The level of hygiene observed, and the measures taken to maintain the hygiene requirement of the facility were found to be satisfactory.

12. Premises

Documented layouts of the facilities were available. Generally, the premises were located, designed, constructed and maintained to suit the operations to be carried out. Production premises were designed to allow production in a unidirectional flow supported by the requisite cleanliness levels.

The Artesunate powder for injection was produced in INJ-I which is dedicated to the product.

Arginine/Sodium Bicarbonate Injection as the solvent for product MA168 (Arginine +Sodium Bicarbonate Injection+ Artesunate for Injection 20mg/ml/8.4mg/ml+60mg) has been introduced into INJ-II workshop since last inspection. The product was under assessment at the time of inspection.

Penicillin API, OSD and injections were manufactured in different dedicated blocks on the site. The company decided to remove Penicillin products from the site. This change was still ongoing at the time of inspection and requires follow up in the next onsite inspection.

13. Equipment

Production equipment installed was in general of an acceptable standard. All production equipment reviewed was identified as to its content or purpose with appropriate status of cleanliness identified.

The production lines include power filling lines designed using RABS when necessary. SVP ampule lines were not dedicated. The equipment was in operation and appeared running well at the time of inspection.

Computerized systems and PLC with new interfaces were installed on several pieces of existing equipment. The company is using its SAP system in parallel to its manual inventory system for material management.

14. Materials

Incoming materials were purchased from approved suppliers, sampled and tested according to specifications and testing procedures. Receipt, warehousing and issuing (to production) of materials are managed with WMS (Warehouse Management System).

Batch numbering system and code management were reviewed during the inspection. Some observations noted during the inspection that was listed in the full report regarding material code management were addressed by the manufacturer to an acceptable level.

Product release procedure SMP had been updated since the previous WHO inspection. Finished products were held in quarantine until their final release and stored under appropriate and monitored conditions. No objectional comments were made regarding the sterile product's release.

15. Documentation

In general, documentation was designed, prepared, reviewed and distributed according to a documented procedure. Quality system documents were regularly reviewed and kept up to date.

Approved, signed and dated testing procedures and specifications were available for starting and packaging materials and for finished products.

The procedure for a batch number, production date, period of validity SMP has been updated since the previous WHO inspection. Several BMRs of PQed product batches were reviewed or checked for process validation, production instruction, IPC, and EM etc. CAPAs to the observations made in the previous WHO inspection was checked. No objectional comments was made.

16. Good practices in production

Clean areas for the manufacture of sterile products were classified according to the expected required characteristics of the environment. The production lines of INJ I, II and VI for API compounding, the machine set up for the powder filling line and ampule production line and areas were inspected. CAPAs to the deficiencies made in the previous WHO inspection were reviewed as acceptable in general.

17. Good practices in quality control

The QC function was independent of other departments. QC laboratories including microbiological laboratories were separated from production areas. The Microbiology Laboratory and Microbiology QC test was segregated from the Chemistry Laboratory.

The microbiological laboratory was visited. Microbiological laboratories for media simulation incubation room and sterility test were inspected. Some observations noted during the inspection that was listed in the full report regarding microbiological laboratory condition and management were addressed by the manufacturer to an acceptable level.

Stability monitoring of FPPs

Stability study protocol for accelerated and long term for Arginine/Sodium Bicarbonate injection was reviewed and discussed. The product dossier was under assessment at the time of this inspection.

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***, 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 applicable to sterile manufacturing.

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 WHO Guidelines referenced in the inspection report

1. 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/

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 GMP for APIs*** or ***TRS No. 957, Annex 2***
http://www.who.int/medicines/publications/44threport/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 GPPQCL Guidelines or ***TRS No. 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 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 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