World Health Organization

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

PART 1: GENERAL INFORMATION

Name of Manufacturer	**Qinhuangdao Zizhu Pharmaceutical Co. Ltd**
Buildings	NA
Physical address	No. 10, Longhai Road, Economic and Technological Development Zone, Qinhuangdao, Hebei Province, CHINA
Contact person	Ms Yen Chen, chenying@zizhu-pharm.com Deputy Director, International Business Mr Zhang Mensheng, Site Quality Head (authorized person)
Date of inspection	13 - 16 October 2015
Type of inspection	Routine GMP inspection
Active Pharmaceutical Ingredient(s) included in the inspection	Levonorgestrel (APIMF172) Mifepristone (APIMF170) Ethinylestradiol (APIMF171)
Summary of the activities performed by the manufacturer	Production, quality control, packaging and distribution of APIs and intermediates

PART 2
General information about the company and site

Qinhuangdao Zizhu Pharmaceutical Co Ltd (hereafter QZP), Longhai Road, Economic and Technological Development Zone, Qinhuangdao, Hebei Province, China was inspected by WHO-PQ on the above mentioned dates. The QZP was established in 2006 and located at the west of Qinhuangdao Economic and Technological Development Zone. It is a wholly-owned subsidiary of China Resources Zizhu Pharmaceutical Co., Ltd. (CRZP). The site has an area of 210,000 m^2 and the floor area of about 40,000 m^2. There are 386 employees including 21 QA, 34 QC and 175 production people. At present, QZP produces steroid APIs and intermediates for CRZP's finished products and for domestic and overseas market.

There are 25 key APIs including Levonorgestrel, Mifepristone, Ethinylestradiol, Gestodene, Gestrinone, Tibolone, Quinestrol, Estradiol, Estriol, Desogestrel, Testosterone, Anisodine Hydrochloride, etc produced by QZP (regulatory breakup of these APIs; 9 by CFDA, 2 by EDQM, 3 by WHO, 6 by USFDA, and one by KFDA).

History of WHO and/or regulatory agency inspections

This was the 3rd WHO-PQT inspection at the site after years 2011 and 2012.

The USFDA had inspected the facility in 2014 and an EIR was issued. As there were number of errors in the report, USFDA deemed these errors insignificant and hence refused to correct the report and issued compliance letter. Out of six APIs inspected by USFDA, three APIs are the same as WHO prequalified products.

Focus of the inspection

The inspection focused on the production and control of Levonorgestrel (APIMF172), Mifepristone (APIMF170) and Ethinylestradiol (APIMF171). The inspection covered most of the sections of WHO GMP for APIs, including premises, equipment, documentation, materials, validation, sanitation and hygiene, production, quality control and utilities.

Inspected Areas

- Quality Management
- Personnel
- Buildings and facilities
- Process equipment
- Documentation and records
- Materials management
- Production and in-process controls
- Storage and distribution
- Laboratory controls
- Validation
- Change control
- Rejection and reuse of materials

- Complaints and recalls
- Contract manufacturers (including laboratories)

PART 3: INSPECTION OUTCOME

3.1 QUALITY MANAGEMENT (QM)

Generally quality management systems (QMS) procedures were executed. The site had an acceptable documentation system consisting of procedures, records, specifications and related documentation, approaches and policies to support quality management and quality assurance. The responsibilities of the quality and production units were defined. There was a system and records for self-inspection and annual product quality reviews.

The quality management system did not change since the last WHO inspection in general.

The actions taken or proposed to be taken in relation to the deficiency pertaining to quality management have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.2 PERSONNEL

The QZP site had adequate number of qualified, experienced personnel to carry out the tasks in accordance to the applicable GMP. Individual responsibilities were generally defined in the organisation charts and individual job descriptions.

The heads of production and quality control were independent of each other.

The GMP Training Matrix for new employee was available whereas annual training plan was also available.

The actions taken or proposed to be taken in relation to the deficiency pertaining to personnel have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.3 BUILDINGS AND FACILITIES

Since the last WHO inspection, there were no major changes made on the production and laboratory facilities.

Ethinylestradiol is produced in a multifunctional plant, whereas Levonorgestrel and Mifepristone are produced in a dedicated plant. From the information provided during inspection, it was noted that no batch of Mifepristone was produced since the last WHO inspection. A new API was introduced on a multifunctional plant.

There were no changes made in the synthetic plant. In general, the reactor systems were suitable for the processes being used to manufacture the APIs of interest though these were not inspected. The final processing area was classified to Grade D (ISO 14644 Class 8) level.

During inspection of the clean area, it was found that containment was not adequate as verified by the inspectors using a pressure differential meter. Although, it was claimed that clean room was maintained at a negative pressure to the atmosphere, this could not be demonstrated as there was no magnehelic gauge provided between airlock and corridor.

Purified water system was comprised of 1-stage reverse osmosis (RO) and electron de-ionizer (EDI) technology with a secondary circulation loop serving twelve points of use (PoUs) in the Multifunctional Plant 3. Sanitation of the secondary loop is via Ozone injection into the system.

The actions taken or proposed to be taken in relation to the deficiency pertaining to premises have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.4 PROCESS EQUIPMENT

There were documents to support the installation, cleaning and maintenance of equipment.

Preventive maintenance schedules for the HVAC were viewed and found to be acceptable. All environmental parameters were monitored manually as there was no computer system for monitoring.

Qualification of new blender/drier was reviewed. Installation and operational qualification were available. There were user requirement specification (URS) and design qualification comparing company requirements with supplier offer. But the performance qualification has not been carried out.

The actions taken or proposed to be taken in relation to the deficiency pertaining to process equipment have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.5 DOCUMENTATION AND RECORDS

The standard operating procedures (SOPs) and other documents were controlled according to the document control SOP. There had been no changes made to the document control SOP since the last inspection.

The actions taken or proposed to be taken in relation to the deficiency pertaining to documentation and records have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.6 MATERIALS MANAGEMENT

Materials were sourced from approved suppliers and some key starting materials were produced on site. On receipt, they were quarantined, sampled and tested before acceptance into approved stores for subsequent use. The storage of starting materials, intermediates and finished APIs was needed improvement. The storage conditions were regularly monitored.

The key starting materials produced for WHO products were not identified as an approved vendor and therefore were not part of the approved vendor list. Materials at different manufacturing stages were identified with a unique batch number and stage of processing.

The actions taken or proposed to be taken in relation to the deficiency pertaining to the materials management have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Production processes were guided by documented procedures and detailed instructions. Production processes were either conducted in dedicated facilities or on campaign basis in multipurpose workshops and equipment. There were in-process controls conducted at appropriate stages to monitor the quality of the intermediates and APIs. There were cleaning procedures available.

The production record (bilingual) of Ethinylestradiol (EE) with 2 year expiry was reviewed. The synthesis route of EE started from Estrone, crude EE and EE. The batch production record is divided into three stages (crude EE, 1st purified EE and EE). The final stage was tested for identification/ID (compared against working standard), residual solvents (THF, Acetone and Ethanol), assay and related substance tests. It was noted that another stage, “micronization”, was included before material was dispatched to the customer.

The production record of LNG was reviewed. The manufacturing process consists of 5 stages starting from LNG intermediate I, LNG Intermediate II, LNG Intermediate III, Crude LNG, and LNG finished API.

The key starting material was produced on site in fermentation plant.

The SOP for blending described procedure for blending. The batches meeting specification will be taken for blending as stated in the procedure. The SOP for retest date described procedure for assigning retest date based on the oldest production date for date of manufacturing.

The actions taken or proposed to be taken in relation to the deficiency pertaining to production and in-process controls have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

Materials at different stages processing were identified with unique batch numbers and stage of processing. Intermediates and finished APIs were packed using packaging materials meeting the relevant specifications.

3.9 STORAGE AND DISTRIBUTION

The QZP had a logistic or warehouse department which housed starting materials, packaging materials, solvents, intermediates, and finished APIs. It was noted that there was common entrance/exit for the receipt/dispatch of these materials. There was common sampling and dispensing room available for sampling and dispensing of various materials. Such practices could potentially pose contamination, cross contamination issues and product mix-up.

The existing system of storing quarantine and approved materials needed further attention.

The actions taken or proposed to be taken in relation to the deficiency pertaining to storage and distribution have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.10 LABORATORY CONTROLS

The QC laboratory was situated on the first floor of a separate block. The premises, facilities and utilities were separate from production and were in a good state of repair. There were dedicated rooms for activities like wet chemistry, instrumentation, hot areas, balance room, retention sample room, reference standard room and stability study chamber area. There were adequate pieces of equipment with up to date calibration status.

The microbiology laboratory was separated from the chemical laboratory. There were stability chambers for the different storage conditions and records of charging and withdrawal of samples for testing were available. The autoclave for plate/media sterilization was a single door unit which could pose a contamination problem and test reliability.

The quality control laboratory included the instrument lab (HPLCs, GC, Karl Fisher Titrator, and FTIR), physic-chemical lab and balance room.

There were a number of issues raised pertaining to the existing control of electronic data.

The actions taken or proposed to be taken in relation to the deficiency pertaining to laboratory controls have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.11 VALIDATION

The overall validation policy was explained in the document Validation Master Plan. The validation of manufacturing processes, cleaning and analytical methods were documented. Cleaning validation report was reviewed as an example.

The actions taken or proposed to be taken in relation to the deficiency pertaining to validation activities have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.12 CHANGE CONTROL (CC)

There were no significant changes made to change control procedure since the last inspection. This section was not inspected in detail.

3.13 REJECTION AND RE-USE OF MATERIALS

Management of recovered solvent procedure (QZ01/SMP08/009/5 dated 23/9/2015) was available which listed the names of API which required recovery of solvent. From the list, it was noted that LNG for domestic market required recovery of solvent from stage I, and company has separate product code for WHO market and domestic market. The company claimed that recovered solvents were not used for WHO products.

The actions taken or proposed to be taken in relation to the deficiency pertaining to rejection and re-use of materials have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.14 COMPLAINTS AND RECALLS

There were minor changes made in the complaint procedure since the last inspection.

There was no change made in product recall procedure since the last WHO inspection.

There was minor change made in returned procedure, otherwise rest of the information remain same as from the last inspection.

There was no complaint, recall or returned received for any of the APIs produced for WHO markets. There was no complaint received in 2015.

The actions taken or proposed to be taken in relation to the deficiency pertaining to complaints and recalls have been considered acceptable and their satisfactory implementation will be verified during future inspections.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

Not inspected

PART 4: 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:

- ***Levonorgestrel (APIMF172),***
- ***Mifepristone (APIMF170)***
- ***Ethinylestradiol (APIMF171)***

manufactured at Qinhuangdao Zizhu Pharmaceutical Co., Ltd, 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.