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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer

Part 1	**General information**
Company information	
Name of Manufacturer	SHOUGUANG FUKANG PHARMACEUTICAL CO., LTD
Corporate address of manufacturer	Registered address: NO.666 of Donghuan Road，Shouguang City，Shandong Province， P.R. of China-Manufacturing address: North East of Dongwaihuan road, Dongcheng Industrial area, Shouguang city, Shandong Province, P.R. of China.
Inspected site	
Name & address of manufacturing site	SHOUGUANG FUKANG PHARMACEUTICAL CO., LTD North East of Dongwaihuan road, Dongcheng Industrial area, Shouguang city, Shandong Province, P.R. of China.
Synthetic Unit/Block/ Workshop	Workshop 101 – B # W19 & W32 Workshop 101 – B # W47 Workshop 102 – B # E01, E03, E04, E05, E06, E07
Desk assessment details	
Date of review	31/7/2019 – 21/10/2019
APIs covered by this desk assessment	-Sulfamethoxazole (with reference made to R0-CEP-2007-332-Rev00)- PQT No.[HA598] -Trimethoprim (with reference made to R1-CEP-2005-115-Rev00)- PQT No.[HA598] -Sulfamethoxazole (with reference made to R0-CEP-2007-332-Rev00)- PQT No.[HA599] - Trimethoprim (with reference made to R1-CEP-2005-115-Rev00)- PQT No.[HA599] - Trimethoprim (with reference made to R1-CEP-2005-115-Rev00)- PQT No.[HA686] - Trimethoprim (with reference made to R1-CEP-2005-115-Rev00 R1-CEP 2005-115-Rev 01)- PQT No.[HA687]
List of documents submitted	- Updated SMF - List of products [not including intermediates, FP] - APQR Trimethoprim [2018] - APQR Sulfamethoxazole [2018] - Blank Batch production records for Sulfamethoxazole main production steps [Dimethyl oxalate synthesis, Amide synthesis, Amino synthesis,

	Liquid crude product] - Blank Batch production records for Trimethoprim main production steps including oil phase, condensation compound, crude product, purification, neutralization-crystallization-filtration & drying, packaging & labeling. - Complete Batch production record for TMP (Chinese) - Complete Batch production record for SMZ (Chinese) Inspection reports for the last 3 years inspections	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
US FDA	Dates of inspection:	21-25/5/2018
	Type of inspection:	Routine GMP inspection
	Block/Unit/Workshop:	Workshop 111, B # W23, W22 B#W44, Quarantine & sampling area. B#W43, Warehouse # 12 B# W12, Warehouse # 28
	Type of APIs covered:	Omeprazole, Esomeprazole Magnesium Dihydrate and Trihydrate, Metformin HCL (Metformin), Trimethoprim (TMP), Sulfamethoxazole (SMZ), Pantoprazole Sodium， Omeprazole Magnesium & Clozapine.
ANSM [French National Agency of Medicine & Health products Safety]	Dates of inspection:	17-19/1/2018
	Type of inspection:	Full inspection as part of ANSM program for inspection of starting materials manufacturers in third countries.
	Block/Unit/Workshop:	-TMP: Workshop 101, B# W19 & W32 [for crude] and W47 [for purification]. -Phloroglucinol Anhydrous & Dihydrate: Workshop 113, B# W31. -Storage facilities: B#W43 for Solid Raw material. B#W44 for liquid materials in drum. B#47 for finished products Part of W41 for rejected material storage. Liquid farm tank area.
	Type of APIs covered:	Phloroglucinol Anhydrous: RO-CEP 2016-007 Phloroglucinol Dihydrate: R0-CEP 2013-099 Trimethoprim: *R1-CEP 2005-115*

TGA	Dates of inspection:	27-30/3/2017
	Type of inspection:	Re-Inspection (overseas in relation to registration)
	Block/Unit/Workshop:	Workshop 101 Building W32: TMP synthetic step 1 & 3 Building W19: TMP synthetic step 2 Building W47: TMP purification, blending and packaging Workshop 112 Building W12: granule and capsule manufacture -Warehouses, tank farms, utilities and laboratory.
	Type of APIs covered:	Trimethoprim API & finished products.
Part 3	**Summary of the last WHO inspection**	
Date and conclusion of most recent WHO inspection	2-5/2/2015 Conclusion: GMP compliant	
Brief description of manufacturing activities	- The API facilities included dedicated blocks (synthesis, purification and finishing) for SMZ and TMP APIs -The final purification and packaging took place in a clean area with a Grade D environment. - The HVAC system was dedicated in the workshops 101 and 102 -The equipment used for manufacturing TMP and SMZ were dedicated. -Packaging and labelling was performed in areas dedicated for this purpose. -The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC and other testing instruments.	
General information about the company and manufacturing site	Shouguang Fukang Pharmaceutical Co., Ltd (Fukang Pharm.) was established in 1993. In 2003, it was GMP approved by SFDA. The factory occupies 641，910 square meters including 14 workshops 280，410 m2, storage area of 16,620 m2 and quality control area of 1,352 m2. Fukang Pham is a comprehensive enterprise engaged in production, trading and scientific-research of APIs and drug intermediates. There are two DP workshops for Tablets 、Capsules and pellets. There are two chemical product workshops: FP workshop 、104 workshop (NaBr). All the chemical workshops are dedicated and individual. Total 856 employees, 129 of them dedicated to Sulfamethoxazole production & 140 dedicated to Trimethoprim production.	
Focus of the last WHO inspection	-The inspection focused on the production and control of Trimethoprim and Sulfamethoxazole APIs. - The inspection covered most of the sections of WHO GMP for Active	

	Pharmaceutical Ingredients, including Quality Management; Personnel; Buildings 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 Control; Rejection and Reuse of Materials and Complaints and Recalls
Areas inspected	-Workshops # 101, 102 -Warehouses: solid and liquid raw materials, tank farm, finished APIs, packaging materials. -Workshop 101 Production including finishing and packaging -Workshop 102 Production including finishing and packaging -Purified water system -HAVC (TMP) -QC Laboratory: Chemical and Physical Lab
Out of scope and restrictions (last WHO inspection)	None
WHO APIs covered by the last WHO inspection	-Trimethoprim API -Sulfamethoxazole API
Additional products covered by this desk assessment:	None
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:

-Valid Manufacturing authorization license No. 20160126, issued on 1/1/2016 and expired on: 31/12/2020.

-GMP certificate No.:SD20170589 for SMZ bulk production in workshop 102 issued by CFDA on 31/7/2017 and expired on 30/7/2022.

-GMP certificate No. SD20190888 for TMP production in workshop 101 issued by CFDA on 13/3/2019 and expired on 12/3/2024.

b) Site master file (SMF):

-A copy of updated SMF was submitted, Effective date: 19/3/2019, it was reviewed and found acceptable in line with WHO guidance on drafting a SMF.

c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:

List of APIs:

1- Trimethoprim
2- Sulfamethoxazole
3- Omeprazole
4- Lansoprazole
5- Itraconazole
6- Metformin HCI
7- Clozapine
8- Phloroglucinol dihydrate
9- Phloroglucinol anhydrous
10- Pantoprazole Sodium sesquihydrate
11- Esomeprazole magnesium dihydrate
12- Esomeprazole magnesium trihydrate
13- Omeprazole magnesium
14- Trospium Chloride
15- Pellets, Tablets, Capsules.

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

Inspection	**Date**	**Outcome**
TGA [Australia]	**27-30/3/2017**	**GMP compliant**
SFDA [China]	**11-13/5/2017**	**GMP compliant**
MMA [Malta]	**1-4/9/2017**	**GMP compliant**

CDSCO [India]	**2-4/11/2017**	**CAPA submitted**
SFDA [China]	**9-11/12/2017**	**GMP compliant**
ANSM [France]	**17-19/1/2018**	**GMP compliant**
FDA [USA]	**21-25/5/2018**	**GMP compliant**
MMA [Malta]	**26-30/8/2018**	**GMP compliant**
SFDA [China]	**22-24/1/2019**	**GMP compliant**

e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):

-APQR for TMP (year 2018) issued on 29/3/2019, where 623 batch, with total 1246 Ton, batch size: 2000 Kg, Packaging size: 25 Kg/Drum

11 Deviations, 12 OOS, 6 Changes, 2 Complaints, no return or recall, 4 failed batches.

Trends for critical process parameters and CQA & as well as calculated Cpk for process were in place.

Stability study program data was available.

-APQR for SMZ (year 2018) issued on 29/3/2019, where 515 batches were manufactured with total 1030 Ton for packaging size 25 kg/Drum.

10 Deviations, 11 OOS, 7 Changes, 2 complaints, no return & no recall or rejected product.

Trends for critical process parameters and CQA & as well as calculated Cpk for process were present.

Stability study program data was available.

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

Batch manufacturing and packaging records for TMP & Sulfamethoxazole with the analytical part were submitted and found acceptable.

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

-A copy of master batch manufacturing records of TMP were submitted including records for several process steps: Condensation compound of TMP, Oil Phase of TMP, Crude product of TMP, Decolouration process, Neutralization, crystallization, filtration and drying & Packaging.

- A copy of master batch manufacturing records of Sulfamethoxazole was submitted including records for several process steps: Dimethyl oxalate synthesis, Amide synthesis, Amino synthesis, Liquid crude product, Decolouration, Neutralization and crystallization, Filter-process and Washing, Drying & Packaging.

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

-A declaration letter signed by qualified person confirmed that no recall has been done in the last 3 years for their manufactured products.

However, they implement mock recall every year to ensure that our recall procedure is valid**.**

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:
A confirmation letter signed by qualified person was submitted stated that during the last year 2018, There were 31 audits by customers, 2 audits by authorities, 1 self-inspection. The CAPAs for the external audit and self-inspection were all complied and approved.

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 confirmation letter signed by qualified person stated that they had not received any warning letter from any authority.

k) Out-of-stock situations:
-A confirmation letter signed by qualified person was submitted stated that the products [Trimethoprim and Sulfamethoxazole] have no out-of-stock situations and no out of stock situation is foreseen in the upcoming 3 years.

l) Additional documents submitted:
-CAPA report of USFDA inspection.

Part 5	Conclusion – Desk assessment outcome

Based on the previous WHO inspections and on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site ***SHOUGUANG FUKANG PHARMACEUTICAL CO., LTD*** located at **North East of Dongwaihuan road, Dongcheng Industrial area, Shouguang city, Shandong Province, P.R. 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***
   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 GMP Guidelines or WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-Second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. ***Short name: WHO TRS 1010, Annex 9***
https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

4. WHO Good Manufacturing Practices: water for pharmaceutical use. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Forty-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/

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
http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

6. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 2. **Short name: WHO TRS No. 1019, Annex 2**
https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

7. 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://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1

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. 957, Annex 1
http://www.who.int/medicines/publications/44threport/en/

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

http://www.who.int/medicines/publications/44threport/en/

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

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

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

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
http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

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

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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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

http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

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. 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

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***
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 TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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

23. 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

24. 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