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

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Company information | |
| Name of manufacturer | ***China Resources Zizhu Pharmaceutical Co. Ltd*** |
| Corporate address of manufacturer | No 27 W-F-E Workshop Chaoyang North Road, 27<br>*Chaoyang District, Beijing, China* |
| **Inspected site** | |
| Address of inspected manufacturing site if different from that given above | As above |
| Unit / block / workshop number | W-F-E workshop |
| Manufacturing license number | JIN20150204 |
| **Inspection details** | |
| Dates of inspection | 25-28 January 2016 |
| Type of inspection | Routine GMP inspection |
| **Introduction** | |
| Brief summary of the manufacturing activities | Misoprostol tablets are produced using direct compression method without any granulation whereas Mifepristone uses wet granulation. It was noted that 9 batches of Misoprostol tablets had been put up on stability (one batch size 135,000). The WFE workshop is supplied with 5 AHU. The site has a dedicated warehouse for WFE workshop (intermediates stored in WFE workshop). The quality management system is based on drug administration law of China, Chinese GMP, WHO, FDA, and EMA. The WFE workshop and warehouse are separate buildings from other production, QA/QC are located in Technology building; staff employed in the site were 712 employees with 29 in WFE workshop, 28 in QA and 40 in QC laboratories. |
| General information about the company and | China Resources Zizhu Pharmaceutical Co., Ltd (hereafter CRZP) was established in the year 1969 and is located at No.27 Chaoyang North Road, Chaoyang District in Beijing. The site was renamed from Beijing Zizhu Pharmaceutical Co., Ltd |

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| site | (BZP) in June 2013. The site in Beijing is for the finished pharmaceutical products. Key buildings on the site include the building for General Pharmaceutical Preparations, the W-F-E Workshop, and the Microecologics Building, Warehouses, QC labs and the Power Station. The CRZP covers an area of 122,000 $m^2$ with 62,000 $m^2$ of floor area and 45% coverage of green land. |
| History | The manufacturing site was first inspected by WHO-PQT in January 2014, and this is the second WHO-PQT inspection. In addition, the site was inspected by Beijing Food and Drug Administration, the State Food and Drug Administration and Mexican Cofepris. |
| **Brief report of inspection activities undertaken** | |
| **Scope and limitations** | |
| Areas inspected | • Quality Assurance<br>• Sanitization and hygiene<br>• Qualification and validation<br>• Complaints<br>• Recalls<br>• Self-inspection<br>• Personnel<br>• Training<br>• Personal hygiene<br>• Premises<br>• Equipment<br>• Materials<br>• Documentation<br>• Production<br>• Quality control |
| Restrictions | none |
| Out of scope | none |
| WHO product numbers covered by the inspection | Products under assessment<br>Misoprostol 200mcg tablet (RH048)<br>Mifepristone 200mg tablets (RH052) |

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| Abbreviations | SOP – standard operating procedure<br>API – active pharmaceutical ingredient<br>FPP – finished pharmaceutical product<br>PQS – pharmaceutical quality system<br>PQR – product quality review<br>QRM – quality risk management<br>CAPA – corrective actions and preventive actions<br>PpK – Process performance indice |

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| | CpK – Process capability indice<br>MR – management review<br>BMR – batch manufacturing record<br>BPR – batch packaging record<br>MF – master formulae<br>LAF – laminar air flow<br>AHU – air handling unit<br>FBD – fluid bed dryer<br>HVAC – heating, ventilation and air conditioning<br>CC – change control<br>RA – risk assessment<br>CoA – certificate of analysis<br>HPLC – high-performance liquid chromatograph<br>GC - gas chromatograph<br>UV - ultraviolet-visible spectrophotometer<br>IR – infrared spectrophotometer<br>FTIR - Fourier transform infrared spectrometer<br>TLC – think layer chromatography<br>LOD – loss on drying<br>KF – Karl Fisher<br>NMR - nuclear magnetic resonance spectroscopy<br>NRA – national regulatory agency<br>URS – user requirements specifications<br>DQ – design qualification<br>IQ – installation qualification<br>PQ – performance qualification<br>OQ – operational qualification<br>FAT – factory acceptance test<br>MB – microbiology<br>TAMC – total aerobic microbial count<br>FMEA - failure modes and effects analysis<br>FTA – fault tree analysis<br>PHA - process Hazard Analysis<br>HACCP - hazard analysis and critical control points<br>PM - Preventive maintenance<br>WHOPIR – WHO public inspection report<br>EM – environmental monitoring<br>LoD – Limit of detection<br>BDL – Below detection limit |

| **Part 2** | **Brief summary of the findings and comments (where applicable)** |
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***Brief summary of the findings and comments***

**1. Pharmaceutical quality system**

A quality assurance system was in general terms implemented and maintained. Quality Assurance (QA) and Quality Control (QC) departments were independent from production. The QA Head reported to the General Manager. Production and control operations were specified in writing. The necessary controls on starting materials, in-process checks and finished products were in place.

**2. Good manufacturing practices for pharmaceutical products**

In general, good manufacturing practices were implemented. The necessary resources were generally provided. The procedures and manufacturing instruction were established. Qualifications and validations were performed, adequate premises and equipment were available for production, in-process controls and storage, and operators were trained.

**3. Sanitation and hygiene**

This area was generally considered acceptable, from what was seen during the inspection of production and from microbiological/environmental monitoring test results.

In changing room, panels showing the garments to be worn were available.

**4. Qualification and validation**

The key elements of a qualification and validation programme were defined and documented in a validation master plan. Validation master plan (VMP) for WFE workshop was available. It was noted that VMP described covering of three products (Misoprostol, Mifepristone and Levonorgestrel) for validation.

**5. Complaints**

There were no changes made to complaint procedure since the last WHO inspection. It was also noted that the company did not receive any complaint for any of the WHO prequalified products since the last WHO inspection.

**6. Product recalls**

There were no changes made to recall procedure since the last WHO inspection. It was also noted that the company did not recall any WHO prequalified products since the last WHO inspection.

## 7. Contract production, analysis and other activities

The tests for particle size distribution (PSD) and metal element tests were contracted to these laboratories based in China. It is noted that these contracted laboratories are accredited to ISO-17025. The company has procedure including the provision to send questionnaire to these contracted laboratories.

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

The SOP on the management procedure for self-inspection/internal audit was reviewed and noted that self-inspection had to be conducted at least once per year for WFE workshop. A multi-disciplinary team from QA, technical, engineering with prior manufacturing experience was used for self-inspection. It was noted that the checklist used was not adequate because it did not have provision to write observations as it was limited to ticking yes/no column.

## 9. Personnel

In general, there were sufficient qualified personnel to carry out the tasks for which the manufacturer was responsible. During on-site inspection correct garments was observed.

## 10. Training

A procedure on training was in place, and the HR Director described brief procedure on training management including training needs from production & laboratory, evaluation of need by QA, training plan, assessment on training etc. The common topics will be included in company level training plan whereas department level training is approved by quality. The HR was responsible for the implementation and follow-up of the training plan. The QA supervisor was identified as one of the key GMP trainers who provided training to key production and laboratory personnel, and in turn, these personnel impart training to their respective department personnel. After imparting training, trainees have to be assessed using multiple choice questions with criteria of more than 80% was expected. In case failure of obtaining the minimum rate, only a second choice to be retrained was allowed. Training plan for WFE workshop for year 2015 was available which included training on SOPs and regulatory requirements / guidelines. In general, the training program was appropriate; however, some consideration should be given to invite external trainer or consultant and to send employees for external training in order to have different perspective and insights.

## 11. Personal hygiene

This area was generally considered acceptable.

## 12. Premises

In general the buildings and facilities used for manufacture and quality control were located, designed, and constructed to facilitate proper cleaning, maintenance and production operations. Quality control laboratories were separated from production areas.

## 13. Equipment

Balances and other measuring equipment with appropriate range and precision were available for production and control operations and were calibrated on a scheduled basis. Calibration due-date labels were attached to the equipment. Equipment in production area were non-dedicated and were shared between the two products under PQ.

## 14. Materials

In production, dispensed starting material and intermediate products were identified during the different production stages using proper labels that include the identity and status of each material or product. Materials were obtained from approved suppliers by CRZ.

It is noted that active Mifepristone and Misoprostol were received and stored at WFE warehouse. Upon receipt of request, sampling and dispensing of these actives were carried out in WFE workshop and after sampling / dispensing, the materials stored in WFE workshop. For excipients, materials were received in WFE warehouse and then sampled & dispensed within the dedicated area before transferred to WFE workshop. The temperature mapping was initially conducted on empty warehouse, which was again performed with materials for seven days each in summer and winter season. It is noted that mapping will be repeated once every three years. The refrigerator used to store Misoprostol was also temperature mapped.

## 15. Documentation

In general documents were designed, prepared, reviewed, approved, signed, dated and distributed with care by the appropriate responsible persons. Reproduced documents were clear and legible. Documents were regularly reviewed and kept up to date.

## 16. Good practices in production

In general, raw materials for manufacturing of tablet were dispensed, processed, packaged and distributed under appropriate conditions. Actual yields were compared with expected yields at designated steps in the production process. Processing status of operation room was labelled with product names and batch numbers. In-process controls were performed by the production and QC analysts. Manufacturing areas were accessed through secondary change rooms.

All core manufacturing, sampling and dispensing areas were as per ISO 8 classification and with dedicated air handling units to maintain temperature, relative humidity, and pressure differential with plenum HEPA filter.

It was noted during the inspection of WFE workshop on day 2 that the manufacturing process of Misoprostol and Mifepristone was carried out in closed equipment with a use of glove boxes for the transfer of these APIs, granulator / mixer / dryer, 45 station compression machine. The WFE workshop is negatively pressurized to contain the API. The compression machine was equipped with metal detector, de-duster, IBC

bin (blender) for loading of blended material, tablet receiver, in-line vacuum, one arm and was operated using PLC. The API storage room (305) housed two refrigerators for the storage of Misoprostol 1% dispersion whereas SS cabinets were used for the storage of Mifepristone. The temperature of refrigerator was 3.9°C and it was linked with alarm as claimed. Two different batches of Mifepristone were stored in SS cabinet. The API dispensing room housed a down-flow booth (Esco) which was used for the dispensing of excipients. The dispensing of API was performed in a glove box equipped with two stations: transfer and work stations. The in-process control laboratory was managed by production, and production and QC operators are responsible to carry on IPC tests on scheduled frequency. It was noted that 7 days clean hold time was set for IBC and hose pipes. It was noted during the inspection of glove box that there were two pressure transducers and six pressure indicators available to monitor pressure, and the actual pressure of the glove box was monitored by the PLC and the value was read on the screen. The alarm test was recorded in the logbook.

Production planning procedure defined production capability of each workshop, and noted that campaign production was required for WFE workshop. A specific procedure on production planning in WFE workshop was available and described that one batch could be produced at one time, and only one product could be produced at one time.

## 17. Good practices in quality control

The quality control lab consisted of a chemistry section, instrumentation section and a microbiology section. The laboratory was equipped with HPLC, GC, UV, FTIR, balances etc. upon inspection of instrumentation section based at second floor, it was noted that laboratory had 11 of the HPLC systems whose 3 HPLC systems were dedicated for WFE workshop. Also, laboratory had 2 GC equipped with head space. Different software were used by the laboratory make of HPLCs such as Chemstation, ezchrom and Empower2.

Finished product specification of Mifepristone 200mg tablet was available. It was noted that specification had been submitted to WHO in October 2015, and some minor changes were made in January 2016. There was no in-process specification available as it was understood that in-process tests were at the time of inspection part of the batch manufacturing record.

Finished product specification of Misoprostol 200mcg tablet was reviewed and noted that there were no changes made in the specification except some editorial changes. There was no in-process specification available as it was understood that in-process tests were at the time of inspection part of the batch manufacturing record.

The stability studies program for Misoprostol and Mifepristone tablets were reviewed. It was noted that 9 batches of Misoprostol (total number of manufactured batches: 12 commercial including lot 45130301 for WHO submission) and 5 batches (total number of manufactured batches: 5 batches including 2 submission and 3 process validation batches) of Mifepristone were placed for stability studies. For long term, three conditions were used 30°C/75% and 30°C/65% and 25°C/65%, whereas for submission and process validation batches, products were stored at 40°C/75%. Company claimed that the methods of analysis for stability test are the same as routine method of analysis.

During the review of stability studies results, it was noted that the templates used to print chromatograms were inconsistent in terms of scale as well as key info such as area %. The chromatograms did not bear any information pertaining to integration type, relevant printouts were not attached as well as no review of audit trails to name a few.

**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, ***China Resources Zizhu Pharmaceutical Co Ltd, China*** ,located at Chaoyang North Road, 27, Chaoyang District, Beijing, 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-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/
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-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 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
    *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
    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

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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
***Short name: WHO TRS 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