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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Active Pharmaceutical Ingredient Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Qinhuangdao Zizhu Pharmaceutical (QZP) Co. Ltd.
Corporate address of manufacturer	Site: No.10, Longhai Road, Economic and Technological Development Zone, Qinhuangdao, China DUNS number: 531050371 *GPS: N39°55.366', E119°27.802'*
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Same as above
Synthetic unit /Block/ Workshop	Not applicable
Inspection details	
Dates of inspection	15-19 October 2018
Type of inspection	Routine inspection
Introduction	
Brief description of the manufacturing activities	Qinhuangdao Zizhu Pharmaceutical Co. Ltd. (QZP) manufactures the following Active Pharmaceutical Ingredients (APIs): Levonorgestrel, Mifepristone, Ethinylestradiol, Quinestrol, Gestodene, Gestrinone, Anisodine Hydrobromide, Tibolone, Testosterone, Prednisone Acetate, Norgestrel, Progesterone, Ethisterone, Meclofenoxate Hydrochloride, Misoprostol, Danazol, Testosterone Propionate, Diclofenac Diethylamine, Barium Sulfate, Estradiol, Dienogest, Desogestrel, Estriol, Ulipristal Acetate, and Estradiol Cypionate.
General information about the company and site	Qinhuangdao Zizhu Pharmaceutical Co. Ltd. (QZP), a wholly-owned subsidiary of China Resources Zizhu Pharmaceutical Co., Ltd (CRZP), was established in 2006 and officially put into operation in 2009. QZP located at the west part of Qinhuangdao Economic and Technological Development Zone with an area of 210,000 m^2 and the floor area of about 40,000 m^2 produces hormones APIs and intermediates for CRZP's finished products and export.
History	The manufacturing site has been regularly inspected by WHO Prequalification Team (PQT). The site was last inspected by WHO-PQT in December 2017. In addition, the site has been inspected by the FDA of

	Hebei Province (July 2017), CFDA (September 2017), Mexican COFEPRIS (April 2017) and USFDA (Nov-Dec 2016).
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The objectives of the current inspection included: ✓ Verification of CAPA following the last WHO PQ inspection held in December 2017 ✓ Review the status of WHO position paper based on the current inspection ✓ Conduct a routine GMP inspection as the last inspection was limited to laboratory inspection ✓ Verification of whistle-blower' email
Restrictions	None
Out of scope	None
WHO APIs covered by the inspection	Mifepristone (APIMF170) Ethinylestradiol (APIMF171) Levonorgestrel (APIMF172)
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
KF	Karl Fisher
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory

MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
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
RO	Reverse osmosis
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer

Part 2	**Summary of the findings and comments**

1. Quality management

In general, there was a GMP Quality Management System in place. High level description of the quality system was given in the Site Master File. Management reviews are arranged once a year. Report of the last management review was presented. QA, QC heads of production and facilities and top management participate in the management review. It was discussed that the management review should develop to support improvements and not only to receive an one-sided summary reports of the previous year.

Risk management procedures for avoiding cross-contamination were reviewed. In general, the basic principle to avoid cross-contamination during production and purification, is to use dedicated manufacturing lines or manufacturing lines where similar products are manufactured.

Product quality review procedure was discussed. The procedure was recently revised, and several changes were made e.g. incorporation of statistical tools, criteria to calculate alert limit, completion timeline, review and approve responsibility etc. The PQR is performed for the batches produced between Jan and Dec every year. The revised procedure described that process capability will be applied if more than 30 batches are manufactured in one year. The CpK criteria was set to be less than 1, between 1.00 and 1.33, between 1.33 and 3.0 and more than 3.0.

GMP self-inspection management procedure was discussed. The procedure was revised to incorporate data integrity element. The self-inspections are performed twice per year. Should there be a need to perform more frequent audits, it will be considered. The self-inspection schedule of 2017 was discussed.

Supplier management procedure described the assessment and audit processes of suppliers were reviewed and found acceptable. Decision to perform an on-site audit versus desk review (document audit) is made based on the criticality of the material. For the year 2018 there were 27 audits planned, including 13 on-site audits. Audits for the year 2018 had been performed timely according to plan.

Management of deviations was reviewed and was found to be adequate. 33 deviations had been registered in the year 2016, 49 in the year 2017 and 36 in the year 2018 until the time of the inspection. Handling and documentation of the above-mentioned deviations had been performed appropriately according to the SOP.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Personnel

The organization chart was up to date and it had been approved by the General Manager. Job descriptions and training records of the Quality Head (QP) as well as the Supervisors of QC, QA and Production were reviewed. Training programme for the year 2018 was reviewed and found to be appropriate.

Technical department is an independent department reports to the General Manager of the site. Its main responsibility is to develop and optimize the manufacturing processes which is supported by a small-scale laboratory.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

3. Buildings and facilities

Buildings in general were in an acceptable condition and maintained properly. Some malfunctions were detected in equipment and pressure cascades. AHU area and the Water purification plant were in good order. Access control was managed by manual locks. Water leakage was noticed in the room (1112).
There were separate AHU units for the Levonorgestrel and Mifepristone production areas in the Purification Plant. Location of the exhaust of the air is on the roof and intake of the air on the walls separated by an adequate distance to prevent cross-contamination through air. HEPA-filters are staged in a separate utilities storage room. According to the maintenance personnel, if only one HEPA unit from a box of two is needed, the whole box is transferred to the AHU-room, one is taken with the box resealed and returned to the storage room.

Purified water was used in the cleaning purposes. City water was used as the raw water for the purified water plant. Water is treated first by a multimedia filter, and active charcoal filter, then treated with a softener and then run through two 0.5 um filters before the RO-system. Sanitization of the PW tank is by ozone. Cleaning procedures of the dispensing area were reviewed. There was no clear list of materials to indicate, which of the two cleaning methods (using water or alcohol) should be used following dispensing of the material. In addition, the procedure did not describe in adequate details all the components / material observed in the dispensing area (i.e. the plastic boxes to store equipment). It was identified that the cleaning method had not been validated.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

4. Process equipment

Equipment Reliability Management Procedure describes the Plan for preventive maintenance that is created annually. The Plan for the 2018 was reviewed and according to the follow up of the plan, maintenance actions had been performed timely. The SOP Management Procedure for measurement describes the annual calibration plan. The annual calibration plan for 2018 was reviewed indicating that calibrations had been attended to timely. Spot checks performed during the facility tour confirmed that calibration was generally performed in time Equipment in AHU, water plant and QC were in general in acceptable condition. In production areas several cases were identified, where the maintenance of equipment had not been properly performed (several solvent tanks not having proper measuring scales but only some markings without calibration labels, manholes of several tanks were not closed with steel lids but with covers of some other material.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Documentation and records

Documentation was mainly in Chinese and it was evaluated by using translation provided by the Chinese – English interpreters. SOPs are reviewed every three years, with the review confirmed by an authorization stamp. All documentation was paper based and managed manually.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

6. Materials management

All incoming materials are received in the Logistic Building at one receiving area. There was a list of approved suppliers available, but the warehouse operator was not aware that there could be changes in the list documented on separate sheets. This may cause a risk of accepting materials from a supplier that has been removed from the approved suppliers list. The receiving area was not temperature controlled, but there were no time limit for long-time materials storage. There was no centralized inventory system to manage the status and locations of materials following release from the quarantine areas, this data being only available on loose sheets attached to materials.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

7. Production and in-process controls

The inspection team visited the Synthetic Plant 2 which produces crude Mifepristone (intermediate step 1, 2 and 3). The crude Mifepristone was transferred to the warehouse before moved to the purification plant. Although synthetic plant 2 is claimed to be a dedicated plant, it was noted that in 2014, a trial batch of another API was produced. This trial API has not been scaled up, hence only Mifepristone is being produced. The synthetic area was equipped with two change rooms with appropriate personnel protective equipment (PPE) and gowning (gown, hairnet, shoe cover, face mask).

Purification of Mifepristone and Levonorgestrel was performed in a separate building, identified as the purification plant in separate suites. The inspectors visited the Mifepristone area. Change rooms were equipped with adequate gowning and PPE. Decolouration, purification and centrifugation are done in a non-classified room 1112. Material is then moved to the D classified area (room 1015). Inspectors visited the classified area, as there were no windows with a view to the Class D production rooms from the non-classified corridor. Entrance to the classified area is through airlocks, with the necessary additional gowning. Storage of the primary packaging materials (room 1020) and API quarantine room (room 1021) are located in the same area.

There were not many production activities during the facility tours, and therefore it was not possible to observe the working practices performed by the operators in actual production. Methods for transferring materials to the tanks were explained by the staff in the synthesis plant. It was noticed that the operators did not always follow the gowning and hygienic procedures correctly (two operators were in the synthesis area without wearing appropriate protective clothing, and when entering the dispensing area via gowning room, the operator did not close-up the gown properly and did not sanitize hands.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

8. Packaging and identification labelling of APIs and intermediates

These operations could not be observed (no production running for this stage) but were explained and partially demonstrated by the operator.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Storage and distribution

The incoming solid materials, intermediates and finished APIs are stored in the logistic building. During the visit of the warehouse, procedures such as receipt of incoming materials, operation of

sampling booth and management procedure for raw materials in warehouse were reviewed. Separate area was provided for the storage of quarantine and approved materials. Sampling was performed by the quality control personnel under the supervision of QA. Different sampling plans (n+1, p and r) were used for the sampling of incoming materials and intermediates.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

10. Laboratory controls

The laboratory was moved to a new building since 6th September 2018. It was claimed that all the laboratory equipped had been requalified before putting in use. The laboratory was spread on the third and fourth floor. The samples are received in the third-floor laboratory which has wet chemistry, stability, retention and reference standards. The fourth floor has microbiology, GC and HPLC equipment areas. The laboratory has the biometric access which was accessible to QC, QA and in-charge of calibration activities. The laboratory has 9 client servers and 21 user accounts for chromatographic systems. To access Empower-3, analysts were required to login separately through Windows and Empower. The laboratory has 13 HPLC connected to server. The date/time stamp were locked as noted during the inspection except time zone. Separate HPLC rooms were used for the testing of intermediates and finished APIs. Five user types (administrator, analyst, chemist, manager IT and reviewer) were created for Empower-3.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Validation

Validation Master Plan was reviewed. VMP was made at the beginning of the year and had been updated during the year 2018 twice. Re-validation frequency is 3 years, if there no specific reasons to perform re-validation earlier occur (change in procedures or some abnormality).

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

12. Change control

The SOP "Management procedure for change control" was reviewed and was found to be adequate. There had been 77 changes in the year 2016, 88 in the year 2017 and 79 in the year 2018 until the time of the inspection.

Handling and documentation of the changes had been performed appropriately according to the SOP.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

13. Rejection and re-use of materials

Management procedure for reprocessing and reworking was discussed. The definition of reprocessing was in line with WHO API GMP guideline. The reprocessing was applied in two situations, one when product did not meet specification i.e. OOS and secondly for tailing batches. The reprocessing is done using the same process. Whereas reworking is performed using a different processing method against the approved process. It was claimed that reworking is not allowed for intermediates and finished APIs manufactured for WHO, FDA and EU markets. It was noted that only reprocessing was done for the intermediates and finished APIs manufactured for WHO, FDA and EU markets. It was claimed that a careful assessment was done to ensure quality of the intermediate and API are not adversely affected.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Complaints and recalls

One complaint had been registered in the year 2016 and one during 2017. Until the time of the inspection, there had been no complaints during 2018. Both complaints received in the years 2016 – 2018 were reviewed.

There had been in the year 2016 one simulation recall and in the year 2017 there had been one recall because of the USA FDA findings. In the year 2018 there had been no recalls until the time of the inspection. The recall of the year 2017 had been closed and the product had been destroyed in USA.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Contract manufacturers (including laboratories)

Not inspected.

Part 3	Conclusion – Inspection outcome

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, ***Qinhuangdao Zizhu Pharmaceutical Co. Ltd.***, located at ***Site: No.10, Longhai Road, Economic and Technological Development, Zone, Qinhuangdao, China*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines for APIs.

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. ***Short name: WHO GMP for APIs or WHO 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*** or ***WHO TRS 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-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/
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.
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile 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 8. ***Short name: WHO HVAC Guidelines*** *or* ***WHO TRS No. 1010, Annex 8***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

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.
   Short name: WHO TRS 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.

Short name: WHO TRS 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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.
Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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.
Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***Short name: WHO TRS 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. ***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

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. ***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

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. ***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

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production 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

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 GDRMP guidance or WHO TRS No. 996, Annex 5
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. 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 Multisource guidance or WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf