20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**Reyoung Pharmaceutical Co., Ltd**
Corporate address of manufacturer	No.1 Ruiyang Road, Yiyuan County Shandong 256100 P.R. China
Inspected site	
Name & address of inspected manufacturing site if different from that given above	N/A
GPS Coordinates	118° 10′ 41″ E, 36° 10′ 31″ N
Unit / block / workshop number	Plant B, Building B2, Workshop 316
Inspection details	
Dates of inspection	18-20 & 23-24 October 2023
Type of inspection	Initial GMP Inspection
Introduction	
Brief description of the manufacturing activities	Workshop 316 is found on the ground floor of Building B2 in Plant. The automated warehouse is located in Building B3 along with other storage facilities while the QC department is found in Building B4. Plant B is licensed to manufacture solid dosage forms (tablets and capsules).
General information about the company and site	Reyoung Pharmaceutical Co., Ltd (hereinafter referred to as Reyoung), was founded in 1966. In January 1998 the company changed its name to Shandong Reyoung Pharmaceutical Co., Ltd. In June 2008, the Chinese name was further changed to "Ruiyang Zhiyao Youxian Gongsi", and in August 2020, the name was further amended to "Ruiyang Zhiyao Gufen Youxian Gongsi". Reyoung covers an area of 1,200,000m^2 with a construction area of 420,000m^2 and three registered addresses: - No. 1, Ruiyang Road, Yiyuan County, Shandong Province, - No. 219, Jingshan Road, Yiyuan County, Shandong Province, and - No. 288, Jingshan Road, Yiyuan County, Shandong Province. Reyoung has 3 manufacturing units dedicated to API, Oral Solid

	Preparations and Small Volume Injections (OSP & SVI) and Powder for Injection (PFI) respectively. Plant B is located on No. 1, Ruiyang Road, Yiyuan County, Shandong Province, and belongs to the OSP & SVI unit.
History	This was the first inspection of the FPP workshop 316
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	Documents reviewed included but were not limited to: • Quality Manual – management review meetings • Organization Chart • Job descriptions for key personnel • Personnel training and hygiene • Product Quality Review • Quality Risk Management • Complaints and Recalls • Deviation handling and CAPA • Change control • OOS and OOT investigations • Material release • Vendor qualification • Validation and qualification • Equipment calibration • Data integrity • Sampling and testing of materials • Batch processing records • Materials management system • Analytical methods – stability • HVAC system • PW system Areas visited: • Raw materials, packaging materials and FPP warehouses • Sampling and dispensing areas • Tablet manufacturing operations • QC laboratories
Restrictions	N/A
Out of scope	FPPs not submitted to WHO Prequalification were not included in the scope of this inspection
WHO products covered by the inspection	Sulfamethoxazole / Trimethoprim tab 400/80 mg/tab Sulfamethoxazole / Trimethoprim tab 800/160mg/tab
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate

API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation
BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
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
GPT	Growth promotion test
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
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
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
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments (where applicable)**

1. Pharmaceutical quality system

A documented system for quality assurance was established based on GMP. The principles of the system including but not limited to, QRM, Change control, Key personnel, CAPA, Supplier qualification, Service provider qualification, Complaints, Pharmacovigilance, Recalls/returns, APQR, Self-inspection, Technology transfer, Batch Release, and Material management, were described in the Quality Manual. There were procedures in place covering key quality elements.

Quality Management Review

Management review was described in the QM, and a written procedure was in place. Management review meetings were held annually. All department Heads and Managers as well as the President of the company, had to participate in the meeting. The minutes of the 2023 meeting were reviewed. Quality policy, supplier qualification, effectiveness of the documentation, storage of the products, cleaning activities, completion of the production plan, qualification/validation activities, OOS, changes, CAPA, deviations, rejected/reprocessed batches, PW, HVAC, APQR, adverse reactions, feedback from the clients, complaints, recall system, audits, QRM, contract manufacturing, sales of the products, resources, follow-up of any issues from the previous QMR and recommendations were among the topics that were discussed.

Quality Risk Management

QRM was incorporated in the company's PQS. A procedure was in place and included and referred to the ICH Q9 principles. QRM was applicable to all GMP related aspects onsite (e.g., facilities, equipment, utilities, supplier qualification, deviations, OOS, changes, manufacturing processes etc.). Risk assessment tools were defined and their application in a particular GMP area was detailed (e.g., for OOS investigations FMEA, 5WHY and Ishikawa diagram were used). Instructions on the use of each tool were defined in the SOP. Examples of risk assessments related to the introduction of new products and of the relevant manufacturing process were reviewed.

Product Quality Review

PQRs were conducted based on a written procedure. The QA department was responsible for establishing the APQR plan at the beginning of each year. In case of no production, a review of stability, complaints, and deviations was performed. The PQR had to be completed within 2 months from the target date. The

PQR plan for 2023 was reviewed. There was provision to perform trend analysis for the different parameters based on a written SOP.
The 2022 PQR of Sulfamethoxazole/Trimethoprim 800/160 mg/tab was reviewed. No batch was manufactured in 2022. The PQR included a review of the qualification of suppliers, quality agreements, OOS (no OOS results had been recorded), utilities, stability studies, changes, validation, returned products, complaints, CAPA, and self-inspection.
The 2021 PQR of Sulfamethoxazole/Trimethoprim 400/80 mg/tab was also reviewed. 6 batches were manufactured.

Change control

The change control procedure provided guidance on the management and implementation of changes. It was applicable to all GMP related areas except the issuance and revision of SOPs, which was governed by a different procedure. A change request could be initiated by any employee of a department and had to be endorsed by the department head before being registered by the QA department. QA would assign a team to perform the risk/impact assessment. Following the risk assessment, the change request would be classified, accepted, or rejected. A plan for implementation would follow a positive risk assessment, and the QA department would be responsible for monitoring the implementation. In case of foreseen delays, a justification would have to be provided, and the new proposed date would have to be approved by the Quality Head. The effectiveness check for minor changes took place one week after implementation, while for major or critical changes, effectiveness was evaluated after production of 3 product batches regardless of whether the change was directly related to the product or the manufacturing process. Change controls were registered by department and the 2022 and 2023 logbooks per department were made available. One change was recorded for the laboratory in 2022. A New PW system user point was added, and this change was discussed in detail.
The production department had registered 9 changes in 2022. Examples of change control in production were checked.

Deviations

The procedure on Deviation Management was made available. The deviations were classified as critical, major, or minor depending on their impact on product quality and GMP. The Head of the Department was notified of the deviation. The QA department was responsible for assembling a team to investigate the deviation. Investigations were initiated immediately. Each department had a dedicated logbook for recording deviations following the same format. Examples of deviation handling were reviewed.
A deviation review was performed every 3 months. The most recent review for the period January to September 2023 was checked. 8 deviations were recorded. The 2022 annual deviation review was spot-checked. 10 minor deviations were recorded.

CAPAs

The CAPAs were handled according to a written procedure. The QA department was responsible for recording and monitoring CAPA records. CAPAs were codified as YYXXSS where YY stands for year, XX for the department and SS was a serial number. The logbook for recording CAPAs for 2023 was presented, and the following examples of CAPAs were reviewed.

Batch Release

Batch release was performed according to a written procedure. The production department had to review the relevant BMR and the QC department had to review the analytical record for the batch. The QA

department had to review the BMR and analytical record, verifying among others, the following parameters: marketing authorization, qualifications/validations carried out and approved, key process parameters met requirements, test results met specifications, materials were from approved suppliers, audit trail, analytical results were reliable, changes had been closed out and communicated to the authorities, BMR was completed contemporaneously, entries were reliable, storage conditions were met, OOS, OOT, deviations were dealt with. A separate checklist had to be completed by each department. The authorized person for batch release would review the production checklist, the QC checklist, the QA checklist, and the original deviations, OOS/OOT, change records, where applicable, before approving the release. The QC department was responsible for drafting and approving the CoA (3 levels - issuer, reviewer, approver) which was prepared and signed off before release.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection.

2. Good manufacturing practices for pharmaceutical products

Good manufacturing practices were generally implemented. Manufacturing processes were clearly defined in SOPs and systematically reviewed. Necessary human and physical resources with adequate premises, equipment and utilities were provided for the current manufacturing activities. Qualifications/ validations, calibrations and maintenance were performed according to prepared protocols and followed the relevant established procedures. The manufacturing processes followed procedures as defined and documented in the BMRs and BPRs. The personnel were appropriately qualified, and their responsibilities adequately defined.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

3. Sanitation and hygiene

Premises and equipment were generally maintained at an acceptable level of cleanliness, and they were appropriately labelled, and records were maintained. Procedures for gowning and hygienic behavior in production areas were available. There was appropriate gowning in all areas for staff and visitors, including pictorials and hand washing and sanitization before entry to production areas.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

4. Qualification and validation

Validations and qualifications were performed according to the site policy and documented procedures. Necessary resources in production were provided, including qualified and trained personnel, adequate premises, equipment and services, appropriate materials, approved procedures and instructions, laboratories and equipment for in-process and other controls. There was a procedure in place for establishing the annual VMP which took place at the end of the year for the following year. The 2023 VMP was presented. A list of the facilities, equipment, utilities, processes, and systems planned to be validated during the year, was part of the VMP. Target and completion dates were monitored and recorded. In case of postponement or delay the target date could be amended based on justification. An example of requalification postponement was reviewed.

Bottle filling line

The qualification of the bottle filling line was reviewed. The strategy for qualifying the line was not defined. URS included the specifications for the line while DQ, IQ, OQ were performed individually for each station of the line (i.e., bottle cleaning, desiccant feeding station, tablet counting, weight checking station, capping, induction sealing, 2nd capping, labelling) and PQ was performed for the whole line.

Compression machine

A risk assessment was carried out to identify the devices and parameters to be qualified on the compression machine. Among the parameters that were verified were access levels, login details, access privileges, memory capacity of the PLC, minimum and maximum speed, dedusting power, compression force. The requalification report was presented.

PW System (QC and R&D)

Qualification of the extension of PW loop (7 new user points) was conducted during 19.02.2022-24.03.2023. The extension of the loop was designed, constructed, and qualified by Shijiazhuang Honour Pharmaceutical Equipment Co. Ltd and approved by Reyoung. URS, DQ and IQ documentation was available. The loop P&ID and points of welding, the welding certificate and the qualification of the person performing welding were presented. During the performance qualification sampling and testing for Appearance, TOC, conductivity, and microbial growth were conducted daily for all user points for 30 days. Other tests such as pH, nitrates, heavy metals, ammonia, volatile solvents were conducted daily on 3 user points considered as critical.

Process Validation

The PV protocol and report of Sulfamethoxazole/Trimethoprim 800/160mg tabs was reviewed. Three consecutive batches (211106, 09, and 12) of 150000 tablets were manufactured and assessed. A risk assessment was carried out to identify critical process parameters for each of the manufacturing steps (dispensing/sieving, granulation, compression, bottle filling, labelling/outer packaging) and determine critical quality attributes to be monitored during validation.

Computerized Systems

There was a procedure in place describing the validation of computerized systems. Spot-checks were made on the original validation of warehouse management system.

Cleaning validation

The procedure for cleaning validation was reviewed. The worst-case product was determined based on toxicity, solubility, assay, cleanability, and potential hazards. Cleaning validation was performed every 5 years in case of no changes. Cleaning verification was carried out every year. The last cleaning validation for the production line was reviewed. The initial PDE had been determined by the Head of R&D based on literature. Later, PDE was determined by a service provider. A comparison study was performed for the PDE results determined by the company and the service provider. The results were comparable. Cleaning verification was performed in 09.2023 and was reviewed.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection.

5. Complaints

The procedure for handling complaints was reviewed. The Customer service department received the complaint. In collaboration with the QA department, complaints were classified as quality related, medical, falsified product or other complaints. The quality related and falsified product complaints were managed by the QA department and handled according to the quality complaints handling procedure. Complaints were classified into 5 categories according to their severity, namely class I, II, III, IV, and V. There was provision for a trend analysis to be performed every 3 months and then annually. No complaints for the last 3 years had been recorded.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

6. Product recalls

The SOP on Product recall adequately described the actions for recalling a product, conducting the necessary investigations, and evaluating the effectiveness of the process. Recalls were categorized into three classes: Class I, Class II, or Class III according to patient impact and urgency. The assessment team consisting of the Quality Manager, the Sales Manager, and the QP, made a decision about whether a recall was needed. In case of exported products, the relevant Regulatory Authority would be informed. The recalled products were stored in a dedicated area of the warehouse and were appropriately marked. The procedure for mock recall was reviewed. A mock recall was performed annually. The most recent mock recall was reviewed. A reconciliation of the quantities was performed. and the mock recall effectiveness was assessed.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

7. Contract production, analysis and other activities

There was no contract production or testing in place for Sulfamethoxazole / Trimethoprim tab

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

Qualification of suppliers was performed according to the procedure SMP-01-008 (V.08, effective date 01.03.2022). Vendors were classified according to the importance of the material they supplied. Three categories were defined: category A (i.e., APIs, primary packaging materials), category B (i.e., excipients) and category C (i.e., secondary packaging materials). An annual quality assessment of all material suppliers was performed. For suppliers in categories A and B, an on-site audit had to be performed every 3 and 5 years, respectively. The disqualification of a supplier was handled through the Change Control procedure. The 2022 and 2023 on-site audit plans (SOR-SMP-01-008-02) and the verification of the on-site audits (SOR-SMP-01-008-01, V.03, 01.03.2022) were reviewed.
The list of approved suppliers for Sulfamethoxazole/Trimethoprim, the qualification documentation of the API suppliers, including the on-site audit, as well as the qualification of the supplier of bottles and caps, including the on-site audits were reviewed.

Any observations related to this section have been adequately addressed and the implementation of CAPA will be verified at the next inspection

9. Personnel

There was an adequate number of personnel suitably qualified by education and training to perform and supervise the manufacture of FPPs. The personnel met during the inspection appeared to be knowledgeable about GMP. Organization charts reflecting administrative and operational hierarchy were in place. The overall company organogram and the quality unit organogram were presented. Key personnel responsibilities were defined in job descriptions. The job description of the authorized/qualified person to perform batch release in Plant B was reviewed. There were 3 more authorized/qualified persons performing batch release in Reyoung. According to the batch release SOP the batch release responsibilities could only be delegated to another authorized/qualified person. Additionally, the job descriptions of the QA manager and QC Manager were reviewed.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

10. Training

There was a procedure in place for training of personnel. The SOP included the principles for conducting induction training of newly recruited personnel and providing continuous and repeated training to existing personnel. Induction training was further elaborated in a separate SOP, and it was divided into three stages (general GMP and company culture training, area specific training and job specific training). Written and practical examinations were carried out to qualify newly recruited personnel. Routine/continuous training was divided into two levels: basic training (refreshment GMP training) and specific training (focused training according to needs). The annual training plan was prepared at the end of the previous year for the following year. The 2023 training plan was reviewed. Records of basic training were reviewed. Trainers had to be qualified and their qualification criteria were defined in the training SOP. A list of qualified trainers was available. Examples of trainers' qualifications and relevant documentation were reviewed.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

11. Personal hygiene

The personal hygiene at the facility was considered appropriate regarding the manufacturing and packaging operations carried out, and in line with the GMP guidelines. There were procedures in place adequately defining the concepts of occupational health and hygiene. Personnel were medically examined before being employed and periodically thereafter, according to a written procedure. No contract or short-term personnel were employed. Every year, a plan for personnel medical examinations was established by each department, compiled by the environmental protection department, and approved by the QA department. The 2023 medical examination plan was presented. Personnel suffering from illness were required to report to their supervisors and were excluded from working in the production areas.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

12. Premises

Layouts of the facilities were made available. Personnel and material flow charts were presented, except for the warehouse. In general, premises were constructed, designed, and maintained to suit the operations

to be carried out and prevent the risk of contamination of materials and products. At large, the design of the premises was such as to minimize the risk of errors and permit effective cleaning and maintenance. The high bay warehouse was separated in two major sections according to temperature, namely: 10-30°C and 8-20°C (RH <85%). In the high bay API, excipients and packaging material were stored. Additionally, the warehouse had 4 floors. On the 1st floor, receipt of materials took place, and the sampling room was located. On the 2nd floor there were administration offices. On the 3rd floor finished products (2 rooms, 10-30°C) were stored, and there were 3 rooms for return goods (10-30°C, 20-25°C, 8-20°C), 1 room for rejected material, and 1 room for ID testing. On the 4th floor the HVAC system was installed and there were a room dedicated to storage of controlled substances, a room for working garments, and a room for storing empty hard-shell capsules.
Workshop 316 was located on the ground floor of building 2 (3 floors). The workshop was divided in the production area and the utilities area (HVAC, compressed, PW system supplying to workshops 316, 311, 318, power station, spare equipment/utensil storage). There were different entries for personnel and materials including appropriate airlocks. Personnel entered and exited the facilities through the same rooms. Finished products after secondary packaging, which was conducted in an unclassified area, were automatically transferred to the warehouse.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

13. Equipment

In general, equipment was installed and adequately maintained to suit the requirements for the dosage forms manufactured. Production equipment was of good standard and appeared to be well maintained. The workflow in the facility was appropriately designed, and the equipment appeared to be installed to facilitate production and reduce the risk of contamination and mix ups. All production equipment reviewed was identified as to its content or cleanliness status by appropriate labels. The main types of production equipment used in the manufacture of Sulfamethoxazole / Trimethoprim tab included a mill, a high-speed mixer/granulator, an FBD, a mixer, a compression machine (equipped with a metal detector and deduster), and a bottle filling line.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

14. Materials

Raw materials and packaging were stored in an automated high-bay warehouse, which also included storage areas that required manual handling (3rd and 4th floor). Temperature and relative humidity were controlled and monitored, and a dedicated HVAC system was installed. The logbook (SOR-SOP-03-02006-01) of recording filter DP for this HVAC Unit (HVAC031401) was reviewed.
A check list was used for material receipt and included, among others, checks on the CoA, the status of the supplier, the batch number, the quantity received, and the label details. The check list for the receipt of Berberine Hydrochloride batch:M2310070176 was reviewed.
The Warehouse Management System was used to manage materials and finished product inventory and status.
There was a sampling area in the warehouse, with 2 sampling booths. One booth was used for sampling raw materials and the other one for sampling packaging materials. The area included separate personnel

and material airlocks. The usage logbook of the sampling booth for raw materials was reviewed. Pressure differentials were monitored between different grade rooms.
Identity testing was performed on each container of raw material by Near-Infrared spectroscopy. The NIR device was stored on the third floor, and the procedure for usage was reviewed.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

15. Documentation

A documentation system was in place including procedures for the creation, issuance, review, approval, and withdrawal of quality documents. A procedure for issuing logbooks was also in place. The different levels of the documentation hierarchy were adequately defined.
The documentation system was divided into 4 levels:
1st level - QM, SMF, Department responsibilities.
2nd level - SMP, process description, quality specifications, roles responsibilities.
3rd level - SOPs.
4th level - records, protocols etc.
For logbooks and supporting records, a control number was given by the document controller, which was recorded on the logbook for monitoring the distribution of the serial numbers and was stamped on each record. The control number was codified as XXYYUUVV where XX stands for the year, YY for the month, UU for the department and VV was a serial number.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

16. Good practices in production

In general, there were procedures in place providing appropriate instructions for the activities, operations, and processes taking place in the manufacturing areas. Manufacturing and packaging batch records were maintained and completed contemporaneously.
The materials were transferred automatically from the warehouse to the material receiving area before entering the clean area. A barcode reader was in place to scan the received materials. The incoming materials were registered and temporarily stored in the staging area. The logbook for recording temperature and humidity of the area was presented. A balance was in place to verify the weight of the incoming materials.
The dispensing area was equipped with one dispensing booth and 2 balances. A material was first transferred to the sieving room, if necessary, and then to the dispensing area. The logbook for the usage and cleaning of the mill was reviewed. Dedicated flexible hoses were used for each material, where appropriate. The logbook for the usage of flexible hoses was checked.
Manufacture of Sulfamethoxazole / Trimethoprim tabs included the following major steps: dispensing the APIs and excipients according to the BMR, wet granulation, drying, lubrication, checking the granules, compression, bottle filling, and final packaging.
The FBD filter bags were stored in a dedicated area. A logbook for usage was in place.
There was a dedicated area for the storage of clean bins. The SOP for cleaning was reviewed.
The bottle filling line consisted of several stations including the bottle feeding and cleaning station (vacuum), the desiccant dispensing station, an automatic weighing station, the tablet filling station (two

dispensing nozzles -16 channels), a second bottle weighing station, and finally a linear capping and induction sealing station. Secondary packaging was carried out in an unclassified area.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

17. Good practices in quality control

The Quality Control laboratories were separated from the production areas and tasked with the physical, chemical, instrumental, and microbiological analysis of starting and packaging materials, intermediates, and finished products. The laboratories included the sample receipt area, the GC room, the HPLC room, the documentation control room, the instrumentation room, the stability chamber room, the packaging material testing room, and the microbiological monitoring area. The QC laboratory was appropriately organized and equipped.

A sample receipt and distribution procedure and registers were available. The logbook for registering finished products was checked. During the receipt, different parameters such as quantity of sample, integrity of package, and batch number were checked. The logbook included among others the quantity allocated and used for the different tests and a reconciliation at the end of the batch analysis. The required quantity for each analysis was defined in a written procedure. The allocation of the analytical work and sample were decided by the lab supervisor. The sample allocation logbook for GC/HPLC was checked. There was a procedure in place defining the timeframe for completing a test.

There was a separate retained sample room (T:20-25ºC and RH:35-65%). Retained samples were withdrawn and handled according to the procedure SOP-02-010153 (V.02, effective date 01.09.2023).

Stability studies

There was a dedicated area where 7 stability chambers were installed. 3 chambers were in use and 4 chambers were used as back up. Logbooks for each product/batch were maintained indicating the batch number, strength, stability conditions, date, chamber, and location in the chamber. A second logbook was available for managing the quantities per product/batch placed in stability studies. A procedure was in place, providing the necessary instructions for conducting stability studies. Stability conditions for each chamber were monitored via a software. The stability protocol of Co-Trimoxazole was reviewed in detail.

OOS/OOT results

The procedures for handling OOS and handling of OOT were reviewed and discussed in detail. The QC analyst was responsible for registering the OOS in the relative logbook. An OOS review was performed quarterly and then annually. The 2022 OOS trend analysis was presented. In 2022, five OOS were reported. The OOS trend analysis from January to September 2023 was also reviewed. During that period, three OOS were reported. Examples of OOS handling were reviewed.

Any observations related to this section have been adequately addressed, and the implementation of CAPA will be verified at the next inspection.

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, **Reyoung Pharmaceutical Co., Ltd**,located at **No.1 Ruiyang Road, Yiyuan County Shandong 256100, P.R. China** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

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 WHO Guidelines referenced in the inspection report**

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.
   Short name: WHO TRS No. 986, Annex 2
   https://www.who.int/publications/m/item/trs986-annex2

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.
   Short name: WHO TRS No. 957, Annex 2
   https://www.who.int/publications/m/item/annex-2-trs-957

3. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9.
   Short name: WHO TRS 1010, Annex 9
   https://www.who.int/publications/m/item/trs1010-annex9

4. WHO Good Manufacturing Practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fifth Report. Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 3.
   Short name: WHO TRS No. 1033, Annex 3
   https://www.who.int/publications/m/item/annex-3-trs-1033

5. 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
   https://www.who.int/publications/m/item/annex-4-trs-929

6. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 4.
   Short name: WHO TRS No. 1052, Annex 4
   https://www.who.int/publications/i/item/9789240091030

7. 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 3.
   Short name: WHO TRS No. 957, Annex 3
   https://www.who.int/publications/m/item/trs957-annex3

8. 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 TRS No. 1010, Annex 8
   https://www.who.int/publications/m/item/Annex-8-trs-1010

9. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1019), Annex 2.
   Short name: WHO TRS No. 1019, Annex 2
   https://www.who.int/publications/m/item/trs1019-annex2

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 4
    https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1044-annex4-technology-transfer-in-pharmaceutical-manufacturing.pdf

11. WHO good manufacturing practices for sterile pharmaceutical products. Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2022 (WHO Technical Report Series, No. 1044), Annex 4.
    Short name: WHO TRS No. 1044, Annex 2
    https://www.who.int/publications/m/item/trs1044-annex2

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***

https://www.who.int/publications/m/item/trs943-annex3

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
https://www.who.int/publications/m/item/trs961-annex2

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
https://www.who.int/publications/m/item/trs981-annex2

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
https://www.who.int/publications/m/item/annex-3-trs-981

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
https://www.who.int/publications/m/item/tr961-annex14

17. Good Manufacturing Practices: Guidelines on validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Third Report Geneva, World Health Organization, 2019 (WHO Technical Report Series, No. 1019), Annex 3.
Short name: WHO TRS No. 1019, Annex 3
https://www.who.int/publications/m/item/trs1019-annex3

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
https://www.who.int/publications/m/item/trs992-annex4

19. 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
https://www.who.int/publications/m/item/trs961-annex9-modelguidanceforstoragetransport

20. 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
https://www.who.int/publications/m/item/trs992-annex5

21. WHO Recommendations for quality requirements when plant – derived artemisinin 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
https://www.who.int/publications/m/item/trs-992-annex-6

22. Guideline on data integrity. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 4.
Short name: WHO TRS No. 1033, Annex 4
https://www.who.int/publications/m/item/annex-4-trs-1033

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.
Short name: WHO TRS No. 996, Annex 10
https://www.who.int/publications/m/item/trs966-annex10
24. Stability testing of active pharmaceutical ingredients and finished 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 10. ***Short name: WHO TRS No. 1010, Annex 10***
https://www.who.int/publications/m/item/trs1010-annex10

25. Points to consider when including Health-Based Exposure Limits in cleaning validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fifth Report Geneva, World Health Organization, 2021 (WHO Technical Report Series, No. 1033), Annex 2.
Short name: WHO TRS No. 1033, Annex 2
https://www.who.int/publications/m/item/annex-2-trs-1033

26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.
Short name: WHO TRS No. 1025, Annex 6
https://www.who.int/publications/m/item/trs-1025-annex-6

27. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.
Short name: WHO TRS No. 1025, Annex 3
https://www.who.int/publications/m/item/trs-1025-annex-3-water-for-injection

27. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-Fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.
Short name: WHO TRS No. 1025, Annex 4
https://www.who.int/publications/m/item/trs1025-annex4

28. Good trade and distribution practices for pharmaceutical starting materials. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 6.
Short name: WHO TRS No. 996, Annex 6
https://www.who.int/publications/m/item/annex-6-trs-996

29. WHO guidelines for preparing a laboratory information file. *WHO Expert Committee on Specifications for Pharmaceutical Preparations.* Forty-Fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 13.
Short name: WHO TRS No. 961, Annex 13
https://www.who.int/publications/m/item/trs961-annex13

30. WHO good manufacturing practices for excipients used in pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-seventh Report. Geneva, World Health Organization, 2024 (WHO Technical Report Series, No. 1052), Annex 1.
Short name: WHO TRS No. 1052, Annex 1
https://www.who.int/publications/i/item/9789240091030