**PART 1: GENERAL INFORMATION**

<table>
<thead>
<tr>
<th>Name of Manufacturer</th>
<th>Zhuhai Rundu Pharmaceutical Co. Ltd</th>
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<tbody>
<tr>
<td>Unit number</td>
<td>NA</td>
</tr>
<tr>
<td>Production block</td>
<td>Workshop 1</td>
</tr>
<tr>
<td>Physical address</td>
<td>No.6 North Airport Road, Sanzao Town, Jinwan District, Zhuhai City 519041, China. Tel: +86-756-7630000</td>
</tr>
<tr>
<td>Contact person and email address</td>
<td>Mr Zhou Jian Quality Director / Quality authorized person <a href="mailto:zhoushijian@rdpharma.cn">zhoushijian@rdpharma.cn</a></td>
</tr>
<tr>
<td>Date of inspection</td>
<td>19 - 22 October 2015</td>
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<tr>
<td>Type of inspection</td>
<td>Routine GMP inspection</td>
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<tr>
<td>Active Pharmaceutical Ingredient(s) included in the inspection</td>
<td>WHOAPI-176 - Piperaquine Phosphate</td>
</tr>
<tr>
<td>Summary of the activities performed by the manufacturer</td>
<td>Production and control of APIs and intermediates</td>
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</table>
PART 2
General information about the company and site

Zhuhai Rundu Pharmaceutical Co. Ltd No.6 North Airport Road, Sanzao Town, Jinwan District, Zhuhai City 519041, China was inspected by the WHO Prequalification Inspection Team on the above mentioned dates. The site commenced production in 1997 under Mintong drug institute and was merged with Rundu in 2007 and is wholly owned by Sanxin Chemical Company since 2010.

From the opening meeting presentation, it was noted that site produces APIs, intermediates and finished dosage forms for domestic and overseas markets. The API workshop 1 produces (floor 1+2A+2B) Piperaquine Phosphate (in short PQP, the product in question), Irbesartan, Voriconazole, Levobupivacaine HCl, Lansoprazole, Rabeprazole Sodium, Valsartan, Olmesartan medoxomil, Candesartan cilexetil. In addition, API workshop 2 (floor 3A+3B) produces pharmaceutical intermediates of Sartan API and pharmaceutical intermediates of Candesartan cilexetil. The API workshop 4 produces intermediates. The workshop 3 ceased operation since the end of 2012 due to having small capacity and converted to producing dosage forms. The manufacturing site is located on site of area 26,200m² and Piperaquine Phosphate (PQP) was manufactured in a dedicated synthetic area in a multipurpose comprehensive workshop. The powder processing was conducted in a multipurpose area. The site rented two warehouses (Beishan warehouse for intermediates, API and FPP and Andi warehouse for storage of raw materials, packaging materials and sampling activities) which are around 500 meter away from the main site. It was claimed that personnel working in rented warehouses are employed by Rundu.

It was noted that Zhuhai Rundu is constructing another manufacturing site just across the existing site which is currently under construction. The construction will be completed sometime in June 2016. On this new site, the company intends to manufacture APIs for WHO and EDQM markets.

History of WHO and/or regulatory agency inspections

This was the 3rd WHO inspection of this site after year 2012 (April and October). In addition, the site was inspected by following authorities:

<table>
<thead>
<tr>
<th>Inspection Time</th>
<th>Products</th>
<th>Certificates No.</th>
<th>Inspected/Issued by</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011.03.11-13</td>
<td>Irbesartan</td>
<td>20110429-133-H-68-17</td>
<td>KFDA</td>
</tr>
<tr>
<td>2012.11.09-11</td>
<td>Bulk drug (Rabeprazole sodium, Lansoprazole, Irbesartan, Levobupivacaine Hydrochloride, Piperaquine phosphate, voriconazole)</td>
<td>GD20130064</td>
<td>CFDA</td>
</tr>
</tbody>
</table>
Focus of the inspection

The inspection focused on the production and control of Piperaquine Phosphate (WHOAPI-176). 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)

The company had an organogram that showed independence of the quality unit from production. The responsibilities of the quality unit were implemented through three departments namely QA, QC and other related systems which included material management system, facility & equipment system and production system. There was a system for product quality review which was performed annually. The responsibility for batch release was entrusted to the qualified person (QP) who was the head of the quality unit and was deputized in this respect by the head of QA.

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 site had adequate numbers of staff who showed a lot of commitment to their work and willingness to learn.
The hygiene of the staff was generally adequate. The instructions were provided for gowning before entry to the production areas, similar step by step instructions should also be provided during exit of the production areas.

Training SOP, Training matrix and sample of training tests results were viewed. These seemed to be in order and no obvious deficiencies were observed.

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

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.

Piperaquine phosphate was manufactured in a multipurpose production workshop 1. There were specific rooms and equipment (reactors, filters, containers and centrifuge) dedicated for the condensation steps of PQP but the saltification, crystallization and powder processing was conducted in multipurpose equipment. The design of airlocks, doors and pressure differentials needed to be improved to strengthen containment measures.

Generally, the manufacturing site is appropriately designed which is easy to clean. The company should pay more attention on status labeling of various equipment and areas, e.g. flow sensor of PW system, part valves of AHU system.

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

3.4 PROCESS EQUIPMENT

The workshop one has more than 40 reactors which are mainly made of stainless (SSR) and glass-lined (GLR) reactors. The equipment was mainly included SS and GL reactors, SS centrifuge, filters, tray dryer, rotary cone vacuum dryer/blender and milling machine. Most of the reactors inspected were provided with adequate charging and fume extraction facilities. The equipment qualification documentation reviewed was not detailed enough to provide confidence in its adequacy. For more detail, refer to section on validation. Validated cleaning procedures were in place and it was found to be adequate. For more detail, refer to section on validation.

An adequate preventive maintenance system for process equipment was in place which was sighted and found to be satisfactory.

The preventative maintenance schedules were viewed which gave daily, monthly, half-yearly and yearly activities. Preventive maintenance schedules for the HVAC were viewed and
found to be acceptable. All environmental parameters are monitored manually as there is no computer system for monitoring.

The calibration certificates for the particle counter, manometer pressure gauges, thermos-hydro meter and lux meter were viewed.

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

In general, there was a system of documentation covering all relevant areas however, their control and review should be improved. The design of log books were loose pages but numbered. It was claimed that SOPs were reviewed after two years, since no update was required hence dates were not changed. But the review action was recorded in separate loose numbered pages.

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

There was a system for evaluating and approving suppliers of starting materials and an approved vendor list was in place but was not reviewed. Materials were sampled and tested on receipt before being approved for use.

The materials were generally stored adequately in rented warehouses. These warehouses were not equipped with air handling units, instead split air conditioners and portable dehumidifiers were used in all of the store areas. More comprehensive mapping studies are needed to justify air handling and sensor locations.

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

3.7 PRODUCTION AND IN-PROCESS CONTROLS

Piperaquine Phosphate (PQP) was manufactured in three steps. Piperazine hexahydrate was condensed with 4, 7 dichloroquinoline to produce intermediate one (IM-I) which was isolated and tested. The IM-I was reacted with 1-bromo-3-chloropropane to produce Piperaquine intermediate two (IM-II) which is reacted with phosphoric acid to produce PQP.

Critical process parameters (CPPs) and in-process controls (IPCs) were defined as sighted from the review of PQR. It is important that the company should learn from the review of PQR and improve the manufacturing process to have consistency in CPPs and IPCs.
Throughout the batches produced in a year. For more detail, refer to section on quality management.

The commercial batch size of PQP is around 120kg and batches were routinely blended to produce a bigger commercial batch. The blending process validation of PQP was performed and details are provided under validation section.

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

3.8 PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

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

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.

3.9 STORAGE AND DISTRIBUTION

The rented warehouses were inspected and some of the issues noted under section on observations.

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 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 IR, HPLC, GC, UV spectrophotometers and Malvern particle sizer. The lab was scattered over few floors (a) seventh floor (b) sixth floor and (c) fourth floor as various activities were carried out in different floors.

There were some issues noted in the microbiology laboratory. These should be addressed if any new or facility alterations are envisaged.

Out of specification (OOS) procedure described investigation procedure occurred in the laboratory and to confirm validity of OOS. The procedure applicable to microbiological, physical chemical testing of raw materials, intermediates, finished products, stability samples, water samples, cleaning validation samples, and a separate procedure is available on OOT. It was however noted that a common procedure was available with common flow chart without
providing any detail for investigation of microbiology failure before repetition performed. It is to be noted that a detailed investigation would be required before repeating any microbiology tests.

The procedure on Agilent OpenLab Data Store provided hierarchical authority management of the Agilent OpenLab data Store. The procedure was supported with annex which provided description of the privileges.

Electronic data of PQP batches was reviewed which revealed that adequate attention should be given to ensure data integrity. This was evident from the privileges given to chemists & analysts, use of manual integration but reviewed by manager, audit trail of generic projects was not enabled although it isn’t used ever etc. For more detail, refer section on observations.

It was noted that there was no primary reference standard and impurities available for PQP. The characterization of PQP through IR, UV, NMR, Mass Spectra, Elemental Analysis, ICS, TGA, DSC, and XRD was performed by an outside laboratory.

It was noted appropriate controls are required with immediate effect to ensure data generated from the testing of raw materials, intermediates and finished API are reliable.

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 validation management procedure was available which described process, cleaning, and analytical methodology. The procedure did not state revalidation frequency as there was a separate procedure titled “Process Validation Management Procedure”. This procedure stated that processes will be revalidated every three years including any change based on change control procedure.

Process validation protocol for PQP and Process validation report for PQP were reviewed and noted that three batches of PQP were taken after incorporating new centrifuge. For more details, refer to the section on observations.

Validation and qualification documentation for the HVAC should be improved. Logical sequential activities from one stage to the next should be improved. There was insufficient cross reference between documents to provide confidence that the required parameters were met.

Blending process validation protocol of PQP was available. It was noted that three batches were used for blending and same was extended to two more batches (blending time 60 minutes and rotation speed 5rpm/min). In general, this section was found to be acceptable. One batch was put up for stability monitoring. The batch record of blended batch was reviewed and noted that relevant information pertaining to sub-batches and shelf life based on the oldest batch was found to be in order. The finished API label was verified and noted that
this blended batch was sold in China meeting the Chinese Pharmacopoeia specification. WHO-PQT required specific storage condition of below 30°C.

Cleaning validation described general requirements and principles to validate cleaning procedures used to clean equipment for manufacturing of APIs, intermediates and dosage forms. It was noted that risk assessment was carried out before the start of the validation. The procedure in general provided basic requirements before conducting cleaning validation. The procedure also described that cleaning is done through manual, clean out of place (COP) and clean in place (CIP). CIP is applicable for dosage forms but not for the APIs. The samples were collected using rinse sampling, swab sampling and residue limit was defined based on therapeutic dose & no observed effect level (NOEL). The calculation example was presented in the procedure which is common for API and dosage form. The procedure also described revalidation strategy including changes made in existing cleaning validation. In general, the procedure was found to be adequate.

Cleaning validation protocol for PQP was available which identified Higenamine API as worst case among all the APIs based on minimum acceptance of the residue /toxicity. Three consecutive batches of PQP were taken for cleaning validation. The cleaning validation report was available which concluded cleaning validation on three consecutive batches was found to be within limit or below LOQ and hence cleaning validation was concluded as acceptable.

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

3.12 CHANGE CONTROL (CC)

There was no major made in change control procedure from the last WHO inspection. The change controls were raised as noted from the review of PQR of PQP.

This section was not evaluated in depth during this inspection.

3.13 REJECTION AND RE-USE OF MATERIALS

Reprocessing and rework procedure for APIs and intermediates was available. The procedure described definition of reprocessing and reworking as per WHO GMP for API. The reprocessing and reworking applies to the rejected intermediates and APIs. The batches after reworking will be put up on stability to ensure quality is equivalent. The expired batches will be reprocessed and reworked to obtain fresh shelf-life or retest. The procedure stated that stability testing will be performed on reprocessed and reworked batches.

The logbook for reprocessing and reworking was maintained and noted that two products were reprocessed.

There was no reprocessing performed in 2015. It was also noted that there was no reworking performed in 2014 and 2015 for any products.
Blending procedure for intermediates and APIs was reviewed. The procedure stated that blending will be done for compliant batches with same specification to have batch size around 300kg or 500kg. The final blend batch has to be tested and put up for stability studies. The procedure stated that all the batches used for blending should be traceable, and blending process for every product will be validated. The specific blending process using blender is defined in the respective report. The shelf life or retest will be set based on the oldest batch used in blending.

In general, this section was found to be satisfactory with the information available and traceable.

3.14 COMPLAINTS AND RECALLS

There was no major change made in the complaints and recall procedure since the last inspection. For more details, refer section on quality management.

3.15 CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

This was not evaluated during this inspection.

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:

- **Piperaquine Phosphate (APIMF176)**

  manufactured at **Zhuhai Rundu Pharmaceutical Co Ltd, 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.