## Part 1
### General information
### Manufacturers details
<table>
<thead>
<tr>
<th>Company information</th>
<th>QILU TIANHE PHARMACEUTICAL CO. LTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of manufacturer</td>
<td>QILU TIANHE PHARMACEUTICAL CO. LTD</td>
</tr>
<tr>
<td>Corporate address of manufacturer</td>
<td>No. 849 Dongjia Town, Licheng District, Jinan, China</td>
</tr>
</tbody>
</table>

### Inspected site
<table>
<thead>
<tr>
<th>Address of inspected manufacturing site if different from that given above</th>
<th>Same as above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit / block / workshop number</td>
<td>No.6,11 &amp; 20 Workshop 1: Building No.11 (Synthesis) Building No.06 (Synthesis) Building No.20 (Salification, final crystallization, drying and packing, clean zone)</td>
</tr>
</tbody>
</table>

### Manufacturing license number
| Lu 20160009 |

### Inspection details
<table>
<thead>
<tr>
<th>Dates of inspection</th>
<th>19-22 January 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of inspection</td>
<td>Routine GMP inspection</td>
</tr>
</tbody>
</table>

### 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). |

This inspection report is the property of the WHO
Contact: prequalinspection@who.int
**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 m². 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**

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
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 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 was considered 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


   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/

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

   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1


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

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

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

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

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

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

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


Short name: WHO TRS No. 992, Annex 4


Short name: WHO TRS No. 996, Annex 3
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf


http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex03.pdf