World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Company information	
Name of manufacturer	Livzon (Group) Pharmaceutical Factory
Corporate address of manufacturer	No. 38 Chuangye Road North, Jinwan District, Zhuhai, Guangdong 519045, P. R. China
Inspected site	
Address of inspected manufacturing site if different from that given above	No. 38 Chuangye Road North, Jinwan District, Zhuhai, Guangdong 519045, P. R. China
Unit / block / workshop number	Small volume injection line, Building P08
Manufacturing license number, (delete if not applicable)	Yue20160261 GMP certificate CN20120041
Inspection details	
Dates of inspection	30 October to 02 November 2017
Type of inspection	Follow up inspection
Introduction	
Brief summary of the manufacturing activities	The WHO inspection concentrated on the production and quality control of small volume injections FPP and specifically activities at Building P08 which include manufacturing, packaging, labelling, testing, storage and distribution of small volume injections (Ampoules). The inspection focused on the manufacturing of the antibiotic, Kanamycin ampoule small volume injection. The manufacturing of the injections is executed on four production lines which include powder for injections, lyophilized powder for injections and biological products.

General information about the company and site	Livzon Pharmaceutical Factory is solely-owned subsidiary of the Livzon Group. The company was established in 1989 and relocated to the current address in March 2014. The company currently operates only one ampoule line with other lines catering for small-volume vials, freeze-dried powder injection, powder for solution for injection, bio-engineering products, soft capsule, tablet, hard capsule, granula, suppository, gel, ointment etc. At the time of the inspection the company employed 734 staff members. The company also has manufacturing facilities in Shanghai. Since the last WHO inspection, the manufacturing of cephalosporin products have been contracted to a third party manufacturer, however all quality control testing remains with the site.
History	The previous WHO inspection was performed in March 2017.which resulted in a number of non-compliances identified. The intention of the follow up inspection was to verify the execution of the CAPA as per the Livzon undertaking.
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	• Quality Management system and CAPA review • Management review • Deviation control and change control • OOS and investigation • Process Validation • Batch manufacturing record and review • Equipment qualification • Computerised system validation • Buildings and facilities • Finished products warehouse • Production • Chemical quality control laboratory • Stability program • Analytical method validation
Restrictions	The inspection was restricted to the ampoule line, and associated support functions including finished goods warehouses.
Out of scope	All other products and workshops were outside of the inspection scope and were not visited.
WHO product numbers covered by the inspection	Antibiotic ampoule injection, 2ml:500mg Antibiotic ampoule injection, 3ml:1g

Abbreviations

AHU	air handling unit
ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
APQR	annual product quality review
BDL	below detection limit
BMR	batch manufacturing record
BPR	batch packaging record
CAPA	corrective actions and preventive actions
CC	change control
CFU	colony-forming unit
CoA	certificate of analysis
CpK	process capability index
DQ	design qualification
EM	environmental monitoring
FAT	factory acceptance test
FBD	fluid bed dryer
FMEA	failure modes and effects analysis
FPP	finished pharmaceutical product
FTA	fault tree analysis
FTIR	Fourier transform infrared spectrometer
GC	gas chromatograph
GMP	good manufacturing practice
HACCP	hazard analysis and critical control points
HPLC	high-performance liquid chromatograph
HVAC	heating, ventilation and air conditioning
IR	infrared spectrophotometer
IQ	installation qualification
KF	Karl Fisher
LAF	laminar air flow
LIMS	laboratory information management system
LoD	limit of detection
LOD	loss on drying
MB	microbiology
MBL	microbiology laboratory
MF	master formulae
MR	management review
NMR	nuclear magnetic resonance spectroscopy
NRA	national regulatory agency
OQ	operational qualification
PHA	process hazard analysis
PM	preventive maintenance
PpK	process performance index
PQ	performance qualification
PQR	product quality review
PQS	pharmaceutical quality system

QA	quality assurance
QC	quality control
QCL	quality control laboratory
QRM	quality risk management
RA	risk assessment
RCA	root cause analysis
SOP	standard operating procedure
TAMC	total aerobic microbial count
TFC	total fungi count
TLC	thin layer chromatography
URS	user requirements specifications
UV	ultraviolet-visible spectrophotometer

Part 2
Brief summary of the findings and comments

1. Pharmaceutical quality system

A formal documented system for quality assurance was established, with procedures covering key quality elements being in place. Operations were specified in written form and GMP requirements were essentially being met. The procedures that were reviewed and discussed during the inspection were generally of a satisfactory standard. Managerial responsibilities were appropriately specified in written job-descriptions. Product and processes were monitored and these results considered during batch release; regular monitoring and reviews of the quality of pharmaceutical products were being conducted according to documented schedules and procedures.

During the previous WHO inspection the company was found deficient in its site management review processes, however the current inspection revealed that management reviews now follows Standard Management Procedure. Meeting records of quarter one and two 2017 were reviewed. The CAPA to these major deficiency reviewed during the inspection was considered to be acceptable.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented and followed. Manufacturing processes were defined and documented and were performed in well-designed facilities.

Necessary human and physical resources were provided, including qualified and trained personnel, adequate premises, suitable equipment and services, appropriate materials, containers, approved procedures and instructions, laboratories and equipment for in-process and other controls. Qualification and validation activities were performed. Manufacturing processes and batch manufacturing records were reviewed and discussed.

3. Sanitation and hygiene

Premises and equipment were maintained at a good level of cleanliness. The company had a standard operating procedure in place as the basis for its approach to personal hygiene and sanitation in its production facility, with appropriate hand washing required and change facilities. Clean areas were cleaned frequently in accordance with an approved written programme.

4. Qualification and validation

During the first WHO inspection of the site, process validation of commercial batch sizes had not been completed. Since that inspection process validation for the two strengths and ampoule sizes of kanamycin injection have been performed. This essentially closes as corrective actions the major observation made in the last inspection. The process validation protocol and report were reviewed were essentially of an acceptable standard.

The revised approach to sterilization validations was reviewed. Data and analysis was generally acceptable for the terminal sterilization process. Non-compliances observed during the inspection that was listed in the full report regarding the qualification of sterilizers used for the sterilization of equipment used for filling operation were addressed by the manufacturer to a satisfactory level.

5. Complaints

The complaints procedures were not inspected during this inspection. The Kanamycin products have not yet been commercialized.

6. Product recalls

Recall procedures were not inspected during this inspection, however the inspectors discussed generally the challenges of multiple market supply that might arise post pre-qualification.

7. Contract production, analysis and other activities

According to the company, there was no use of external scientific, analytical or other technical assistance in relation to the products in the inspection scope.

8. Self-inspection, quality audits and suppliers' audits and approval

Self-inspections (internal audits) were performed routinely according to standard procedures which covered basic GMP topics. Internal audits were required to be performed once a year. Self-inspections were not reviewed during this inspection.

9. Personnel

Personnel generally appeared aware of the principles of GMP and records showed that they received initial and continuing training, including hygiene instructions, relevant to their responsibilities in the production process. Steps were taken to prevent unauthorized people from entering production and QC areas and appeared to be effective. An organization chart was available and considered acceptable. Responsibilities for production and QC/QA were well separated.

10. Training

Training was provided for all personnel whose duties take them into manufacturing areas or into control laboratories but was not reviewed in detail during the inspection.

11. Personal hygiene

Personnel were required to undergo health examination. Eye optical examination was required for operators who perform visual inspection of injections.

Changing and washing before entry to production areas followed written procedures. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product. The protective clothing washing and sterilization operations followed standard operating procedures. Extensive hand washing was required of visitors as they entered the various areas.

12. Premises

The premises consisted of several production blocks with a total of four production lines in building P08 including the terminally sterilized SVP production line on which Kanamycin is produced. This production line was not dedicated to Kanamycin injections.

Manufacturing areas were generally of a good standard and suitable for the activities conducted therein. Exposed surfaces were smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and permitted the repeated application of cleaning agents and disinfectants, where used.

The inspected areas used for ampoule washing, solution compounding, filling and inspection complied with the acceptable standard and suitable for this type of production activity for a terminally sterilized ampoule.

Changing rooms were designed as airlocks and used to provide physical separation of the different stages of changing. Changing rooms were flushed with filtered air. The final stage of the changing room was in the at-rest state, the same grade as the area into which it leads.

Storage areas were of sufficient capacity. Receiving and dispatch bays were separated and protected materials and products from the weather.

QC laboratories were separated from production areas. QC areas including that for microbiological control were spacious and well designed. Adequate storage space was provided for samples, reference standards, solvents, reagents and records.

13. Equipment

Equipment installed was of a good standard.

The equipment was in operation at the time of inspection. The line appeared to be running smoothly without excessive intervention.

The manufacturing/compounding vessel and filter system were partially equipped with automated CIP and SIP systems.

Computerized systems were used in the warehouse for material management and control warehouse logistic and cost administration.

A LIMS system was used in the QC lab to manage the material and product status via testing results and its release.

14. Materials

Non-sterile antibiotic API was supplied by the Livzon's API manufacturing site. Packaging materials were purchased from approved suppliers.

Finished products were held in quarantine until their final release, and stored under appropriate and monitored conditions.

The process validation batches were kept in a segregated room where inventory was being managed manually with tally cards and written manual records. The ampoules viewed were kept in bulk in large cartons box after labelling at the time of inspection.

15. Documentation

In general, documentation was managed according to a documented procedure. SOPs and log books were kept and provided traceability.

BMRs were retained for each batch processed. Batches were numbered according to a Management procedure of product batch number and validity terms. It allows for differentiation between the commercial batch, a trial/demon or validation batch.

The antibiotic injection BMRs for process validation batches were reviewed and discussed.

Approved antibiotic product specification and testing procedure were available for inspection.

Electronical data including production video records in the production area were reviewed and discussed.

16. Good practices in production

Clean areas for the manufacture of terminal sterile products were classified according to the required characteristics demanded by GMP for the environment. Clean rooms and clean-air devices were routinely monitored while in operation. For filling zone, particle and microbiological monitoring was undertaken.

Preparation, filtration and filling of Kanamycin solutions were performed according to written procedures. Sterilization was performed with vacuum steam sterilizer followed by manual visual inspection. The equipment, procedure and records were reviewed. The frequency to check the integrity of vent filters in several pieces of equipment were checked and discussed.

The packaging area for ampoules was spacious and most secondary packaging operations essentially of a manual nature.

17. Good practices in quality control

The general QC laboratory was inspected. The premises were generally of an acceptable standard and well equipped. The OOS procedures for chemical and microbial testing were reviewed. The SOP for microbiological OOS handling was revised and found to be acceptable.

A LIMS system was used in the QC lab. HPLC and GC used for testing have been fully networked since the last inspection. Data integrity management, access control and privileges assigned to different level were reviewed and discussed.

The HPLC used for testing antibiotic injection was networked with software. An in-house testing method was being used for Kanamycin injection. Non-compliances observed during the inspection that was listed in the full report regarding analytical method validation were addressed by the manufacturer to a satisfactory level.

Stability study management regarding sample receipt, register and testing were inspected. Access control to the stability room and chambers was reviewed. The clock and time zone in the computer used to monitor chamber conditions were inaccessible and blocked. Documents reviewed were satisfactory. The receipt and withdrawal of stability study samples was controlled and recorded.

PART 3

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, **Livzon (Group) Pharmaceutical Factory located at No. 38 Chuangye Road North, Jinwan District, Zhuhai, Guangdong 519045, P. R. China**, was considered to be operating at an acceptable level of compliance with WHO good manufacturing Practices for pharmaceutical products.

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-eighth 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-sixth 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 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
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
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. Fiftieth 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

22. 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 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. Fiftieth 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. Fiftieth 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