DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternationalresponses@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	01/08/2024-01/16/2024 FEI NUMBER 3007373503

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
Ms. Yan Zhang, Vice President of Quality	
TO: FIRM NAME Jiangsu Hengrui Pharmaceuticals Co., Ltd (Huanghe Road Site)	STREET ADDRESS 38 Huanghe Road, Economic and Technological Dev Zone
CITY, STATE, ZIP CODE, COUNTRY Lianyungang, Jiangsu, 222047 China	TYPE ESTABLISHMENT INSPECTED Finished Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic and sterilization process. Specifically,

A) Product contact equipment including [redacted] (b) (4) stopper drums, [redacted] (b) (4) were sterilized without outer wrapping and transferred from a Grade A Cart to inside of the RABS without cover in Workshop [redacted] (b) (4) Filling Room [redacted] (b) (4) There were no physical separations between Grade A areas (outside the RABS and [redacted] (b) (4) and Grade B area (the rest of the room). Airflow visualization study did not include the transitions between Grade A and Grade B.

B) During our observation of the filling process of production batch [redacted] (b) (4) njection USP [redacted] (b) (4) ng [redacted] (b) (4) ml batch number [redacted] (b) (4) manufactured for the US Market per your firm, we observed a routine intervention of adding stoppers to the filling line performed, which we observed with start time of 3:58 pm and stop time of 4:03 pm; however, upon review of your batch record, we observed the start and stop time recorded by your firm to be 4:00 pm to 4:01 pm (16:00 – 16:01), which was significantly different than our observed documented intervention time. Upon further review of procedure PO-1 01 007, titled "Operating Procedure for Filling Post", effective date 11/30/2023, procedures with respect to when an intervention starts and stops is not clearly defined.

C) There is no assurance that your process simulation studies (media fills) performed in your [redacted] (b) (4) [redacted] (b) (4) General Parenteral workshops are representative of the current commercial manufacturing

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operations. The validation plans for your media fill studies do not appear to adequately incorporate the nature and frequency of interventions incorporating worst-case activities and conditions with respect to operator interventions, such as start and stop time of interventions performed and the total time for interventions performed during media fill and commercial batches.

D) Production operator requalification procedures with respect to performing routine and non-routine interventions are inadequate. During our review of (6) six media fill studies across all (b) (4) manufacturing workshops, we observed operators who performed the bulk of interventions, operators who performed several interventions, and operators who performed no interventions during media fill studies, who were all considered to be requalified as a result of the media fill study participation. As a result, there is no assurance that all production operators participating in commercial manufacturing operations are adequately qualified to perform interventions during aseptic operations.

OBSERVATION 2

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product. Specifically,

Your container closure integrity test for (b) (4) Injection (USP) (b) (4) mg (b) (4) mL (b) (4) is inadequate. The test used empty vials instead of filled vials. Microbial Challenge Study was conducted without a positive control. Dye ingress study was conducted using human eye detection with results "not detected" without specifying the limit of detection.

OBSERVATION 3

Equipment and utensils are not cleaned appropriately to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. Specifically,

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Your cleaning validation studies for (b) (4) cleaning of multi-use filling equipment (b) (4) cleaning of vials, stoppers and (b) (4) for (b) (4) are inadequate.

A.) Worst-case contaminants (hardest to clean products) determinations did not take into consideration the concentrations of the contaminants for all equipment. In addition, (b) (4) was not considered as a contaminant for (b) (4) cleaning validation, whereas the firm's stopper processes include a (b) (4) step for some products.

B.) (b) (4) limits of (b) (4) cycles for cleaning validations were not necessarily worse than the routine cleaning cycles.

C.) Swab sampling included the (b) (4) tank, but it did not include the (b) (4) with 2 small outlets positioned 90 degrees from the (b) (4) which should be considered a worse case than the (b) (4) tank.

D.) (b) (4) esting was not preformed after cleaning of vials, stoppers and some (b) (4)

E.) Testing of residual active contaminants (products) of swab and rinse samples includes some "not detected" results. However, the limits of detection were not provided in the report.

OBSERVATION 4

The quality control unit lacks responsibility to approve all procedures or specifications impacting on the identity, strength, quality and purity of drug products. Specifically,

A) The Quality Unit lacks adequate control over the issuance of controlled documents, such as production

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batch records, validation protocols and reports, change controls, and standard operating procedures. During the walkthrough of our inspection on 01/08/2024, we observed original executed pages of batch records, validation reports, change controls which had been discarded in a waste bin. When these original records found in the waste bin were compared to the archived official records, the information, such as production data did not always match.

B) The Quality Unit lacks adequate control over the issuance of master production batch records purported to be controlled under your procedures PR-416 titled "Preparation of Batch Records, Issuing, Review and Filing Management Program", effective date 06/20/2023 and QS-001 titled "Controlled Documents Management (DMS System), effective date 06/16/2023. During the inspection, it was observed that batch records are issued to production personnel using software DMS for control of records, however, production personnel can duplicate the batch record using a QR barcode on the printed batch record, which was determined to have occurred during the current inspection. For Example, see above for information regarding original executed/filled out batch record pages found in the firm's trash bin during our walk through of the firm's grounds.

C) Official eye exam results from medical professionals for visual inspection operators are not reviewed and managed by the Quality Unit.

D) Parenteral drug products awaiting destruction in your waste area are not secure. During our walkthrough on 01/08/2024 we observed (b) (4) doors to your waste building open and no personnel present. This building is located directly across a public sidewalk and public street with an approximate 3.5-foot fence. Per your firm, the fence is secured with an alarm in case a private citizen climbs over the fence, however during our inspection we found the alarm was not functional.

E) There is no adequate data integrity program in place to include statistically sound comprehensive review of electronic data by the Quality Assurance Unit for standalone and network systems, to ensure completeness, consistency, and accuracy of all chromatographic and non-chromatographic electronic

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data generated by the Quality Control Laboratory.

OBSERVATION 5

Records associated with drug product production and within the retention period for such records, were not made readily available for authorized inspection. Specifically,

During our walk-through inspection of your firm's discard waste building, we requested to be taken to the area where office waste is discarded, an approximate (b) (4) walk from our location. As soon as we requested to be taken to this area, we observed at least one individual make a phone call on the cellphone. After finishing up the task at hand, we were diverted from taking what appeared to be the shorter path (path we walked before), and instead directed around outside the firms side gate walking on the street to the front gate of the firm, which added another approximate (b) (4) to our walk. Upon walking towards the outside waste bins inside the facility, we observed a female personnel in a rapid-like manner placing documents in the waste bin, along with approximately 2 to 3 other individuals watching her, with two of the individuals standing in front of the passenger's side door. We observed one of the individuals taking their hands from the front to their back in a rapid-like manner with what appeared to be torn documents in hand, and immediately after noticed the presence of an approximate 8-inch stack of documentation under the vehicle. The contents of the documents identified within this stack and the additional waste bins are described above in Observation 4. These events along with the review of the contents of the documents introduced a delay in our ability to perform the remainder of the inspection in a timely and effective manner.

OBSERVATION 6

Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Specifically,

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Your firm's GMP related computerized systems and equipment spread across (b) (4) manufacturing workshops are not 21 CFR part 11 compliant. For Example:

A) Your firm operates (b) (4) portable non-viable particle monitoring equipment used to perform and generated test data for non-viable particle (NVP) count used in environmental monitoring/cleanroom qualification activities in Grade B and Grade C areas in support of general (b) (4) parenteral manufacturing operations. (b) (4) equipment have no time stamped audit trail, data management, alarm management, and archival and retrieval of records capabilities. Subsequently, our review found that equipment qualification activities for these equipment have never been performed by your firm.

Additionally, during the inspection on 01/11/2024, we requested your firm to take us to the viewing window of your workshop (b) (4) in order to observe your MET ONE 3400 NVP equipment located in the Grade B cleanroom. Upon arrival, we were told to wait until personnel gowned and entered the cleanroom to show us the interface for the equipment. Approximately twenty (20) minutes later, your personnel came inside our non-classified area with the MET ONE 3400 equipment in hand, your firm stating that he had misunderstood our request and brought the equipment out of the cleanroom. Upon review, we observed the interface, which read "USB Flash Drive Not Installed" and read "NO DATA" when we clicked on the "Historical" tab. After asking your firm why there was no data on the equipment where a "Historical" tab exists, when they had claimed this machine was in use, your firm claimed that no internal storage existed. When we asked to verify this by performing a test, to see whether the data would appear, your firm was not able to perform this test, claiming there was an equipment error. The series of actions by your firm described in this paragraph delayed our inspection.

B) Your firm operates (b) (4) integrity test equipment and (b) (4) integrity equipment used in support of general (b) (4) parenteral manufacturing operations. The mentioned equipment does not have time stamped audit trail, data management, alarm management, and archival and retrieval of records capabilities.

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OBSERVATION 7

Buildings used in the holding of a drug product are not maintained in a good state of repair. Specifically,

During our walkthrough of your warehouse facility (b) (4) refrigerator (2 – 8 °C) on 01/12/2024, we observed what appeared to be a pool of water (approximately 100 square feet) on the floor of the warehouse with pallets of released finished parenteral drug products stored directly over this water. In addition, we observed a second pool of water near additional released finished drug product pallets under an air condenser, which we observed to be leaking from what appeared to be rusted and inadequately taped pipes. Furthermore, the metal beams connecting the pallets racks under this condenser appeared to be corroded, with an attempt to cover this with additional coat of paint. Finally, we observed black mold like growth on the floor below and around the condenser, which are approximately a foot from released finished drug products. Drug products stored in this area included (b) (4) Injection (b) (4) ml batch number (b) (4) (USA), (b) (4) Injection (b) (4) mg batch number (b) (4) (USA), (b) (4) Injection (b) (4) mg batch numbers (b) (4) (b) (4) (UK), (b) (4) Injection (b) (4) mg batch numbers (b) (4) (UK), and (b) (4) Injection (b) (4) mg batch number (b) (4) ready to be shipped for the US and international markets.

OBSERVATION 8

Washing and toilet facilities lack hot and cold water. Specifically,

During the inspection of your (b) (4) parenteral drug product workshop # (b) (4) we observed that there is no hot/warm water in the washing facility prior to the entrance of the Clothes Sterilization room (b) (4) Grade D on 01/11/2024. Additionally, your workshop manager, confirmed that there is no warm/hot water

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at any of the hand washing stations for the entire workshop, including the washing facility inside the entrance to Grade C and Grade B areas. This workshop is used for manufacture of aseptically filled and (b) (4) sterile drug products for the US Market.

***DATES OF INSPECTION**

01/08/24 (Mon), 01/09/24 (Tue), 01/10/24 (Wed), 01/11/24 (Thu) 01/12/24 (Fri), 01/15/24 (Mon) and 01/16/24 (Tue)

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