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

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	**QILU TIANHE PHARMACEUTICAL CO. LTD**
Corporate address of manufacturer	No. 849 Dongjia Town, Licheng District, Jinan, China
Inspected site	
Address of inspected manufacturing site if different from that given above	Same as above
Unit / block / workshop number	No.6 ,11 &20 Workshop 1: Building No.11 (Synthesis) Building No.06 (Synthesis) Building No.20 (Salification, final crystallization, drying and packing, clean zone)
Manufacturing license number	Lu 20160009
Inspection details	
Dates of inspection	19-22 January 2016
Type of inspection	Routine GMP inspection
Introduction	
Brief summary of the manufacturing activities	A non-sterile Amikacin Sulfate is produced in Workshop No. 1, in particular, facilities number: 6#, 11# and 20#. The product was developed and started commercial manufacture since 1980s. The workshop 1 was inspected and approved by PMDA, WHO, USFDA and German Authority. The CEP is issued by EDQM. The batch size of Amikacin Sulfate is about 600Kg with an annual output of about 450 tons. The batch size was scaled up from 300kg to 600kg in 2015. The synthesis is done in buildings 6 and 11 which are dedicated for Amikacin Sulfate whereas part of the building 20, where finishing steps are performed, powder processing area is shared with other two APIs (Celecoxib and Olmesartan).

General information about the company and site	Qilu Tianhe Pharmaceutical Co., Ltd. is one of the subsidiaries company affiliated to Qilu Pharmaceutical Group, it was founded as Qilu Pharmaceutical Eastern Plant in 1997 and the name was changed to Qilu Tianhe Pharmaceutical Co., Ltd. in 2006. It is located at No. 849 Dongjia Town, Licheng District, Jinan City, Shandong Province, PR, China. Qilu Tianhe Pharmaceutical Co Ltd is dedicated to the development & production of APIs through chemical synthesis and finished dosage forms for human use. The total area of Qilu Tianhe is 280,000 m^2. There were around 1500 employees at the site.
History	This was the second inspection conducted by WHO PQP. The site had been licensed by the Local Food and Drugs Administration, and had also been inspected and approved by USFDA, PMDA and German Authority. However the inspection scope in terms of facilities and products did not fully overlap the WHO inspection.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	The inspection focused on the production and control of Amikacin Sulfate (non-sterile) API. 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.
Restrictions	None
Out of scope	None
WHO product numbers covered by the inspection	Amikacin Sulfate (non-sterile APIMF186)

Abbreviations	SOP – standard operating procedure API – active pharmaceutical ingredient FPP – finished pharmaceutical product PQS – pharmaceutical quality system PQR – product quality review QRM – quality risk management CAPA – corrective actions and preventive actions PpK – Process performance indice CpK – Process capability indice MR – management review BMR – batch manufacturing record BPR – batch packaging record MF – master formulae LAF – laminar air flow

	AHU – air handling unit FBD – fluid bed dryer HVAC – heating, ventilation and air conditioning CC – change control RA – risk assessment CoA – certificate of analysis HPLC – high-performance liquid chromatograph GC - gas chromatograph UV - ultraviolet-visible spectrophotometer IR – infrared spectrophotometer FTIR - Fourier transform infrared spectrometer TLC – think layer chromatography LOD – loss on drying KF – Karl Fisher NMR - nuclear magnetic resonance spectroscopy NRA – national regulatory agency URS – user requirements specifications DQ – design qualification IQ – installation qualification PQ – performance qualification OQ – operational qualification FAT – factory acceptance test MB – microbiology TAMC – total aerobic microbial count FMEA - failure modes and effects analysis FTA – fault tree analysis PHA - process Hazard Analysis HACCP - hazard analysis and critical control points PM - Preventive maintenance WHOPIR – WHO public inspection report EM – environmental monitoring LoD – Limit of detection BDL – Below detection limit

Part 2	**Brief summary of the findings and comments (where applicable)**
	WHO good manufacturing practices for active pharmaceutical ingredients

Brief summary of the findings and comments

1. Quality management

The quality management system was generally well established and documented but was not adequately implemented. The site organizational structure was reviewed and was acceptable. Quality-related activities were defined and documented. The Quality Assurance department was independent from production. The persons authorized to release intermediates and APIs were specified. The production and quality control procedures were generally satisfactorily defined and were followed.

2. Personnel

According to the SMF, key personnel were suitably qualified with appropriate tertiary qualifications and experience in the manufacture of APIs and pharmaceutical products.

Training procedure was available which provided procedure for training of personnel at the time of joining and periodical training. A training schedule for 2016 for workshop 1 was available which included training on SOPs, GMP, Chinese Pharmacopoeia and CFDA regulations. The GMP training for QC personnel was also available. It was claimed that employee can be retrained once only however training SOP did not state this aspect. A separate procedure was presented in Chinese without having "red original" stamp. It was confirmed that HR procedures are not under quality system. There was no cross reference of this HR procedure to training procedure.

An SOP on personal flow, material flow and personal hygiene for synthesis area was available for personnel working in workshop-1. Similarly, another procedure with same title was available for clean area / powder processing area.

3. Buildings and facilities

The design and interior finishes of the workshop visited was suitable for API production. The inspected workshop and facilities dedicated to the manufacture of Amikacin Sulfate were clean and maintained to an acceptable level. The final purification and packaging took place in a clean area with a Grade D environment which is shared with two other APIs. Entry to the clean area of manufacturing and packaging areas was through appropriate change rooms though inspectors looked through the window only the area for salification.

Two different water grades were used for Amikacin sulphate production: synthesis water and Purified Water. Synthesis water was produced by drinkable water using a double RO and it was used in the synthesis steps of Amikacin sulfate production. Purified water was produced by drinkable water through a pre-treatment station and double RO and it was used as a solvent in the latest steps of the process; the specifications were met the EP monograph for PW.

4. Process equipment

Equipment used for Amikacin Sulfate was generally of a good standard and suitable for intended use. The equipment used for manufacturing of Amikacin Sulfate were dedicated for the synthesis stages whereas equipment were shared with two other APIs in Clean room.

5. Documentation and records

The SOP on management of document was in place. It was noted that the batch records kept 1 year after expiry, 5 years being approved by qualified person and with retest period three years after material is distributed. The procedure also described the content of an SOP. A separate procedure was also available on numbering system including revision of SOPs.

6. Materials management

An SOP on the management for suppliers was available; also power-point slides were available to explain the procedure. Although, procedure provided certain criteria for disqualification of approved vendors, there was no mentioning to react on warning letter, non-compliance and notice of concern etc. An approved vendor list was available dated 21/12/2015 and Kanamycin (Shandong Qilu King Pharmaceutical Co. Ltd.)

and PHBA which is updated every time there is an update. A separate supplier list was maintained, it was however noted that key starting materials for Amikacin are purchased directly from the manufacturers. Kanamycin manufacturer was last audited in May 2014 and was found to be acceptable. The primary packaging material i.e. LDPE transparent bags of different sizes is supplied by the same vendor, and these are tested in-house by the laboratory.

7. Production and in-process controls

Production of Amikacin Sulfate took place in dedicated facility for synthesis part whereas clean room facility was shared with two other APIs.

Production operations in Workshops 1 was reviewed and generally found acceptable. Most of reactors and material tanks were labelled with the batch in progress in general and the associated batch documentation was up to date.

In-process sampling and testing was conducted as specified in the relevant BMR. IP tests were conducted in the IPC lab which was briefly inspected to verify pH test of the concentrated Amikacin Sulfate. There was no blending SOP available as it was claimed that blending was not carried out.

8. Packaging and identification labelling of APIs and intermediates

Packaging and labelling was performed in areas dedicated for this purpose. These areas were appropriately designed and classified as Grade D.

9. Storage and distribution

Starting materials and APIs were stored in temperature monitored and controlled areas. Inspection of warehouse located in building 8 covered material receiving area, storage of quarantine, approved and rejected materials, sampling rooms (first floor), finished product / Amikacin sulfate store (second floor) and primary and secondary packaging material store (third floor).

10. Laboratory controls

The quality control laboratory no. 1 was dedicated to analysis of non-penicillins products and it was located in building #1: microbiology (1st floor) and chemical physical laboratory (2nd floor). The company had an organized and suitably equipped QC laboratory. Equipment included HPLC, GC, IR and other testing instruments.

The QC testing was conducted as specified in the relevant specification and according to documented test methods. The sample receiving and distribution logbook was checked. Samples for testing were kept in a designated area.

Primary pharmacopoeial reference and working standards were available. It was noted that Amikacin sulfate identification with IR absorption spectroscopy was compared with working standard instead of primary reference standard.

The Amikacin Sulfate non-sterile was used for sterile formulations as claimed by the company. The product was tested for microbiological limit and pyrogen test. The microbiology lab was not inspected.

11. Validation

The company's validation policy was described in a Validation Master Plan. Responsibilities were well defined and an annual validation plan was required to be prepared. Various types of validation were described with guidance on when each should be used.

Requirements for the qualification of equipment and utilities were included in the abovementioned Validation Master Plan. Periodic requalification was required, depending on criticality.

12. Change control

An SOP on change control was available. It was noted that change control is based on risk assessment approach and a flow chart was available as part of the procedure. The concern department will raise change control before QA will issue a form. The changes were classified into critical, major and minor. The procedure did not describe timeline for the completion and tracking of changes. A major change pertaining to increase in batch size was reviewed which was closed on 24/8/2015. It was however noted that no risk assessment was performed for this change as batch size increase was within 10 fold as the procedure was not clear on risk assessment.

Change control classified as critical was reviewed to understand if risk assessment was performed. As Olmesartan was introduced to clean area used for Amikacin Sulfate, a risk assessment part of the change control was performed according the Quality Risk Management Procedure.

13. Rejection and re-use of materials

There were locked dedicated areas in the warehouses for rejected materials. They were empty at the time of inspection.

The SOP on reprocessing and reworking described definition of these terms as per WHO API for GMP. For reworking, concurrent validation was required and the impurity profile had to be compared with fresh / non-reworked batches. Also, due consideration was given for placing batches for stability studies. There was no reprocessing done for EP grade material, and no reworking was performed on Amikacin Sulfate.

Three solvents namely acetone, acetonitrile and ethanol were recovered. Ethanol was recovered from step 6 of synthesis that is from washing and centrifugation of Amikacin Sulfate crude stage and from step 7 that is from washing and centrifugation of Amikacin sulfate. Recovered ethanol was used back only in step 6; it was noted that the recovered ethanol was not assigned with unique code. There are two different specification sets of ethanol however specifications of recovered solvent was not justified as total impurity was set to 1.5% without impurity profile, no ratio set for fresh to recover and storage / holding time.

14. Complaints and recalls

Handling procedure for customer complaints was available which provided process flow chart. The timeline set was 20 working days, it was however noted that complaints were not classified or categories into any category based on risk, otherwise action could be taken on priority and in accordance to the criticality. It was noted that there was no complaint logbook maintained. The complaints were directly reported on complaint investigation form. The printed list of complaints was found to be an uncontrolled document.

15. Contract manufacturers (including laboratories)

No manufacturing activities were outsourced for the inspected API. It was noted that certain tests were contracted out for the inspected API such as pyrogen tests.

PART 3

Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the deficiencies listed in the Inspection Report, as well as corrective actions taken and planned:

Amikacin Sulfate (non-sterile) (APIMF186) manufactured at ***Qilu Tianhe Pharmaceutical Co Ltd, China*** wasconsidered to be manufactured in compliance with WHO GMP for Active Pharmaceutical Ingredients.

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

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eight Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, 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. 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-six Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, 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 http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 5 http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

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

7. WHO Good Practices for Pharmaceutical 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
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
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
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
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
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
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
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
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
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
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
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
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 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
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. WHO good manufacturing practices for biological products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3
Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf

22. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5

http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

23. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf

24. WHO good manufacturing practices for biological products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 3 http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf