World Health Organization

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Prequalification Unit Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Desk Assessment of Finished Pharmaceutical Product (FPP) Manufacturer

Part 1	**General information**	
Company information		
Name of Manufacturer	**Qilu Pharmaceutical Co., Ltd.**	
Corporate address of manufacturer	No. 317, Xinluo Road, High-tech Zone, Jinan, Shandong, 250101, P.R. China	
Inspected site		
Name & address of manufacturing site	No. 317, Xinluo Road, High-tech Zone, Jinan, Shandong, 250101, P.R. China	
Production Block/Unit	Workshop No. 6	
Desk assessment details		
Date of review	09-13 October 2020	
Products covered by this desk assessment	TB319 Amikacin (sulfate) Solution for injection 500mg	
Part 2	**Summary of SRA/NRA inspection evidence considered (from most recent to last)**	
AEMPS	Dates of inspection:	27.05 – 01.06.2019
	Type of inspection:	Initial inspection
	Block/Unit:	Building K-001 - Workshop nr.21 Building K-002 - Workshop nr.6 Building K-003 Building K-004 Building K-301 QA/QC Building
	Type of products/Dosage forms covered:	Cefalosporins Powder for Injection and general small volume parenterals
USFDA	Dates of inspection:	19 – 27.09.2019
	Type of inspection:	Routine, surveillance inspection
	Block/Unit:	Workshop 21 Workshop 19
	Type of products/Dosage forms covered:	Powder for Injection and Tablets

Part 3	Summary of the last WHO inspection
Date and conclusion of most recent WHO inspection	Workshop No 6 was inspected during 16 – 20.01.2017 The site was found to be in compliance for the manufacture of terminally sterilized small volume parenterals.
Brief description of manufacturing activities	Production, packaging, quality control and release of powder for injection, small volume parenterals (SVP), tablets, granules, hard capsules, eye drops, Inhalers, sterile APIs, psychotropic drugs
General information about the company and manufacturing site	Qilu was founded in 1958 as a State-owned company and in 2003 converted to a share-holding corporation. The Corporation includes 9 drug or drug product manufacturing sites. Qilu Pharmaceutical Co. Ltd mainly focuses on developing, manufacturing and marketing generic drugs in the therapeutic areas of oncology, cerebrovascular, cardiovascular, respiratory, antimicrobial products, and others. The site under inspection was located in the High-Tech Zone, devoted mainly for the production of finished dosage and sterile API, and it covers 67,185 m2. There were four production buildings, five auxiliary buildings and 2 power buildings.
Focus of the last WHO inspection	Terminally sterilized small volume parenterals TB319 Amikacin (sulfate) Solution for injection 500mg
Areas inspected	All areas and processes related to the manufacture and quality control of Amikacin (sulfate) Solution for injection 500mg
Out of scope and restrictions (last WHO inspection)	Any areas, processes and products not of interest to WHO Prequalification
WHO products covered by the last WHO inspection	TB319 Amikacin (sulfate) Solution for injection 500mg
Additional products covered by this desk assessment:	N/A
Abbreviations	**Meaning**
AHU	Air handling unit
API	Active pharmaceutical ingredient
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:

The company provided a copy of the manufacturing authorization: Lu20160001 valid until 31.12.2020. According to the license the site is authorized to manufacture aseptically prepared powders for injection (Cephalosporins included), small-volume terminally sterilized solutions, tablets, granules, hard capsules, eye drops, inhalers, sterile APIs and psychotropic drugs.

The company provided the GMP certificate issued by CFDA on 07.09.2016, following an inspection. The certificate is valid until 06.09.2021 and covers small volume parenterals and solutions (including anticancer drugs).

The company also provided the GMP certificate issued by AEMPS following an inspection on 01.06.2019. The certificate covers aseptically prepared beta lactam powders (cephalosporins) for injection and terminally sterilised small volume liquids

b) Site master file (SMF):

SMF version SMF-B-07B issued on 27.12.2019 was provided.

According to the SMF there are seven separate buildings. Building (K) 001 consists of four floors. 4th floor is for production of powder for injection (Cephalosporins) for foreign market. 3rd floor and 2nd floor are also used for the manufacture of powder for injection (Cephalosporins), in which, 3rd floor is for both foreign market and domestic market, and 2nd floor is for domestic market only. Cephalosporins API is stored on the 1st floor. Movement of raw materials between buildings should be checked at the next inspection.

Building (K) 002 consists of four floors. The 3rd floor and the 4th floor are used for small-volume parenteral solution production, wherein, the product manufactured on the 3rd floor is for both foreign market and domestic market, and the product manufactured on the 4th floor is for domestic market. Building (K) 003 is where Cephalosporin finished products are stored both on the 2nd floor and 3rd floor. The API of Tenofovir Disoproxil Fumarate is stored on the 1st floor. The third floor to the sixth floor are used for the manufacture of ophthalmic preparation. Movement of materials and personnel should be checked at the next inspection

Building (K) 004 is mainly for the production of oral dosage form and relevant warehouse, wherein, API and excipients for SVP and oral dosage form (general category) and finished products for oral dosage form (general category) and SVP are stored on the 1st floor. The 4th floor is used as the warehouse of packaging materials.

Building (K) 202 is where Quality Assurance and Quality Control department are located More specifically on the 2nd, 3rd and 4th floor; the 1st floor is still under construction.

Reprocessing procedure and practices should be checked at the next inspection.

c) List of regulatory inspections performed in the last 3 years and their outcome:

AEMPS 27.05 – 01.06.2019 GMP compliant
USFDA 19 – 27.09.2019 GMP compliant

d) List of all the products and dosage forms manufactured on-site:

The company provided lists of products manufactured per workshop. Amikacin injection along with other 16 injectable products are manufactured in Workshop 6. More specifically, Amikacin injection is manufactured on the third floor of Workshop No. 6 and the products manufactured on the same line are as follows:

No.	Product name	Strength
1.	Metaraminol Injection	1ml:10mg
2.	Tropisetron Hydrochloride Injection	2ml:2mg/5ml:5mg
3.	Granisetron Injection	1ml:1mg/3ml:3mg
4.	Ondansetron Injection	2ml:4mg/4ml:8mg
5.	Monosialotetrahexosyl Ganglioside Sodium Salt Injection	2ml:20mg/2ml:40mg
6.	Ropivacaine Hydrochloride Injection	10ml:50mg/10ml:0.1g
7.	Ibandronate Sodium Injection	
8.	Edaravone Injection	20ml:30mg

The list was provided following a clarification query. It is noted that Ibandronate Sodium is not included in the original list of products manufactured in Workshop 6. The introduction of Ibadronate Sodium in Workshop 6 should be checked at the next inspection.

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

No PQR was provided and no completed BMRs were provided. According to the company Amikacin was last manufactured in 2014. It is noted that APIMF186-Amikacin disulfate from Qilu Tianhe was withdrawn on 25.09.2020

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

See above

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

Both original and English translated master batch records were provided. Although some of the translated text does not provide very detailed instructions, generally, the records did not give rise to any concerns.

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

A signed confirmation by the Deputy Director of Quality Management was provided. No product has been recalled from the market in the last three years

i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with:

A written confirmation was provided, stating that a full self-inspection of Workshop No 6 where WHO PQ products are manufactured, was carried out in 2019. A CAPA plan was implemented based on identified deficiencies and all observations have been closed out.

j) Copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product:

No notice of concern or any other restrictive regulatory action was issued by any authority against the site or products manufactured at site.

k) Out-of-stock situations:

The company provided a signed statement by the Deputy Director of Quality Management. No out of stock situation occurred in the last three years and no out of stock situation is foreseen for the next year.

l) Additional documents submitted:

Drawings of the HVAC system of the 3rd floor of Workshop No 6 were provided.

A dedicated SMF to Workshop 6 was provided, including WFI generation system. The additional documentation did not give rise to any concern.

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 **Qilu Pharmaceuticals Co. Ltd., Workshop 6** located at **No. 317, Xinluo Road, High-tech Zone, Jinan, Shandong, 250101, P.R. China** is considered to be operating at an acceptable level of compliance with WHO GMP guidelines.

This compliance status shall be valid until **30 June 2022** or when another inspection is conducted by WHO or by a stringent regulatory authority. It remains the prerogative of WHO to carry out an inspection any time prior to that.

Part 6	List of guidelines referenced in this 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 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 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 3.
   Short name: WHO TRS No. 957, Annex 3
   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. 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

21. 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

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

24. 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

25. 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

26. 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