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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	**Jiangsu Grand Xianle Pharmaceutical Co., Ltd**
Corporate address of manufacturer	No 1, Zhongshan Seven Road, Coastal Industry Park, Economic Development Zone, Binhai County, Yancheng City, Jiangsu Province, P.R. of China - 224555
Inspected site	
Address of inspected manufacturing site if different from that given above	– (same address as given above)
Unit / block / workshop number	Workshop 5 for synthesis (building 4); cleanroom
Manufacturing license number	No.: SU20160338
Inspection details	
Dates of inspection	19 to 22 July 2016
Type of inspection	Initial GMP inspection
Introduction	
Brief summary of the manufacturing activities	The total area of the facility was about 133,333 square meters and was enclosed by a brick wall. The construction area was about 60,000 square meters which was approximately half of the total area. The construction of the manufacturing site was completed in 2012 and was made of concrete columns and beams with external brick walls. It was used for the manufacturing of 12 steroidal hormone APIs (according to manufacturing licence dated January 1, 2016) including Medroxyprogesterone Acetate (C505) API and Megestrol Acetate (C504) API) and intermediates. The clean areas of the two APIs were completely separated: a clean area of 230 m^2 for the refining of Medroxyprogesterone Acetate (hereafter as MPA) API; a clean area of 230 m^2 for the refining of Megestrol Acetate API; and a general area of 430 m^2 for the manufacturing. The production started up in 2013 after Qualification and Validation activities had completed.

	One building (no. 1) contained administration offices and QC labs. The total area of administration office with the first and the second floor is about 1,500 m^2. The total area of QC labs with the third and the fourth floor was 1,500 m^2.
General information about the company and site	Jiangsu Grand Xianle focused on the manufacturing of steroids API & intermediates. Building 4 produced MPA, building 5 produced Dexamethasone, building 6 produced Betamethasone, building 7 was a fermentation area and building 8 was for extraction. In addition, building 21 was used for prednisone, building 18 for betamethasone (different steps), building 20 for Dexamethasone (different steps), building 9 as a warehouse for solids, building 10 to 15 & 20 were for liquids, building 15 was a tank farm, building 16 an engineering department, building 17 was waste treatment station, and building 23 for storage of obsolete equipment and solid waste. At the opening meeting, the company clarified that building 4 was workshop 5 which manufactured MPA for complete manufacturing including clean area (Class D) for crystallization, centrifugation, drying and packing. At the time of inspection, the total number of staff was 292 and all were full time). There were no contracted employees used by the company. The translation was provided by one company's employee (Mr. Walter Yang) and by an external translator (Mr. Ivan Gu). The opening meeting presentation did not provide any information on the quality management system and regulatory inspections.
History	This was the first WHO-PQT inspection of Jiangsu Grand Xianle Pharmaceutical Co Ltd. It was confirmed that the site had not been inspected by any of the overseas regulatory authority. It had been inspected by the provincial FDA for the manufacturing license. The site had not applied for a GMP certificate from CFDA as it is not a requirement for the site to obtain a GMP certificate for export purposes. It was noted that at the time of the inspection, APIs were not sold to the domestic market as there was no GMP certificate whereas intermediates were being sold to the domestic market (GMP certification was not required). According to company's statement, all APIs were exported (no domestic sale).
Brief report of inspection activities undertaken	
Scope and limitations	
Areas inspected	Workshop 5 for synthesis & clean (building 4)
Restrictions	Not applicable
Out of scope	Not applicable
WHO product numbers covered by the inspection	Medroxyprogesterone Acetate (MPA) APIMF271

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 (where applicable)**

Brief summary of the findings and comments

1. Quality Management

The quality management system was generally well established, documented and implemented. The site organizational structure was presented and was generally acceptable. Quality-related activities were defined and documented. The company had an organogram that showed independence of the quality unit from production. The responsibilities of the quality unit were implemented through QA and QC. There was a system for product quality review which was supposed to be performed annually.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

2. Personnel

An organization chart was available. There was an adequate number of personnel, suitably qualified by education and training, to perform and supervise the manufacture of APIs. The personnel met during the inspection were experienced and appeared to be knowledgeable about GMP.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

3. Buildings and facilities

Buildings were constructed of painted rendered masonry. In general, finishes were appropriate for the activities carried out. Paths and roadways were of concrete or paving slabs. The site had a fire hydrant system. Overall, levels of lighting were adequate. The premises were generally in reasonable state of repair and clean.

MPA was manufactured in a production workshop 5 (synthesis), also referred to building 4. The last purification steps were also done in building 4. There were specific rooms and equipment (reactors, filters, containers and centrifuge) for the condensation steps of MPA and the crystallization and powder processing was conducted in dedicated cleanroom. At the time of inspection, there was no activity being carried out in the cleanroom, therefore AHUs were switched off.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

4. Process equipment

Workshop 5 had more than 15 reactors which were mainly made of stainless (SSR) and glass-lined (GLR) reactors. The equipment was mainly SS and GL reactors, SS centrifuge, filters, tray dryer, dryer/blender and milling machine. Most of the reactors inspected were bearing a label for “out of use” which meant to be cleaned.

Equipment maintenance procedure for plant maintenance (PM) module was followed. The equipment viewed during the inspection appeared to have been suitably maintained and in acceptable condition.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

5. Documentation and records

In general, there was a system of documentation covering all relevant areas however, their control and review was unsatisfactory. The design of logbooks was unsatisfactory as they were loose unnumbered pages. Loose sheets were used as logbook for complaints, change controls and other quality system procedures.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

6. Materials management

There was a system for evaluating and approving suppliers of staring materials and an approved vendor list was in place. Vendor management procedure was in place which provided procedure for the assessment of vendors using questionnaire and on-site audit. The site was audited every three years. The vendors were graded into A,B,C and D based on their performance which takes into account cost, results etc. Materials were sampled and tested on receipt before being approved for use, however, this section was not inspected due to time constraints.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

7. Production and in-process controls

MPA was manufactured in three steps. Critical process parameters (CPPs) and in-process controls (IPCs) were defined as sighted from the review of PQR and batch records. The commercial batch size of MPA was around 110kg and it was claimed that batches produced for WHO will not be blended, however MPA batches were blended routinely as noted during inspection for non-WHO ("non-regulated" according to company) markets without any validation.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

MPA was packed in double (transparent) polyethylene bagged aluminum tin secured with serially numbered seals. The label had all details including the specifications for the API traceable to the material code and process.

The dried powder of the finished MPA was transferred using a valve system connecting the dryer with a transfer PE bag allowing thus a transfer without any production of dust. The transfer bag was brought to another room equipped with protection booth were its content was transferred in a double PE bag, closed and the put in an aluminum tin.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

9. Storage and distribution

The warehouse (building 9) for APIs (temperature controlled: NMT 30°C) and for intermediates was inspected and found in a good shape and clean. About 5-10% of the room for APIs was occupied with carton drums or aluminum tins (MPA).

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

10. Laboratory controls

The QC laboratory was divided into three major sections: Physico-chemical lab, Microbiology lab and Stability chambers & retention samples storage. The premises were supplied with conditioned air and the activities were adequately segregated. The laboratory was equipped with FTIR, HPLC, GC, UV spectrophotometers and balances. The lab was scattered over two floors i.e. 3rd floor for instrumentation and microbiology lab and 4th floor for physico-chemical and stability chambers. The review of electronic data of MPA batches revealed that adequate attention was not given to ensure data integrity.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

11. Validation

Process validation management procedure was available which uses validation type as prospective, concurrent and retrospective validation. The current expectations on the use of three stage process validation have not been introduced by the site as yet.

Process validation protocol & report for MPA was reviewed and noted that risk analysis using RPN was used to for the selection of critical process parameters. The protocol provided details of starting materials, raw materials and packaging materials used in the manufacturing process.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

12. Change control

The change control was described in the procedure, which contained a very detailed form (4 pages) to be used to handle and document chronologically the whole process when a change is requested/ proposed. The form did not contain any line to be used by any operator to start the process of change. According to the SOP it was the supervisor who was in charge to start the process.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

13. Rejection and re-use of materials

The SOP covered the rejected products as well as the reprocessing and reworking of APIs and intermediates. According to the definition of the SOP rejected products were those with confirmed OOS. The definitions of reprocessing and reworking corresponded to ICH Q7.

The actions taken or proposed to be implemented have been reviewed by the inspectors, and these were found to be acceptable. There satisfactory implementation will be verified during future inspections.

14. Complaints and recalls

Product recall management procedure was in place for the management of recalls wherein quality director and general manager were responsible to recall product from the market. The recalls were classified into Class I (within 24 hour), II (within 48 hour) and III (within 72 hours) with 30 and 60 days from domestic and overseas markets respectively. Various mode of communication such as email, fax, telephone, announcement through media should be used to notify the affected customer before recall. No recall reported since three year however no logbook was maintained. It was also noted that no mock recall was performed for domestic and export market.

15. Contract manufacturers (including laboratories)

It was noted during inspection that contracted services were used by the laboratory and the production department for the calibration and requalification of various equipment and instruments. However, this section was not inspected.

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: Medroxyprogestrone acetate manufactured at located at ***Jiangsu Grand Xianle Pharmaceutical Co. Ltd. Yancheng city, Jiangsu Province, 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 report

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. http://www.who.int/medicines/publications/44threport/en/

2. 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/

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 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. 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

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