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**Prequalification Unit Inspection Services**
**WHO PUBLIC INSPECTION REPORT**
**(WHOPIR)**
**Active Pharmaceutical Ingredient Manufacturer**

| **Part 1** | **General information** |
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| **Manufacturers details** | |
| Name of manufacturer | Zhejiang Huahai Pharmaceutical Co., Ltd. |
| Corporate address of manufacturer | Zhejiang Huahai Pharmaceutical Co., Ltd<br>Xunqiao, Linhai, Zhejiang Province 317024,<br>P.R. China. |
| **Inspected site** | |
| Name & Address of inspected manufacturing site if different from that given above | Zhejiang Huahai Pharmaceutical Co., Ltd. (Chuannan site)<br>Address: Chuannan, Costal Industrial Zone, Duqiao, Linhai, Zhejiang, 317016,<br>R.P China. |
| Synthetic Unit /Block/ Workshop | Nirmatrelvir: Workshop W03, Workshop W08, Workshop W18 |
| **Inspection details** | |
| Dates of inspection | 22-25 April 2024 |
| Type of inspection | Routine GMP inspection |
| **Introduction** | |
| Brief description of the manufacturing activities | The Chuannan Site was divided into East Zone and West Zone, consisting of 3 principal areas: i.e., the administration area, the production area, and the storage & utility area. The administration area was in the office building. The production areas were in the northwest part of the East Zone and the northeast part of the West Zone. The East Zone and West Zone had separate storage and utility areas, which consisted of a warehouse, tank area, pump room, hazardous material warehouse, waste gas and a wastewater treatment station. The site manufactured APIs and intermediates, which included ACE inhibitors, SARTANs, Anti-depressants and Anti-Diabetics. No hormones, steroids, beta-lactams or cytotoxins were manufactured onsite.<br><br>The GMP related manufacturing activities included material management (receipt, test, and release), API related manufacturing, test, release, storage and dispatch, and quality management. Material purchasing, product registration affairs and product sale were managed by the headquarters (Zhejiang Huahai Pharmaceutical, Xunqiao.) |
| General information about the company and site | Zhejiang Huahai Pharmaceutical Co., Ltd. was established in January 1989. Currently, the company has expanded and established three separate manufacturing sites:<br>• Zhejiang Huahai Pharmaceutical Co., Ltd (Xunqiao) - Headquarters, API and Finished Drug Product<br>• Zhejiang Huahai Pharmaceutical Co., Ltd (Huanan) – Key Intermediates<br>• Zhejiang Huahai Pharmaceutical Co., Ltd. (Chuannan) (API and Intermediates) of which was established in October 2003 and operations |

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| | started in 2005. The site was in a "national medicine & chemical industrial enclosed area" in the town Duqiao within the city of Linhai. |
| History | This was the fifth WHO PQT inspection. A desk assessment was conducted in 2022. |
| WHO products covered by the inspection | Nirmatrelvir API Non-micronized<br>Nirmatrelvir API Micronized |
| **Brief report of inspection activities undertaken – Scope and limitations** | |
| Areas inspected | • Quality management system<br>• Production blocks<br>• Warehouses<br>• QC laboratories<br>• HVAC system<br>• Water system |
| Restrictions | The scope of the inspection was restricted to the API in the WHO PQ programme. |
| Out of scope | Facilities used for other API production were out of the inspection scope. |
| **Abbreviations** | **Meaning** |
| AHU | Air handling unit |
| ALCOA | Attributable, legible, contemporaneous, original and accurate |
| API | Active pharmaceutical ingredient |
| APR | Annual product review |
| BER | Batch Analysis Record |
| BMR | Batch manufacturing record |
| BPR | Batch production record |
| CC | Change control |
| 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 |
| 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 |
| KF | Karl Fisher |
| LAF | Laminar air flow |
| LIMS | Laboratory information management system |
| MB | Microbiology |
| MBL | Microbiology laboratory |
| MR | Management review |
| NC | Nonconformity |

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|---|---|
| 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 |
| QP | Qualified person |
| QMS | Quality management system |
| QRM | Quality risk management |
| RA | Risk assessment |
| RCA | Root cause analysis |
| RO | Reverse osmosis |
| 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)** |
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## 1 Pharmaceutical Quality management

A system for managing quality was established based on guidelines for Good Manufacturing Practice for APIs, Quality Risk Management and Pharmaceutical Quality System. Quality-related activities were defined and documented. The Quality department was independent from the production department. Responsibilities between QA and Production was addressed in separate SOPs. Persons authorized to release intermediates and APIs were specified. Information on the site was captured in an appropriate SMF, dated 16 January 2024.

***Product Quality Review***

Product Quality Reviews of APIs were conducted annually with QA responsible for APQR. PQR's included statistical analysis utilities, deviations, complaints etc. Several APQRs were verified and found compliant.

***Management review (MR)***

The SOP "Quality Management review" was verified. A standard meeting agenda specified the items to be discussed. Information on product regulatory status was discussed as part of the APQR section. The latest MR meeting Minutes were reviewed. HR confirmed the training status of staff with the attendance list confirming attendance by the invited staff members which included various staff from production and Corporate RA.

***Quality Risk Management***

The SOP "Quality Risk Management" was checked. The quality risk management procedure included initiation, risk assessment, risk control and risk review. Appropriate quality risk management tools i.e., Preliminary Hazard Analysis (PHA), Failure Mode Effects Analysis (FMEA) were implemented. RPN was defined. The risk assessment register for 2023 was checked and discussed.

***Deviations***

Deviations were managed according to the defined SOP. Deviations were classified into major or minor. According to the SOP, deviation investigation should be closed within specified timeline, followed by an appropriate CAPA. The 2023 deviations register for *Nirmatrelvir* was verified. A 2023 site deviation register was also available. Some deviations were verified and found compliant with the procedure.

***CAPA***

An appropriate SOP was available and verified. The SOP addressed the handling of complaints, recalls, deviations, OOS/OOT and self-inspections. QA was responsible for the follow-up and implementation of CAPAs.

***Internal audit/ Self inspections,***

Internal audits were managed according to the Self-inspection Management Procedure and were performed yearly in accordance with an approved self-inspection schedule prepared by the QA department. The frequency of self-inspections was confirmed by risk, which was based on an internal or external audit, quality system operation or quality events of the previous year. All areas were covered at least once per year. The inspection team was organized by QA and joined by related departments. The inspection team consisted of the head of quality of each site and a multidisciplinary team from the list of qualified auditors who were certified. Conflict of Interest was addressed as audit team members could not inspect their own departments. Following the issuing of the inspection report, appropriate CAPA were established to address the observation. QA tracked CAPA progress until closure. A general Inspection Template was used that addressed Opening meeting, closing meeting etc. and a departmental specific checklist.

Several inspection activities were verified that included the composition of an inspection team, self-inspection schedule for 2024, self-inspection schedule for 2023 and some inspection reports for different production areas.

***Product release***

The SOP addressing Final product release was verified. The production department reviewed batch production and packaging records of each batch, received certificate of analysis of finished product, confirmed compliance and completed the “Product Release Form” and submitted it to product QA along with batch production records for further review. Product QA reviewed and confirmed compliance by completing the “Product Release Form” and submitting it to the Qualified Person or delegated for conclusion to either release or reject the batch.

Product release was authorized by the Qualified Person, Head of the QA Department. At the Chuannan Site, additional staff were authorized for product release which included inter alia: QA Manager, Vice QA Manager and Assistant QA Manager. The SOP required certification of the delegated staff’s specific experience, qualification, and training in product release requirements.

CoAs were issued for each batch of intermediate and API. Final CoAs were dated and signed by the delegated QP.

***Data Integrity***

Data on production and material were managed manually with the implementation of computer systems limited to the use in the QC laboratory including a new LIMS (still under development) and computerized systems for HPLC, GC, and TOC. The LIMS in the laboratory was initiated in 2023.

The SOP addressing "Data Integrity Management System" was verified. Risk assessment and ongoing training on data integrity were required. Data integrity requirements for Service providers and contractors were addressed. Adherence to ALCOA principles was addressed. Control over blank templates for data recording was addressed. The HPLC Data integrity was verified which was included in a separate report.

All deficiencies raised in this section have been addressed satisfactorily.

**2. Personnel**

Number of personnel according to the Site presentation totaled 1828. The company had an organizational chart that showed that there was separation between the responsibilities and reporting of the quality and production units. Responsibilities were defined and documented in job descriptions. The organogram was signed and dated by the Site General Manager. Several job descriptions were reviewed which included that of the Qualified Person and Production Corporate with the Signature log for the QC laboratory verified and found acceptable.

***Training***

An adequate number of qualified trained and experienced personnel was available. Training was addressed in an appropriate SOP. The SOP was applicable to new employees and current employees. Written training records were kept for all employees. Training was conducted at three levels i.e., Corporate (basic GMP), Departmental (SOPs) and on the job. (Specific job SOPs and GMP). One GMP refresher course was presented per annum. The training plan for a specific Workshop was verified and found acceptable.

Several training records for staff were verified and found acceptable:

- Team Leader for inspection of Production Area
- QA Manager, trained as delegated QP for purposes of product release
- IR Chemist: trained in IR use.
- HPLC chemist.

The company was not using the services of consultants.

***Personnel Hygiene***

Personnel sanitation procedures were in place for the common manufacturing areas and the Class D clean room manufacturing areas. Direct contact was avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk products. It was observed that personnel performed their duties in an organized and diligent manner.

Deficiencies raised in this section have been addressed satisfactorily.

**3. Buildings and facilities**

The buildings at the Chuannan site comprised of an East Zone and A West Zone. Buildings and facilities used in the manufacture of intermediates and APIs were located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Manufacturing, warehouse, and quality control facilities of the WHO products were in both zones.

Production facilities (Class D clean area) were designed to prevent potential contamination with the differential pressure between adjacent rooms. Air change rates for Class D were set. It was observed during the inspection that differential pressure between rooms were verified by production staff. The flow of materials and personnel through the building or facilities was designed to prevent mix-ups or contamination. Permanently installed pipework was appropriately identified. Adequate lighting was provided to facilitate cleaning, maintenance, and proper operations.

Laboratory areas and operations were separated from production areas. Separate warehouses for chemicals / starting material and finished API were available. All areas were access controlled.

***Purified Water (PW) system, Workshop W08***

Several purified water systems were operated at the Chuannan Site. The PW system located in Workshop W08 was visited. The P & ID of PW system was documented. Source water was supplied by the municipality. After pretreatment, the PW was prepared by two RO systems. PW was in continuous circulation at ambient temperature. PW system was seen to be in good order.

The SOP addressing "Purified water system operation and maintenance procedure" was checked. Conductivity, TOC and flow rate were monitored online with pH offline. Sanitization was performed periodically. Sampling was performed at the supply sampling points, final return of PW, storage tank and after the 2nd RO in accordance with written procedures. The material used for the generation system and for the distribution system were documented. The PW specifications and testing procedure were verified. The 2023 annual quality review of the PW confirmed that all results were well within limits.

***HVAC, Workshop W08***

The AHUs supplying air to Workshop W08 Clean Area were briefly visited. The SOP "Operation and maintenance procedure of HVAC system in clean zone" was verified. HEPA integrity test was performed once a year by PAO, with the acceptance criteria defined in the SOP.

***Nitrogen system***

Nitrogen was used in the manufacturing process. This was not inspected in detail due to time constraints.

Deficiencies raised in this section have been addressed satisfactorily.

**4. Process equipment**

*Design and construction*

Equipment used in the manufacture of *Nirmatrelvir* appeared to be of appropriate design and size for its intended use. In general cleaning and maintenance appeared satisfactory. Manufacture and material transfer took place in closed systems wherever possible. Equipment installed in the above-mentioned production workshops were multi-purpose and each piece of equipment had a unique identification number.

*Equipment maintenance and cleaning*

The equipment viewed during the inspection appeared to have been generally suitably maintained. Equipment status labels and identification labels were available.

Written procedures were established for equipment preventive maintenance. Several documents were reviewed:

- "Periodic maintenance regulation on production equipment" that proposed a maintenance plan at the end of each year. Each type of equipment had its own maintenance frequency.
- "Equipment qualification management procedure".
- W18 equipment maintenance plan for 2023 was checked. The maintenance of Micronizer performed in December 2023 was checked.
- "Management regulation of measuring instrument" addressing calibration which was the responsibility of the engineering department. Instrument Calibration Plan for Workshop W03 in 2024 were available.

**5. Documentation and records**

Documents related to the manufacture of intermediates and APIs were prepared, reviewed, approved, and distributed according to written procedures. The issuance, revision, superseding and withdrawal of all documents were controlled with maintenance of revision histories as per appropriate SOPs. SOPs were reviewed periodically, and the reviewed records were kept with QA. A manual documentation system was used with a computerized system limited to certain QC-laboratory activities, i.e., HPLC, GC, etc.

*Batch numbering system and BMR management:*
Batch numbering and BMR were managed in accordance with appropriate procedures which were verified and found acceptable. Procedures were established for retention of documents with production, control and distribution records retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records were retained for 3 years after the batch was distributed.

Deficiencies raised in this section have been addressed satisfactorily.

**6. Materials management**
Incoming starting materials and finished API products were quarantined after receipt until released for use or distribution. Status of raw material was indicated, with respect to material under quarantine or approved. Starting material, packaging material and finished API products were stored in different warehouses under specified conditions. A secured area for return and rejected materials was in place. The starting material and finished goods were managed by a manual system.

Written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials were available and verified:

- "Management procedure for receipt, storage, distribution and return of materials.
- "The Sampling procedure of API raw materials"
- "Management procedure for raw material and intermediate samples"
- "Material receiving test management procedure"

The Warehouse was responsible for requesting a Material to be tested. QC performed the sampling, testing and release of each batch of raw material ,as part of the quality unit.. Sampling was conducted in a sampling cabinet at a defined sampling room.

***Supplier Qualification***

A supplier management system was established to manage supplier qualification, supplier management and change. Suppliers of raw materials were evaluated by quality, purchasing, QC, technical department, and finally approved by the Quality Manager before being included on the authorized suppliers list. An annual evaluation was conducted for each supplier, organized by the Quality Department. A system for evaluating the suppliers of critical materials was in place. Changing the source of supply of critical raw materials was done according to a Change Control procedure.

The Quality Department was responsible for organizing on-site audits of suppliers. Audits were conducted as per the audit schedule or when a new supplier had been identified.

The SOP "Management System of API Material Supplier" was verified and the supplier qualification for the starting material supplied by one of the approved suppliers was checked. The supplier was added to the Approved supplier list in September 2022.

***Environmental Waste Management***

Environment, Health and Safety were managed by the EHS department, which required wastewater to be collected and treated by the wastewater station. Due to time constrains, this section was not inspected in detail.

Deficiencies raised in this section have been addressed satisfactorily.

**7. Production and in-process controls**

The chemical area of Workshop W03 and W08 and Class D clean area of Workshop W08 were briefly visited. *Nirmatrelvir* API was not in operation in Workshop W03 and Workshop W08. At the time of the inspection, the synthesis manufacturing process of one of the APIs was conducted in Workshop W08. The areas were found to be of suitable standard, clean, and logically organized to suit their intended purpose. In-process sampling was performed at defined stages during processing. In addition, the document "Product Cross-contamination Risk Assessment for Workshop W03" was verified.

***Blending***

SOP "Management of material and product in workshop" was checked.

Deficiencies raised in this section have been addressed satisfactorily.

**8. Packaging and identification labelling of APIs and intermediates**

Written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials were available.

Containers provided adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

The Packing procedure for finished Products, was verified. The SOP "Pre-production check and clearance management procedure", was verified. In addition, the SOP "Blending-packaging position clearance record" called for line clearance with the requirement to record the prior batch number, clearance of previous batch, all previous batch labels removed, and clean area. Line clearance was done before and after labelling/packaging procedures. During the inspection no packaging/labelling operations were performed.

Deficiencies raised in this section have been addressed satisfactorily.

**9. Storage and distribution**

There were different warehouses in the West Zone. The Warehouses were designed and built with reference to GMP requirements. Temperature and humidity control were introduced. Records were maintained of these conditions. Material was segregated and stored on pallets.
The following warehouses had been visited:

- Warehouse for Released Finished Product (API)
- Warehouse for Quarantine Finished Product
- Warehouse for Rejected Finished Product
- Warehouse for primary and secondary packaging components
- Warehouse Comprehensive East Zone
- Warehouse for Category A hazardous material.

APIs and intermediates were released for distribution to third parties after they have been released by the quality unit and transported in a manner that did not adversely affect their quality. A system was in place by which the distribution of each batch of intermediate and/or API could be readily determined to permit its recall.

**10.Laboratory controls**
The QC laboratory included the Physicochemical laboratory and Microbiological laboratory.

***Physicochemical Laboratory***
Separate rooms for receiving of samples, GC, HPLC, retention samples stability chambers and reference standards were available. The laboratory had trained personnel, facilities, and equipment suitable for the nature of products and scale of production. The laboratory was responsible for sampling each batch of raw materials and GMP intermediates according to the procedural requirements and conducting laboratory tests on raw materials, GMP intermediates and API to determine whether they meet the specifications, and the issue of an Analysis Report.

Adequate quality control facilities were provided. Procedures were in place describing sampling, testing, approval, or rejection of materials and recording and storage of laboratory data. Specifications, sampling plans and test procedures were available. Sampling and testing of each raw material consignment were performed by quality control as per a sampling plan. Laboratory controls were followed and documented at the time of performance. Any departures from procedures were documented and explained. Laboratory tests were performed for each batch of intermediate and API.

Each batch of raw material was tested by the QC department and released in accordance with the company's procedure. For purposes of the inspection, the laboratory QC testing and QA release of a defined batch of *Nirmatrelvir* were inspected. Specification and test methods were verified, issue of CoA, worksheets and test reports, stability samples and programme, retention samples, equipment suitability, equipment maintenance and equipment usage logs applicable to the required test performed.

***OOS***

OOS results obtained were investigated and documented according to the laboratory procedure. The SOP allowed for:

- Phase I investigation which required a Laboratory investigation involving "5 M'
- Phase II (full investigation with additional lab tests).

If required a retest protocol was prepared by QC and approved by QA. Resampling was only allowed under specific conditions. The OOS Register for 2023 was evaluated.

***Stability studies***

The Stability room was visited. Various stability chambers simulating the four climate zones were available. Each chamber was access controlled. Sample storage locations were controlled. A documented stability testing programme was in place. Test procedures used in stability testing were validated. Stability samples were stored in packaging that simulated the market container. At least one batch per year of API manufactured was added to the stability monitoring programme and tested.

API expiry or retest date was based on an evaluation of data derived from stability studies. Stability study data for *Nirmatrelvir* were verified and found acceptable.

***Reference Standards***

Reagents and standard solutions prepared in the laboratory were appropriately labelled following written procedures with expiry dates defined for reagents. Reference standards were stored at 2-8$^{o}$C. The area was access controlled.

Primary reference standards were available, which were used as working standards. Records were maintained of each primary reference standard's storage and use. For in-house working standards were prepared by characterization of the batch. Standards were appropriately prepared, identified (labelled), tested, approved, and stored. Information on the label identified the material manufacturing date, quantity, retest date, number of vials, opening date, and storage conditions.

***Retention samples***

The retention sample store was visited. Reserve samples of each batch of API were retained for one year after the expiry date, or for three years after distribution of the batch, whichever was longer. For APIs with retest dates, reserve samples were retained for three years after the batch had been completely distributed by the manufacturer. Enough reserve samples were stored in the same packaging system in which the API was stored. The area was temperature and humidity controlled and monitored.

***Laboratory equipment***

All laboratory equipment had usage and calibration logbooks. The following equipment was checked: IR, HPLC, GC, Karl Fischer, and Balances.

IR: equipment and usage SOP was verified. The disk method and preparation were verified. Specifications referenced were limited to USP/JP/CPh/EP.

HPLC: Agilent technologies, and specific equipment was verified. Sequence system suitability, sensitivity and resolution were verified. Assay and Related Substances verification for *Nirmatrelvir*, using HPLC was verified.

Balances: Usage log for balance used in weighing reference standards for HPLC determination of *Nirmatrelvir*, was available.

Karl Fischer: water content for *Nirmatrelvir*, was checked. Temperature and humidity were monitored. Maintenance was conducted regularly. The equipment logbook was verified and found acceptable.

***Microbiological laboratory***

The Microbiological laboratory was briefly visited. The SOP "Procedure of Micro-Lab Clean room" and testing procedure for microbial limit of PW were checked.
The following rooms were available:

- Balance
- Preparation for microbial limit testing
- Microbial limit testing under LAF
- Positive control under LAF
- Sterilization
- Incubation

Separate entrances via changing rooms were provided to the positive control room and microbial limit testing room. The gowning procedure to access Clean Zone A/C area was verified.

Deficiencies raised in this section have been addressed satisfactorily.

**11.Validation**

Validation and qualification were described in the document "Qualification and validation management review procedure" included the policy of process validation, continuous verification, and cleaning validation etc. The 2024 Validation Master Plan (VMP) for Chuannan was available for review.

***Process Validation***

Process Validation was conducted for each intermediate and API according to SOP "Process validation". Products were subjected to Continuous Process Verification. Monitoring and trend analysis of commercial product quality indicated that process and product quality remained in a state of control. Critical manufacturing processes and operation procedures were required to be validated every 5 years.

The process validation documentation for *Nirmatrelvir* API were presented and discussed.

***Cleaning Validation***

Cleaning Validation, defined different types of cleaning:

- Simple cleaning (batch-to-batch cleaning of the same product in a run)
- Routine cleaning (end of a run within a campaign)
- Change over cleaning (change to new product)

Cleaning SOP described the locations for collecting swap samples and rinse samples. Analytical samples for purposes of cleaning verification were collected after each 'change over cleaning' with on-going verification of cleaning conducted once a year.
Cleaning of milling equipment in W08 Clean Area, *Nirmatrelvir* manufacturing was verified. The SOP addressing room cleaning of the milling area, and cleaning of the dust extraction unit confirmed that the cleaning procedure was compliant with the requirements.

***Qualification of W08 – Milling and Sieving***

The procedure "Management regulation on clean buildings", was reviewed. All areas within W08 Clean Area were classified as Class D. An appropriate SOP addressed the HVAC qualification procedure. Requalification was routinely conducted periodically with shutdown of the facility for maintenance when no production was planned. Annual review of air changes was conducted. Pressure differentiation between the Milling area and airlock/ buffer room and airlock/buffer room and corridor was set to confirm monitoring requirements. The 2023 annual review of HVAC for Workshop W08, was verified and found acceptable.

*Campaign manufacturing:*

The SOP addressing prevention of contamination "Preventing management Procedure of Drug Contamination and cross-contamination", allowed for campaign manufacturing and specified cleaning procedures to be followed prior to the manufacturing of the next product.

***Computer validation***

Computerized system used was limited to the QC Lab with software programmes which included HPLC, GC. An electronic LIMS system was under development with the implementation limited to the recording of samples for testing received at the laboratory. Due to the limited implementation of an electronic system, computerised validation was not reviewed in detail.

Deficiencies raised in this section have been addressed satisfactorily.

**12.Change control**

A Change Control system was established to address changes that may affect the production and quality control of the intermediate or API. Action plans were proposed and documented. Timelines for implementation, closure and assessment of adequacy were established. Changes were classified into major, moderate, and minor. The procedure also allowed for a so-called "temporary change" which was discussed. Several changes were checked and discussed during the inspection.

Deficiencies raised in this section have been addressed satisfactorily.

**13.Rejection and re-use of materials**

***Return and rejects***

Return and reject SOP was verified which included return API from subsidiary workshops and commercialized products due to non-compliance. Returned goods within the retest date can be treated in the workshop and released again. QC should issue a full test report. API can be reprocessed. QA could approve reprocessing or reworking if specification could be met. The Returned register for 2023 was verified.

***Reprocessing and Reworks***

SMP "Reprocess and rework management procedure" was verified.

***Recovery of Solvents***

The SOP "Recovered solvents management regulations" and SOP "Assessment and validation management procedure for recovered material" were verified. Recovered solvents were tested and reused in the same process step or early steps of the same product. According to the SOP every time when a new recovered solved was introduced to the process, process validation had to be carried out. The use of recovered solvents, mother liquors, and other recovered materials was documented. Recovered solvents were not used in *Nirmatrelvir* API manufacturing.

Deficiencies raised in this section have been addressed satisfactorily.

## 14. Complaints and recalls

***Complaints and recalls***

Quality related complaints were recorded and investigated according to a written procedure "Customer complaint Management procedure". Complaints were managed by QA to oversee a root cause investigation and impact assessment of the complaint. Complaints were divided into serious complaints and other complaints. Serious complaints need to be communicated to the NRA. The investigation results of a customer complaint were communicated to the complainant within a prescribed timeline. If necessary, a recall of the product may be initiated. Records of complaints were retained to evaluate trends, product-related frequencies.

The timeline for closing a complaint was specified. Complaints were reviewed by QA. Trending was conducted. The 2023 register of complaints was evaluated. The Register included a complaint number and receival date, customer, description, root cause, proposed CAPA, status and status of CAPA at the time of the report. A handling of a specific complaint received was verified with investigation found acceptable.

***Recalls***

The handling of recalls was described in "Product recall management System". Recalls were divided into three grades with each level having a different timeline requirement. The decision to close the recall was based on reconciliation, timelines, and feedback. QA was responsible for making all decisions on recall and for coordinating all relevant actions. Recalls were classified with the corresponding timelines for implementation listed as:

- Grade I – recall within 24h
- Grade II within 48h
- Grade III within 72h

The classification was according to health impact and severity.

To evaluate the efficacy of the SOP, a mock recall was performed once per year in absence of any implemented recall. The latest mock recall conducted by the company was verified and found acceptable.

Deficiencies raised in this section have been addressed satisfactorily.

**15.Contract manufacturers (including laboratories)**

Some manufacturing and product testing were contracted.

Quality agreements evaluated during the inspection confirmed that Contract acceptor and Contract giver responsibilities were defined. Contracts required prior notification of any changes by any party and stated the GMP responsibility and actions of each party. Contract acceptors were only to implement Huahai approved changes, including process, equipment, analytical method, or specifications. Subcontracting was not allowed.

In some instances, a Questionnaire was required to be completed. As per the procedure on vendor approvals, supplier questionnaires/surveys were required to be conducted periodically.

The deficiencies raised in this section have been addressed satisfactorily.

| Part 3 | Conclusion – Inspection outcome |
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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, ***Zhejiang Huahai Pharmaceutical Co., Ltd (Chuannan)*** located at ***Costal Industrial Zone, Duqiao, Linhai, Zhejiang, 317016***, ***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 GMP Guidelines referenced in the inspection report |
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1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2.
   ***Short name: WHO TRS No. 986, Annex 2***

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***

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***

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***

5. 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***

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.
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