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

Part 1	**General information**
Manufacturers details	
Name of manufacturer	**KBN-Zhejiang Pharmaceutical Co., Ltd.**
Corporate address of the manufacturer	KBN-Zhejiang Pharmaceutical Co., Ltd. No. 340 Yunhai Road, Jiaxing, Zhejiang, China
Inspected site	
Name & address of inspected manufacturing site if different from that given above	KBN-Zhejiang Pharmaceutical Co., Ltd. No. 340 Yunhai Road, Jiaxing, Zhejiang, China GPS details: 30.79403 (N), 120.73505 (E)
Unit/block/ workshop number	Building 1 (oral solid dosage form workshop and warehouse) Building 6 (quality control laboratory)
Inspection details	
Dates of inspection	10-14 July 2023
Type of inspection	Routine GMP inspection
Introduction	
Brief description of the manufacturing activities	KBN-ZJ Pharmaceutical Co., Ltd. (KBN-ZJ) was established in 1969 (Name at that time: Jiaxing Nanhu Pharmaceutical Factory). It is located in Jiaxing City, Zhejiang Province. KBN-ZJ is a member of KPC group. It is the manufacturing site for the finished products of the KPC Artemisinin Supply Chain. The site manufactures dosage forms including tablets, hard capsules, dry suspensions, and oral solutions.
General information about the company and site	KBN-ZJ is a pharmaceutical products manufacturer with integration of research & development, production, testing, storage, and sales. The manufacturing site is located at No. 340 Yunhai Road, Jiaxing, Zhejiang, China. It spreads across an area of 29,901 m^2, within which the total building construction area is 13,960 m^2.
History	This was the second WHO PQ inspection of KBN-Zhejiang. The first inspection was performed in October 2021.
Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	The following areas were inspected: 1. Pharmaceutical quality system 2. Personnel and training 3. Hygiene and sanitization 4. Equipment and materials 5. Supplier qualification and self-inspection 6. Production and packaging operations

	7. Quality control laboratory 8. Utilities
Restrictions	None
Out of scope	Other than the product Dihydroartemisinin /Piperaquine (as tetraphosphate) 40mg/320mg film-coated tablets submitted for WHO Prequalification, the rest of the products and areas were out of the scope of this inspection.
WHO products covered by the inspection	Dihydroartemisinin /Piperaquine (as tetraphosphate) 40mg/320mg film-coated tablets (DHA/PQP (40/320) tablets)
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 airflow
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

KBN-ZJ had established and implemented a quality management system based on the WHO GMP TRS 986, Annex-2 guideline, and Good Manufacturing Practice (2010 version). The site had a quality unit consisting of QA and QC, which was independent of production. The following quality system elements were covered:

Quality Manual

A comprehensive Quality Manual was responsible for guiding the policy and procedures of the Company in line with the requirements of Chinese Laws, NMPA GMP and WHO GMP main principles and related technical reports and annexes. The Quality Manual included the Quality Policy "Focus on data integrity and providing customers with quality and cGMP compliant products that are safe and efficacious". A detailed list of the site activities covered by the PQS and the full life cycle of products was included, together with a high-level outline of the responsibilities of senior management for the evaluation and reporting of the effectiveness of the system.

Management Review

Quality System Review described the quarterly review of the effectiveness of the PQS by senior management. The SOP stressed the leadership role of the General Manager to provide the necessary support for the QRM process, review the QRM results and support the implementation of CAPA and

continuous improvement actions arising from the process. The list of PQS elements that were required to be reviewed as well as the metrics used was comprehensive for the annual review and abbreviated for the quarterly reviews. The reports were sent to the management team for review and approval before the meeting. The agenda and attendance list for the meeting held in December 2022 together with the detailed reports and presentation pack complied with the SOP and were found to be adequate. The action items arising from the meeting reflected a level of debate amongst the team and were linked to action plans.

Product quality review (PQR)

The PQR SOP was discussed. A yearly plan was prepared by the QA and different departments were informed for the collection of the data. The PQR was required to be completed by March every year. A list of items that should be included in the PQR was provided in the SOP (e.g. implementation of CAPA from the previous year, product release, in-process, critical process parameters, rejected or reprocessed, changed controls, deviations, customer complaints, recalls, OOS/OOT, abnormal events, method validation, stability data, material quality, supplier management, regulatory registration, self-inspection, external inspection, contracted manufacturing or testing, adverse reaction, product risk assessment, process validation, cleaning validation, equipment calibration/maintenance and utilities). Minitab trend analysis tools (3-sigma standard deviation and process capability index) were used for statistical calculation. Criteria for evaluating the CpK were established. The data were analyzed and reviewed by all the departments. The PQR was finally approved by the General Manager based on the QA Manager's final review.

Quality risk management

The QRM procedure applied to the management of risk identification, assessment, control, communication, and review for the entire manufacturing facility which also identified responsibilities for various personnel. The procedure described how risk would be assessed using the RPN approach (FMEA). Based on the probability of occurrence, severity and detection, a risk priority number would be calculated. The procedure described how risk would be communicated and reviewed. It was noted that as part of the quarterly management review meeting, the risks identified would be reviewed. The risk assessment form and report template were included as annexures to the procedure.

Deviation Management

The Deviation Investigation Procedure was evaluated together with the Deviation Investigation and Handling form (Appendix 1) which followed a stepwise process for the establishment of the root cause and the identification of appropriate corrective and preventative actions (CAPA). The procedure also required a formal evaluation of CAPA effectiveness after implementation. Root Cause Analysis provided support to the deviation procedure as it described the tools required for the investigation of root cause i.e., Brainstorming, Fish Bone Diagram and "5 Whys".

Change Control Management

The approval of all planned changes to GMP activities was managed according to the Change Control Procedure. The SOP included the requirement for the Marketing Authorization Holder to be included in the evaluation of the impact of proposed changes and implementation timelines. The paper-based system relied on a Change Control Form which detailed the impacts to be considered and the approval process to be followed. All change controls followed the same stepwise process and were classified into Major, Moderate and Minor according to the listed criteria.

CAPA Management

The CAPA SOP described the process and documentation required to track the initiation and completion of all corrective and preventative actions (CAPA) raised across various decentralized problem evaluation systems including deviations, customer complaints, product recalls, environmental conditions, calibration failures as well as responses to GMP Inspections. Inspection of the CAPA logbook confirmed that all the CAPA items that arose out of deviations as well as all the individual CAPA items generated in response to the previous WHO Inspection were listed in the log and were tracked in terms of their status and close out versus the declared completion dates. This information correlated with the records for the 2022 management review meeting.

Nitrosamine Risk Assessment

A theoretical risk assessment for Nitrosamines in the DHA/PQP product manufactured in the OSD workshop was performed in May 2021 which considered the potential contamination from raw materials, packaging materials, process, equipment, facilities, and water. It concluded that the calculated nitrosamine risk was acceptable. A second experimental-based study which referenced the European Directorate for the Quality of Medicines and Healthcare (EDQM) and the International Agency for Research on Cancer (IARC) was performed in November 2022. In this study, 6 batches of the DHA/PQP tablets were analysed by Gas Chromatography-mass spectroscopy for NDMA, NDEA, NMEA, NDPA, NDBA, NPIP and NMOR all of which reported concentrations <1ng/ml which were below the acceptable exposure limits of <5ng/ml.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

2. Good manufacturing practices for pharmaceutical products

Manufacturing processes were generally adequately defined and systematically reviewed. Qualifications and validations were performed where required and documents were produced when requested. Necessary resources were provided, and records were made during manufacture. Procedures were in place for tracking corrective and preventive actions and their implementation. A system was available to recall any batch or product from the market and quality defects were required to be investigated.

KBN-ZJ was a multi-product manufacturing site. The WHO PQ inspection was limited to oral solid dosage forms which were produced in Building 1. Building 1 was a stand-alone building with two floors and was constructed in 2003. The first floor contained the Oral Liquid Dosage Form Workshop and a general warehouse, and the second floor housed the General Oral Solid Dosage Form Workshop. The General Oral Solid Dosage Form Workshop was dedicated to the manufacturing of tablets. The workshop covered approximately 1120 square meters in total of which 629 square meters were dedicated to Grade D clean areas.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

3. Sanitation and hygiene

The SOP for Cleaning and Disinfection of the Clean area described the daily, weekly, and monthly cleaning and disinfection schedules for the OSD facility. During operational periods, non-product contact surfaces such as walls and floors were cleaned daily and disinfected weekly with one 75% ethanol or 0.1% benzalkonium bromide solution which was rotated monthly. In addition, the entire facility was disinfected with ozone vapor introduced through the HVAC system immediately before the start of manufacturing activities and monthly during inactivity as per SOP. The SOP described the concentration of the agent, the minimum contact time, and the aeration time post-disinfection. Manufacturing equipment was cleaned with potable water, purified water and 75% Ethanol in water according to equipment-specific SOPs. Cleaning certificates which included clean hold time limits were prepared post-cleaning and were attached to the line clearance sections of the batch documentation.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

4. Qualification and validation

The validation master plan was prepared every year. It provided high-level guidance on validation activities including but not limited to equipment qualification, cleaning validation, process validation, computerized system validation, revalidation, and retrospective assessment. The company should include other validation activities such as personnel qualification (analysts' validation, visual inspection operators).

Cleaning validation management procedure

The SOP related to cleaning validation was discussed. An HBEL approach was introduced since the last WHO PQ inspection and evaluation was made between PDE and 10ppm and cleaning validation was re-performed only for the new equipment (e.g. granulator). Based on the assessment of PDE and 10ppm, it was noted that 10ppm criteria were still found to be more stringent than PDE values. For the OSD block, the company purchased three PDE reports (DHA, PQP and Omeprazole) from a service provider and revalidated the cleaning method.

Process validation

The process validation procedure was designed based on three stages namely process design, process qualification and continued process verification. It was noted that for the new products, the three-stage policy applied whereas for existing products, a risk assessment would be performed. The WHO PQ product fell into the Stage II category. Process validation for DHA/PQP (40/320) tablets was performed following the change of granulator and change of blender position. The company had purchased a new granulator.

Computerized system validation

The computerized system validation procedure was discussed. The procedure applied to KBN-Zhejiang computerized systems used for the handling of materials, products, and more. The procedure referenced WHO guidelines, 21 CFR Part 210, 211, EU GMP and other applicable

standards. The list of equipment and instruments along with details related to software were maintained by the different departments. A live document was maintained with the status of the validation identified for 2023. The company followed a risk-based approach and performed revalidation of computerized systems based on direct impact. For the laboratory equipment and instruments, the company also followed the USP chapter and requalified equipment and instruments annually.

Analytical method validation

The Analytical method validation SOP was discussed. Based on the test parameters (e.g., assay, dissolution), analytical methods were validated in terms of accuracy, precision, repeatability, intermediate precision, specificity, LOD, LOQ, linearity, range, and robustness. The acceptance criteria along with relative standard deviation were described in the procedure and the SOP was referenced to USP and CP. The procedure stated that analytical methods would be requalified every 6 years if no changes were made.

HVAC Qualification and Validation (AHU P155)

The previous HVAC system servicing the OSD workshop in Building 1 was significantly modified in 2022 following changes made to the manufacturing rooms and after the installation of a new AHU unit. The qualification and validation records were reviewed.

Qualification of Purified Water

A new purified water system was installed in 2022 which serviced both the OSD section and liquids manufacturing sections of Building #1. The qualification and validation records were reviewed.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

5. Complaints

The SOP for Customer Complaints applied to all products manufactured on the site including contract-manufactured products but excluded pharmacovigilance which was covered by a separate SOP. Quality Assurance was responsible for the management of the complaint process while the Qualified Person was responsible for the final decision and approval of the CAPA actions which was documented in the complaint processing form. The procedure required the involvement of the contract giver for contracted products and contained timelines for the completion of key steps which differed depending on the classification (Levels 1,2 and 0). No complaints were recorded for 2023 with only one complaint recorded in 2022 for physical damage to tablets (not related to DHA/PQP tablets). The investigation was completed per the SOP with final verification by the QP within the stipulated period.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

6. Product recalls

The procedure for product recalls described the process which was managed and approved by the Qualified Person. The involvement of the MA holder Beijing Holley–Cotec Pharmaceuticals Co., Ltd for the DHA/PQP product and the requirement to contact relevant International Regulatory Authorities were stipulated. No recalls had been instituted with the most recent mock recall completed in December 2020 which was within the three years stipulated in the SOP.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

7. Contract production, analysis and other activities

The Quality Agreement for the contract manufacturing of drugs with Holley-Cotec Pharmaceuticals Co., Ltd was evaluated in conjunction with the SOP Management of Contract Manufacturing SOP for the manufacturing of the DHA/PQP product WHO GMP requirements were included in the definition of quality standards. The agreement expanded on the dual responsibilities for the transfer of information, management of deviations and OOS, audit rights, complaints, recalls, ex-factory release and release for sale as well as the requirement for all proposed changes to be managed via change control between the two parties.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

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

Self-Inspection

The requirement for all departments to undergo self-inspection at least once during a calendar year was described in the SOP. The most recent self-inspection of the OSD facility was performed on 2/12/2022 with no observations. CAPA raised during the 2021 self-inspection was entered into the CAPA register on 9/9/2021 following the updated SOP with all actions completed on 30/11/2021, confirming that the commitment made by the Company from the previous WHO Inspection in CAPA were adequately implemented. In addition to the annual inspection, daily inspections were performed as per SOP which required QA to raise CAPA actions where necessary.

Supplier Management

The SOP for Supplier Management included a flow chart and a matrix of requirements for the different material categories i.e., Class A included API that had a high impact on the quality of the product while Class B included excipients, primary packaging, and secondary packaging and printed packaging. On-site audits of the API suppliers for the DHA/PQP product were performed. The audit reports and supportive supplier management records were adequate and confirmed that the commitments made by the Company from the previous WHO Inspection were adequately implemented.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

9. Personnel

The Company structure was recorded in the Procedure for Organizational Chart which complied with the principles of GMP. The Quality Director, who was also a Qualified Person, was supported by a QA Deputy Manager and a QC Manager and reported independently to the General Manager who was a member of the Board of Directors. Similarly, the Production Director was supported by a Manufacturing Manager and reported directly to the General Manager. Pharmacovigilance reported directly to the General Manager while the Regulatory Department responsible for DHA/PQP (40/320) tablets was managed out of the MA holding Company i.e. Beijing Holley-Cotec Pharmaceutical Limited.

The number of employees engaged in quality management, production, quality control, storage, and distribution.

Department	Number of employees			Total number of employees
	Supervisor	Technicians	Non-technical personnel	
Senior management	1	0	0	1
QA	3	8	1	12
QC	4	11	0	15
Production	6	20	29	55
Engineering	4	4	1	9
Warehouse	1	0	5	6
Purchasing	1	0	0	1
Others (Non-GMP)	5	0	20	25
Total	25	43	56	124

The commitments made by the Company from the previous WHO Inspection and the corresponding CAPA were adequately implemented.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

10. Training

Staff training at all levels within the Company was performed according to the SOP for Personnel Training Management and was managed by the Administration and Human Resources Development Department together with the Quality Department. The 2023 Annual training plan for the OSD Production and QC Laboratory included GMP/QA Systems training, SOP training and workplace-specific training for all staff. The training was performed by qualified trainers who were listed in Annex 8 of the annual training plan. The records for attendance, proof of understanding and competence assessment were inspected for 5 staff members at all levels of the Company which were comprehensive and complied with the SOP. The SOP for Personnel entry and exit included a section on the training for visitors and the SOP for Knowledge Management included the requirement to record the qualifications and experience of consultants.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

11. Personal hygiene

A detailed physical examination was performed annually for all staff according to the SOP for Personal Health Management. The SOP included the requirement that staff with infectious conditions and open wounds/skin lesions were not allowed to enter the manufacturing areas. Adequate gowning for a Grade D environment was provided as per the Personnel entry and exit which included schematics and photographs of the change procedure. Copies of these same photographic instructions cross-referenced to the SOP were available in the change areas. The dress code and hand washing requirements were generally well adhered to except for one incident when a staff member from Office 4 in Building #1 did not follow the dress code procedure on exit.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

12. Premises

The overall manufacturing site was divided into 6 buildings namely, integrated building: General warehouse, Oral, liquid dosage workshop, General OSD Workshop, Penicillin Workshop including Penicillin APIs, Administrative Offices, Utility Machinery Building, Ethanol storage, β-lactams Warehouse, QC Lab and QA, Cephalosporin Workshop.

Building 1 had two floors. The first floor contained an oral liquid dosage forms workshop and a general warehouse. The second floor had a general oral solid dosage forms workshop where Duo-Cotecxin Tablets were manufactured.

Building 2 (Penicillin production building) was a stand-alone building under negative pressure relative to ambient, with filtered exhaust air to prevent cross-contamination. The premise, API storage and HVAC system were independent and separated from systems in other production buildings.

Building 6 was a stand-alone building with three floors. The first floor: warehouse for β-lactams. The Second floor: QC Lab and QA. The third floor: oral solid dosage forms workshop for cephalosporin with a dedicated HVAC system under negative pressure with filtered exhaust air.

HVAC

Since the last WHO PQ inspection, the company installed a new AHU. Two air-handling units were supplied to the OSD workshop. The inspection of the first unit revealed the AHU was adequately maintained. The AHU was equipped with G4, F6, cooling/heating/humidity adjuster, F8 and H14. The ozone generator was used as a disinfectant/sanitizer once a month. The primary filters were washed monthly (or if DP exceeded 1.5 times the initial pressure) with potable water in a big wash basin adjacent to the AHU. The company should consider having a separate area for washing and cleaning primary filters.

Purified water system

Since the last WHO PQ inspection, the company installed a new purified water system. In general, the PW system was well maintained and equipped with required unit operations for generation and distribution purposes.

Compressed air

Compressed air for the OSD workshop was supplied from Building 4 and was filtered at the point of use through a 0.22 µm filter. The integrity of the filters was confirmed on a 3-month basis as per SOP and were replaced every 2 years.

Manufacturing workshop

The overall layout and size of the workshop were adequate for a single product manufactured within the area on a campaign basis. The physical infrastructure and finishes of the processing rooms, stores and corridors facilitated cleaning and sanitization. The overall containment design of the area was based on the processing rooms being at a lower pressure (-15Pa) than the service corridor. Airlocks or buffer rooms which were common MALs and PALs were observed between the processing rooms and the corridor in high dust generating areas with the overall pressure differential between the processing room and the corridor remaining at -15Pa. The processing and storage rooms throughout the workshop were fitted with temperature and relative humidity readers as well as pressure differential gauges between adjacent areas of different pressures which relied on twice daily recording of the conditions in a logbook. These stand-alone systems were not integrated with the central control system (limited to 10 rooms) for the early identification of out-of-specification conditions and/or negative trends.

Warehouse

The general warehouse was on the ground floor of Building 1 and was equipped with dedicated areas for goods receipt, cool areas for API (2-20°C), cold rooms for API (2-8°C), quarantine area for API (10-30°C), general storage areas (10-30°C) and a finished goods cool storage area (2-20°C) used for the DHA/PQP product (MA177) - labelled storage condition of <30°C. The warehouse and the upgraded sampling area were found to be adequate except for one observation due to poor lighting.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

13. Equipment

Since the last WHO PQ inspection, the company installed a new high-shear mixer/granulator which consisted of a stainless-steel bowl with PLC control. The capacity of the Granulator was 75 L. The fluid bed dryer was used to dry the granules using cleaned hot air. The cleaned hot air was supplied by a dedicated air handling unit for the fluid bed dyer. The fluid bed dryer system was controlled by a PLC control panel. The capacity of the fluid bed dryer was 60kg per time. The Blender was a multi-directional motion blender. The production capacity was 300kg/ time. The Tablet Press was a rotary tablet press machine with 40 compression stations. It was dedicated to Dihydroartemisinin and piperaquine phosphate tablets, the capacity of the machine was 52,000 tablets/h-150,000 tablets/h. The Hi-Coater was dedicated to Dihydroartemisinin and piperaquine phosphate tablets.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

14. Materials

Incoming starting and packaging materials and outbound finished products for both the OSD and liquids manufacturing workshops were received and stored in the General Warehouse on the ground floor of Building 1. The incoming goods were compared to a hard copy approved suppliers list and dedusted after which they were entered into the SAP system which generated the required labels and indicated the relevant storage conditions. Storage locations per pallet were not identified. Status control was achieved using different colour labels supported by the change in status on the SAP system.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

15. Documentation

The Quality Department had overall responsibility for the control and management of GMP documentation in KBN-ZJ. The documentation system in KBN-ZJ was managed following the SOP "GMP Documentation Management Procedure", which specified the preparation, edition, approval, distribution, archival, and withdrawal of all GMP documents. The formatting and numbering of all quality documents were also defined in this procedure.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

16. Good practices in production

The inspectors visited the 2nd floor of building 1 in the afternoon of day 2 This floor, housed the general oral solid dosage form workshop where both DHA/PQP (40/320) tablets and Omeprazole tablets were manufactured. An adequate gowning procedure was in place before entering the clean rooms. The change room was equipped with a crossover bench and a hand washing/drying facility. From the 2nd change room onwards, the area was classified as Grade D and 75% ethanol was used as a disinfectant with a validity period of one month. The corridor was maintained at a higher pressure relative to the 2nd change room (limit ≤ -6Pa) as well as to the other core processing areas. A significant improvement was noted from the last PQ inspection, in particular, the floor, doors, buffer rooms and interlocking were renovated, and portable dust extractors and vacuum transfer systems were provided. A new granulator for the WHO PQ DHA/PQP product has been installed since the last inspection. It was noted that dry granules were still charged manually to the blender whereas a new enclosed vacuum transfer system was used to transfer the dry granules from the FBD to the resizer/multimill. to reduce the generation of powder. A second resizer/multimill with manual transfer was used for the wet granule after granulation before transfer into the FBD. Based on the design of the OSD workshop, it would not be possible to manufacture more than one product at the same time. The company confirmed that only one product was manufactured across the OSD workshop at any one time on a campaign basis. A new UDAF was installed in the dispensing area. The dies and punches were stored in a locked room. For WHO DHA/PQP, 50 sets of dies/punches were available, which were rotated regularly. A log was maintained to record their usage with a life span of either 3 million tablets or 5 years. In the compression area, a printer was installed with a balance. A 40-station, single rotary machine, equipped with a metal detector, deduster and dust extractor was used to compress WHO DHA/PQP. A printer was installed with the balance used inside the coating area. A camera system was installed in the blister packing line and the same had been qualified and was in use.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

17. Good practices in quality control

The Central Quality Control Laboratory was located on the second floor in Building No. 6 which was a common quality control laboratory for OSD, Oral Liquid Dosage, penicillin and β-lactam products. The samples were received from different workshops and logged into the logbook before they were stored and distributed for analysis. The samples were accompanied by analytical test sheets and before acceptance of the samples for testing, the responsible QC personnel verified the quantities and storage conditions. A common logbook was maintained for samples coming from all four workshops. The logbook and analytical test sheets were issued by the QA. As all samples were stored in the same cabinet, the company should consider ensuring safety aspects and make appropriate provisions, especially for penicillin and β-lactam products. The laboratory was equipped with 7 HPLC and 1 GC all of which were operated using Empower 3. In addition, the laboratory had UV-VIS, FTIR, TOC, AAS, electronic balances and other equipment for raw materials, intermediates and finished pharmaceutical products testing. The company confirmed that all analytical balances were now equipped with printers. In addition, a new Sartorius balance was purchased which complied with current DI requirements.

Out of Specification and Out of Trend Management (OOS)

OOS were managed according to the SOP for Laboratory OOS/OOT Investigation which referred to relevant MHRA Guideline and included a Table which defined the OOT criteria for a range of test results. There was a clear flow chart which reflected a standard three-phase approach to investigations supported by guidance on hypothesis testing and the conditions for retesting of the original samples. Statistical ranges for the interpretation of retest results were included together with time limits for the completion of the various phases of the investigation. The OOS log confirmed that there was only one OOS reported in 2022 with a further 5 reported in 2023. The investigation records were inspected and found to be adequate.

Dissolution apparatus

The laboratory has three dissolution apparatus and they have recently purchased a new one. The analysis performed on this new apparatus was discussed with the analyst who performed the dissolution of DHA/PQP uncoated tablets. The results were calculated using UV-VIS. The audit trail of the UV-VIS was verified and found adequate. The calibration of the dissolution apparatus was performed using Prednisone tablets and Salicylic acid tablets.

HPLC

The DHA assay test for DHA/PQP uncoated tablets was verified on the HPLC number. Similarly, a related substance test for DHA/PQP-coated tablets was verified. The chromatograms were integrated automatically. A guideline on chromatography methods guided manual integration. The procedure stated that the entire sequence would be reintegrated if manual integration was performed. The access privileges to manually integrate peaks were given to the vice QC Manager which were reviewed by the QC manager before final approval from the QA manager.

Calibration

Most of the equipment and instruments were calibrated by the external laboratory, Zhejiang Province Measuring Institute once a year. Upon review of the HPLC calibration report, it was noted that external calibration was not performed following any pharmacopoeia. The in-house verification covered some of the tests as recommended in the pharmacopoeia.

Reference and working standards

The reference and working standards for both DHA and PQP were available. Single-use vials were prepared and used for both standards. The primary reference standard for DHA was stored between 2 and 8C whereas no primary reference standard exists for PQP. The working standard was supplied by the supplier based on the Chinese Pharmacopoeia standard. A logbook was maintained.

Microbiology laboratory

The microbiology laboratory performed testing of water samples (potable and purified), environmental monitoring and microbial limit tests. The microbiology laboratory was adequately equipped and designed with separate MAL and PAL for the MLT rooms as well as for the handling of microorganisms in a biosafety cabinet. Dehydrated media was used for the preparation of the plates for testing. A growth promotion test (GPT) was performed before the media was used. The GPT of Soyabean Casein Digest Agar was verified and found to be adequate. The strains from CMCC were used. There were two autoclaves one each for sterilization of media, and garments and

another one for decontamination purposes. The material flow was not found to be logical in some instances i.e. the autoclave used for decontamination did not allow for the logical movement of material for destruction as the material had to be moved back to the microbiology laboratory. Incubators were available for both bacteria and fungi.

Stability studies

The laboratory was equipped with 6 stability chambers for different T/RH conditions. The stability chambers (40/75% and 30/75%) were used for DHA/PQP (40/320) tablets. A logbook was maintained, and alarms were recorded and investigated. Two lab persons were responsible for receiving messages.

Retention samples

The retention samples were stored in a separate room under the supervision of QA. There were two rooms for retention samples, one was room temperature which was maintained at 2~30℃ and the other was cool and maintained below 20℃. The WHO product was stored in a cool room and the ethanol was stored at room temperature. A quantity sufficient for three full analyses was retained. A batch of DHA/PQP (40/320) tablets finished product was verified.

The deficiencies related to this section have been adequately addressed and will be verified during future PQ inspections.

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, ***KBN-Zhejiang Pharmaceutical Co., Ltd.***, located at ***No. 340 Yunhai Road, Jiaxing, Zhejiang, 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 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

4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4.
   Short name: WHO TRS No. 929, Annex 4
   https://www.who.int/publications/m/item/annex-4-trs-929

5. WHO good practices for pharmaceutical quality control laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1.
   Short name: WHO TRS No. 957, Annex 1
   https://www.who.int/publications/m/item/trs957-annex1

6. 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

7. 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

8. 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

9. 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

10. 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

11. 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

12. 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

13. 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

14. 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

15. 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

16. 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

17. 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

18. 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

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5.
Short name: WHO TRS No. 992, Annex 5
https://www.who.int/publications/m/item/trs992-annex5

20. 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

21. 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

22. 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

23. 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

24. 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

25. 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

26. 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