# WHO PUBLIC INSPECTION REPORT (WHOPIR) API Manufacturer

## Part 1: General information

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| Name of Manufacturer | Livzon Group Fuzhou Fuxing Pharmaceutical Co., Ltd. |
| Unit number | N/A |
| Production Block | Building 1, 4, 7 and 11 |
| Physical address | Jiangyin Industrial Concentration Zone, Fuqing,<br>Fuzhou City, China. |
| Contact person and email address. | Mr.Han Minghuo<br>Vice General Manager<br>regulation <regulation@fxpharm.com> |
| Dates of inspection | 6 to 10 July 2015 |
| Type of inspection | Re-inspection |
| Active Pharmaceutical Ingredient(s) included in the inspection | Kanamycin Acid Sulfate (KAS), Sterile (APIMF241)<br>Kanamycin Monosulfate (KMS), Non-sterile ( APIMF246) |
| Summary of the activities performed by the manufacturer | Production and quality control of sterile and non-sterile APIs |

## Part 2: Summary

***General information about the company and site***

The company was established in 1985. Fuzhou Fuxing Pharmaceutical Co., Ltd. of Livzon Group was formed in 2005. The main focus of business is the manufacturing and distribution of API and FPP. The API products include Kanamycin acid sulfate, Vancomycin hydrochloride, Teicoplanin, Colistin sulfate. There were about 604 personnel employed on site at the time of inspection. The site was about one and a half hour's drive from Fuzhou city.

***History of WHO and/or regulatory agency inspections***

This was the third inspection conducted by WHO PQP. The site had been licensed by the Local Food and Drugs Administration, but the two APIs in this inspection scope Kanamycin Monosulfate (KMS) and Sterile Kanamycin Acid Sulfate (KAS) were not covered by the Chinese GMP certificate. The site had also been inspected and approved by USFDA 2015 and EU (2013); however the inspection scope in terms of facilities and products of these inspections did not fully overlap the WHO inspection scope.

***Focus of the inspection***

The inspection focused on the production and control of Kanamycin Monosulfate (KMS) and sterile Kanamycin Acid Sulfate (KAS) APIs. The inspection covered all the sections of WHO good manufacturing practices for active pharmaceutical ingredients including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

***Inspected Areas***

The inspection covered the following sections of the WHO GMP for Active Pharmaceutical Ingredients text:

- 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
- Complaints and recalls
- Contract manufacturers (including laboratories)

## PART 3: INSPECTION OUTCOME

### 3.1 QUALITY MANAGEMENT

**Principles**

Responsibilities of the quality Unit(s)
The quality unit was able to demonstrate its independence from operations up to General Manager level. This was considered adequate. The unit was responsible for QA, QC and regulatory affairs. There were 71 personnel in the Quality Unit out of a total of 604 on site. QA are responsible for administering the quality system as well as tasks such as batch release, documentation review, SOP approval and supplier auditing.

Internal audits (self-inspection)
The SOP for self-audits was reviewed. Self-audits were performed at least every 12 months. The 2014 self-inspection report and 2015 self-inspection plan were available for review. The 2014 self-inspection was performed over 5 days and covered all departments of the company.

Product quality review
The most recent PQRs for the two products in question were reviewed. The PQR contents required by the WHO guideline were generally present. Preparation and approval of the PQR was timely.

There were no deviations, no complaints, and no OOS summarised in the Product Quality Review of non-sterile KMS manufactured in 2014.

The deviation and CAPA systems were hard copy paper based systems. Only a very small number of deviations have been raised. All were classified as minor. No issues noted from the examples of deviations reviewed; the issues raised in 2014 appeared to have been satisfactorily addressed.

### 3.2 PERSONNEL

Personnel qualifications

According to the details contained in the SMF, key personnel were seen suitably qualified with appropriate tertiary qualifications and experience in the manufacture of APIs and pharmaceutical products. The organogram presented was approved and dated. The job descriptions of the key personnel reviewed were generally satisfactory.

Training
Training was conducted according to the training SOP. Training was provided for all personnel involved in the production and quality control of the APIs.
The analyst competency list and signature specimen list for the QC laboratory and the training records of the selected personnel were presented for review.

Examples of training and the related records were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding the training were addressed by the manufacturer to an acceptable level.

Personnel Hygiene
Requirements for entry to the manufacturing areas were documented in the "Procedure of personal in/out clean area". Adequate change rooms were provided for entry into manufacturing areas.

## 3.3 BUILDINGS AND FACILITIES

Design and construction
The production buildings 1, 4, 7 and 11 were toured and inspected in as far as they are involved with the manufacture of KMS and KAS:

The design, construction and cleanliness standards of all areas appeared adequate. One of the main recent changes in the design of the critical areas in Bldg 11 has been the change from Grade C to Grade B which has addressed a number of issues which were raised at the last inspection. Note that, although there are efforts to reduce the bio-burden of early stage manufacture (e.g. during inoculation and fermentation), these stages are not deemed to be sterile although personnel did refer to sterilisation steps in these areas.

Utilities
The utilities, the general pipework and in general the production rooms have been designed and maintained to an acceptable standard.

Water
Site purified water and WFI and steam used in Bldg 11 (sterile operations) are generated in Bldg 11 itself. The purified water plant was approx. 8 years old. Clean steam was generated from the WFI. Chemical testing of the condensate was carried out frequently. In addition, non-condensable gases, dryness fraction and superheat were been tested by a specialist contractor. Results appeared consistently satisfactory.

Containment
Plant and rooms used for KMS and KAS were process dedicated. No issues with containment from other, potentially potent APIs were noted.

The whole of Bldg 11 was dedicated to sterile KAS manufacture.

Lighting
Lighting was considered to be adequate in all areas visited during the inspection.

Sanitation and maintenance
All areas visited appeared to be clean and maintained at a satisfactory level.

## 3.4 PROCESS EQUIPMENT

Design and construction

No serious issues were noted with the design and construction of the various process equipment. The equipment was largely dedicated and was located in the areas described above. Equipment was largely restricted to mixing tanks and fixed pipework. The sterile manufacturing part of the process was all contained within Bldg 11. Sterilisation of the final KAS pathway was reviewed. The observation made during the inspection that was listed in the full report regarding the pathway sterilisation was addressed by the manufacturer to a satisfactory level.

Equipment maintenance and cleaning

The maintenance programme appeared adequately scheduled, described and recorded. SOP on usage and maintenance of the steam sterilizer was reviewed. No issues were noted.

Calibration

Calibration in general appeared well controlled. The company were reminded that they retain responsibility for the activity even if contracted out.

Computerized systems

The level of computerisation was low. This has resulted in a number of activities which were manually recorded rather than defined by a printout. As a general comment the company should give consideration to acquiring process evidence via an automated system. This should be implemented to reduce and eliminate the risk of transcription errors, ensure consistency from one process to another and provide increased assurance as to the integrity of the data collected.

## 3.5 DOCUMENTATION AND RECORDS

Documentation System and Specifications

The company had a documentation system in place consisting of organization charts, SOPs, protocols, records, reports, etc. Master production instructions, Batch production records and specifications for the products existed. SOP on Regulation of GMP Documentation Classifying and Coding was reviewed and considered to be acceptable in general.

Records of raw materials, intermediates, API labelling and packaging materials

Records including an approved vendor list were available for review.

## 3.6 MATERIALS MANAGEMENT

General controls

Suppliers of raw materials were approved using a formal process involving audits where the supply was defined as a “key material”. Other material suppliers were not required be audited by the SOP. In all cases samples were

received and tested and the results made up part of the information package for lot consideration of qualification status. Appearance on (or removal from) the approved suppliers list was via a change control. There was a suitable audit schedule which was up to date at the time of the inspection.

Receipt and quarantine
Deliveries were seen to be assessed upon receipt for condition and accuracy. Materials were placed in quarantine and required to be labelled up as such. Processes for receipt and testing of acid and base at the tank farm appeared adequate. Non-compliances observed during the inspection that was listed in the full report regarding the use of two parallel systems handling the materials received were addressed by the manufacturer to a satisfactory level.

Sampling and testing of incoming production materials
Sampling was performed in a dedicated room within the raw materials warehouse. Sampling was performed by a QC team who were responsible for the tools and their cleanliness. SOP was reviewed with no other issues.

Storage
There were two raw materials warehouses within the same building. They both had plenty of room available at the time of the inspection. There was no refrigeration requirement for any of the raw materials used in the products in focus. Finished product was stored in a separate building. Again there was sufficient available space and storage was at low level only. Temperatures were required to be kept below 25$^{o}$C. Non-compliances observed during the inspection that was listed in the full report regarding the temperature mapping and monitoring in the storages were addressed by the manufacturer to a satisfactory level.

## 3.7 PRODUCTION AND IN-PROCESS CONTROLS

### Production operations

Time limits
Media fills have been performed and considered to be acceptable.

In-process sampling and controls
In-process sampling and testing were performed at different stages e.g. fermentation and extraction of KMS.

Blending batches of intermediates or APIs
The initial small incubation flasks were combined together to make a media for further expansion of the fermentation. Other than that there was no combination of batches or part batches.

Contamination control
A programme of environmental monitoring was in place. This included sessional settle plates within the Grade A zone. Results of this monitoring were reviewed and discussed. Other environmental monitoring took place in outer

areas but to a generally low frequency. Non-viable particulates were also measured but the results were not reviewed in detail as the operation was a powder fill.

## 3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

**General**

Packaging and labelling operations

Packaging and labelling was restricted to simple labelling of the Aluminium tins. Non-compliances observed during the inspection that was listed in the full report regarding the means by which labels were generated, provided and controlled were addressed by the manufacturer to a satisfactory level.

## 3.9 STORAGE AND DISTRIBUTION

Warehousing procedures

See 3.6 above.

Distribution procedures

The APIs are released for distribution after they have been released by the quality unit according to the Procedure for Products Release.

## 3.10 LABORATORY CONTROLS

General controls

The micro lab was in the same part of the main building as the analytical lab. Segregation from other areas appeared adequate. Activities included media preparation, environmental and water testing, incubation and viable contamination counting. Also this lab housed the sterility testing and antibiotic potency testing. The lab was spacious and well designed. Generally speaking activities followed the requirements and expectations of GMP. The sterility test room contains a VHP sterilised isolator which should mean that false positive events will be almost zero. The incubation regime is 7 days at20~25$^{o}$C followed by 7 days at 30~35$^{o}$C which was considered appropriate.

Testing of intermediates and APIs

Sample receiving and distribution procedure and log book were reviewed. The procedure of testing RS of Monosulfate, column qualification and raw data in the HPLC were reviewed. Non-compliances observed during the inspection that was listed in the full report regarding the sample receiving and distribution were addressed by the manufacturer to a satisfactory level.

Validation of analytical procedures

The sterility test validation was reviewed and considered acceptable in general.

Stability monitoring of APIs

The conditions used for long term 25±2°C/60%±5% RH and accelerated 40±2°C/75%±5% RH testing were consistent with the ICH / WHO recommendations and suitable records were available.

Reserve/retention samples

The retention samples were packed in the small sized similar material containers of the same nature as those used for the commercial products. The room conditions were 15-25$^0$C, RH not more than 70%.

## 3.11 VALIDATION

Validation policy

In general the company had a policy, procedures, protocols and reports for validation and qualification of their processes, procedures, equipment, utilities etc.

Process validation was performed according to SOP. Process validation protocol and the report for KMS were reviewed and found acceptable generally.

Approaches to process validation

The most recent media fill package was reviewed. The process of KAS was mimicked. This process was considered to be an adequate representation of the routine process. Records appeared adequate.

Qualification

A cross section of equipment requalification packages were reviewed including the requalification of autoclave and other system. All of these had some minor issues; corrective and preventive actions had been taken and found acceptable.

Cleaning validation

Not reviewed on this occasion as equipment is dedicated.

Validation of analytical methods

See 3.10

## 3.12 CHANGE CONTROL (CC)

There was a procedure for change control. The change control register and records were maintained.

## 3.13 REJECTION AND RE-USE OF MATERIALS

The procedure for reprocessing and reworking was in place and reviewed.

There was apparently no recovery of solvents/materials used for Kanamycin Monosulfate and sterile Kanamycin Acid Sulfate nor any evidence of such activity.

## 3.14 COMPLAINTS AND RECALLS

The processes for complaints and recalls were described within suitably titled SOPs. Only one complaint in total (not relating to either of the two products here) had been received since the last WHO inspection in February 2014. This

concerned damaged fibre kegs and missing lead seals. An investigation was carried out and some corrective actions with the keg manufacturer and the transport company were identified.

No recalls have been necessary since the last inspection although a mock recall was performed. The performing and documenting of this was generally satisfactory. Responsibilities and investigation processes appeared adequate.

### 3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

A small number of laboratory activities are contracted out including some specific toxicity testing and pyrogen testing. Some calibration activity was contracted out, including to a government department responsible for the conductivity meter testing. Contract testing agreements regarding the abnormal toxicity and pyrogen testing were reviewed and considered acceptable in general.

## PART 4: CONCLUSION

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, as well as the corrective actions taken and planned, APIs of Sterile Kanamycin Acid Sulfate (APIMF241) and non-sterile Kanamycin Monosulfate (APIMF246) manufactured at Livzon Group Fuzhou Fuxing Pharmaceutical Co., Ltd., Jiangyin Industrial Concentration Zone Fuqing, Fuzhou, Fujian, China were 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.