World Health Organization

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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** |
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| **Company information** | |
| Name of Manufacturer | Livzon Group Fuzhou Fuxing Pharmaceutical Co., Ltd. |
| Corporate address of manufacturer | No. 8 Nangang Road, Jiangyin Industrial Concentration Zone,<br>Fuqing, Fuzhou City, 350309, Fujian Province, P. R. China.<br>Telephone Number: 86-591-85966928<br>Fax Number: 86-591-85966925<br>Email Address: fxqa@fxpharm.com |
| **Inspected site** | |
| Name & address of manufacturing site | Livzon Group Fuzhou Fuxing Pharmaceutical Co., Ltd.<br>No. 8 Nangang Road, Jiangyin Industrial Concentration Zone,<br>Fuqing, Fuzhou City, 350309, Fujian Province, P. R. China.<br>D-U-N-S No. 421260459<br>GPS details: N25°27′38.75″, E119°17′14.35″ |
| Synthetic Unit/Block/ Workshop | • Building 1 – Strains Centre<br>• Building 4 – Fermentation Engineering II<br>• Building 7 – Extraction Engineering I, KMS production line<br>• Building 11 – a dedicated production line used for KAS manufacture from KMS and the sterilization, filling and packaging of KAS |
| **Desk assessment details** | |
| Date of review | 28 October 2019 |
| APIs covered by this desk assessment | Kanamycin acid sulfate – sterile<br>Kanamycin sulfate – non-sterile |
| List of documents submitted | • English Translation Statement.<br>• List of regulatory inspections performed at the site during the last 5 years.<br>• List of full inspection report(s) and final decisions by the regulatory authority.<br>• Manufacturing license, Certificate No. Min20160089 issued on 1/1/ 2016 by Fujian Food and Drug Administration.<br>• Site Master File, Approved date: 30.4.2019.<br>• List of all the products manufactured on-site.<br>• The APQR report for Kanamycin Sulfate, issued on the 6/3/2019.<br>• The APQR report for Kanamycin Acid Sulfate, issued on the 5/3/ 2019.<br>• Completed BMRs for Kanamycin Acid Sulfate and Kanamycin Sulfate.<br>• Blank BMR for Kanamycin Acid Sulfate and Kanamycin Sulfate.<br>• No Recalls Declaration. |

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| | • Self-inspection plan and report.<br>• No Warning Letter Declaration.<br>• No Out-of-stock Situations Declaration. | |
| **Part 2** | **Summary of SRA/NRA inspection evidence considered (from most recent to last)** | |
| Germany authority: Ministerlum fur Sozlales, Gesundheit, Frauen und Familie | Dates of inspection: | 23-25/1/ 2019 |
| | Type of inspection: | Routine inspection |
| | Block/Unit/Workshop: | Not mentioned |
| | Type of APIs covered: | Vancomycin hydrochloride<br>Teicoplanin<br>(as published in EudraGMDP) |
| US Food and Drug Administratio n (US FDA) | Dates of inspection: | 30/7/2018 – 3/8/2018 |
| | Type of inspection: | Routine inspection |
| | Block/Unit/Workshop: | Building 1 with seeding, Strain Center<br>Building 4, Fermentation Engineering II<br>Building 7, Extraction Engineering I<br>Building 11, Refining Engineering I |
| | Type of APIs covered: | Non-sterile manufactured by fermentation |
| Germany authority: Freie Hansestadt Bremen Der Senator Fur Gesundheit | Dates of inspection: | 20-23/4/2017 |
| | Type of inspection: | Routine inspection |
| | Block/Unit/Workshop: | •Primary packing<br>•Secondary packing<br>•Quality control and analysis-Lab<br>•Control and release Batches<br>•Warehousing and distribution<br>•Manufacturing API |
| | Type of APIs covered: | Colistin sulfate |
| **Part 3** | **Summary of the last WHO inspection** | |
| Date and conclusion of most recent WHO inspection | The inspection of Livzon Group Fuzhou Fuxing Pharmaceutical Co., Ltd. was last performed by WHO PQT on 13~17/3/2017. This was the 4th inspection of this site. It was found compliant with 2 major deficiency and 17 listed as Other. | |
| Brief description of manufacturing activities | The manufacturer was involved in the manufacturing, packaging, labeling, testing and storage of the API and/or preparation such as Vancomycin hydrochloride-Precipitated, Vancomycin hydrochloride-Lyophilized, Daptomycin, Milbemycin Oxime, Kanamycin sulfate, Colistimethate sodium, Kanamycin acid sulfate, Colistin sulfate, Colistin sulfate premix 10% | |
| General information about the company | Livzon Group Fuzhou Fuxing Pharmaceutical Co Ltd was founded in 1979 as state-owned company. In 2004 the site was acquired by Livzon group. Jiangyin plant is in operation from 2005. | |

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| and manufacturing site | |
| Focus of the last WHO inspection | Stain centre was located at building No. 1, KMS cell cultures was performed in dedicated rooms. Fermentation process was performed in Building No. 4 in KMS dedicated room and dedicated equipment. Starting from fermentation till crystallisation manufacturing process was performed in close system. Extraction process, crystallisation and packaging of KMS were performed in dedicated rooms using dedicated equipment. KAS was manufactured in dedicated room using dedicated equipment |
| Areas inspected | • Pharmaceutical Quality System<br>• Documentation system<br>• Production System<br>• Facilities and Equipment System<br>• Laboratory Control System<br>• Materials System<br>• Packaging and labelling system<br>• Buildings:<br>Building 1 – Strains Centre<br>Building 4 – Fermentation Engineering II<br>Building 7 - Extraction Engineering I, KMS production line<br>Building 11 – a dedicated production line used for KAS manufacture from KMS and the sterilization, filling and packaging of KAS |
| Out of scope and restrictions (last WHO inspection) | None |
| WHO APIs covered by the last WHO inspection | APIMF241 Kanamycin (acid sulfate) – sterile (KAS)<br>APIMF246 Kanamycin sulfate – non-sterile (KMS) |
| Additional products covered by this desk assessment: | Not applicable. |
| **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 |

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| 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** |
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**a) Manufacturing authorization and GMP certificate granted by the local authority:**
Manufacturing license, Certificate No. Min20160089

- Issued: 1/1/ 2016 by Fujian Food and Drug Administration.
- GMP Certificate was not submitted.

**b) Site master file (SMF):**
Site Master File, Approved date 30.4.2019, was reviewed and found acceptable and in line with the WHO TRS No. 961, Annex 14.

**c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:**
List: Vancomycin Hydrochloride, Daptomycin, Colistimethate Sodium, Milbemycin Oxime, Colistin Sulfate, Kanamycin Sulfate, Kanamycin Acid Sulfate.
The facility does not manufacture any beta lactams, hormones, penicillin, steroids or cytotoxic products.

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

- Germany authority inspection in 23-25/1/2019 compliant.
- US FDA inspection in 30/7-3/8/2018 compliant.
- Germany authority inspection in 20-22/4/2017 compliant.
- WHO inspection in 13-16/3/2017 compliant.

**e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):**
The APQR report for Kanamycin Sulfate issued on the 6/3/2019. It shows that there are not any batches of Kanamycin Sulfate were manufactured during the evaluation period (01/01/2018–31/12/2018). The statistical analysis on the stability test results all the indicators of each batch of finished Kanamycin Sulfate maintained very good stability.

The APQR report for Kanamycin Acid Sulfate issued on the 5/3/ 2019. It shows that there are not any batches of Kanamycin Acid Sulfate were manufactured during the evaluation period (01/01/2018–31/12/2018). The statistical analysis on the stability test results all the indicators of each batch of finished Kanamycin Acid Sulfate maintained very good stability.

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

Kanamycin Sulfate Batch Records (Executed, Batch No. XXX).
Kanamycin Acid Sulfate Batch Records (Executed, Batch No. XXX).

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

Blank master batch manufacturing records of the Kanamycin Sulfate and Kanamycin Acid Sulfate were submitted.

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

No recalls Declaration: There is none of all API's recalls in the past three years.

**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:**

Self-inspection plan, report and CAPA in 2018. The self-inspection included WHO APIs.

**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 warning letter statement: Up to now, the company have not received any warning letter.

**k) Out-of-stock situations:**

A declaration confirming that no out-of-stock situation in the past 3 years, and out-of-stock will never happen.

**l) Additional documents submitted:**

The conclusion of the latest media fill validation report for the WHOAPI-246 Kanamycin API shows that the process procedures and standard operating procedures adopted during the aseptic process simulation test of kanamycin acid sulfate could prevent microbial contamination and ensure that the sterile product meeting the specification can be produced under normal production conditions.

| **Part 5** | **Conclusion – Desk assessment outcome** |
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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 **Livzon Group Fuzhou Fuxing Pharmaceutical Co., Ltd.** located ***at No. 8 Nangang Road, Jiangyin Industrial Concentration Zone, Fuqing, Fuzhou City, Fujian Province, P. R. 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.

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| Part 6 | List of guidelines referenced in this inspection report |
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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