DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parkland Drive, Room 2093 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	14 -29 August 2023 FEI NUMBER 3003404148

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Ms. Zhang Yan, Vice President, Quality Responsible Person

FIRM NAME	STREET ADDRESS
Jiangsu Hengrui Pharmaceuticals CO. LTD.	Dongjin Road, Port Industry Area, Eco & Tech Development Zone
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Lianyungang, Jiangsu 222069 China	Manufacturer

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DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

Observation 1:

Samples taken of in-process materials for determination of conformance to specifications are not representative. Specifically, samples are taken for testing bioburden, appearance, and assay after (b) (4) compounding of (b) (4) Injection, a sterile (b) (4) product distributed to the U.S. market. The sample obtained is not the (b) (4) bulk solution. The compounded solution is transported from Workshop (b) (4) room (b) (4) to the Workshop (b) (4) filling line room (b) (4) where (b) (4) mL of the compounded solution is (b) (4) into the (b) (4) tank. (b) (4) (b) (4)

Observation 2:

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Specifically,

a) SOP QC-868-009, The Determination of Microbiological Experiment Result, does not assure that the (b) (4) will not be disrupted during the (b) (4) reads of the sterility test samples. The procedure requires, "observe (b) (4) during incubation, remove medium from the incubator, observe whether the medium is (b) (4) in a well-lit place, and (b) (4) the medium if necessary".

b) On 15 August 2023, microbiologists performing the (b) (4) reads of sterility test samples were observed not taking care to not disrupt the (b) (4) media canister prior to ensuring that the anaerobic environment was maintained. The (b) (4) canisters were seen with (b) (4) lacking evidence that the anaerobic environment had been maintained.

c) SOP QC-868-009, The Determination of Microbiological Experiment Result, requires "take care to observe the (b) (4) of the (b) (4) not to exceed (b) (4) of the medium", but there is no documentation for the check of the (b) (4)

d) In-process control samples are tested by the Quality Assurance personnel and not manufacturing personnel or Quality Control personnel. For example,

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1) (b) (4) in-process samples are tested for (b) (4) content by equipment located in Workshop (b) (4) room (b) (4) The test equipment does not have a print function and the results are shown on test equipment screen and documented by QA personnel. There is no second review of the test data.
2) Aseptically filled products are sampled and tested for visible particulate matter for Workshop (b) (4) and (b) (4)
3) Quality assurance personnel collect the environmental monitoring samples from filling operations.

e) AQL manual sampling is not performed according to SOP # GR-235, Management Procedure for Visual Inspection of Injections, which requires, "First ensure that the entire batch of product has been inspected at 100%". Currently, AQL samples are obtained at the (b) (4) of the 100% manual visual inspection process. If the AQL limit is exceeded at (b) (4) of the inspection process, the 100% manual inspection is stopped and only the portion that have been inspected is reinspected, causing reinspection of only a portion of the batch.

f) If the AQL inspection limit is exceeded for product manually inspected, the inspection stops immediately and reinspection is performed without initiating a deviation investigation.

g) The AQL sampling and inspection of product inspected on the automated visual inspection machine can fail acceptance criteria (b) (4) times before initiating a deviation investigation.

Observation 3:

Batch production and control records for each batch of drug product produced do not include an accurate reproduction of the appropriate master production or control record which was checked for accuracy, dated and signed.
Specifically, logbook for (b) (4) Tube Replacement Records in Workshop (b) (4) were replaced, with the information in logbook rewritten in the new logbook.

a) The logbook used to document the number of (b) (4) tubing uses documents that (b) (4) tubing # (b) (4) was replaced on 16 July 2023, with signature of the person replacing the tubing and the signature of the person reviewing the information. The information was rewritten on a new form on 14 August 2023 with new signatures. The (b) (4) tubing were originally documented as replaced and integrity tested prior to production of (b) (4) Injection batches (b) (4) and (b) (4) on 17 July 2023 and 18 July 2023 respectively. The information was rewritten as replacement of (b) (4) tubing with integrity test on 14 August 2023.

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b) The logbook used to document the number of (b) (4) tubing uses documents that (b) (4) tubing # (b) (4) was replaced on 19 July 2023, with signature of the person replacing the tubing and the signature of the person reviewing the information. The information was rewritten on a new form on 14 August 2023 with new signatures. The (b) (4) tubing were originally documented as replaced and integrity tested prior to production of (b) (4) Injection batch (b) (4) on 19. The information was rewritten as replacement of (b) (4) tubing with integrity test on 14 August 2023 but the individuals documented as performing the activity changed with new signatures.

c) The logbook documents that (b) (4) tubing # (b) (4) was replaced on 10 August 2023, with signature of the person replacing the tubing and the signature of the person reviewing the information. The information was rewritten on a new form on 14 August 2023 with new signatures. The (b) (4) tubing were originally documented as replaced and integrity tested prior to production of (b) (4) (b) (4) njection batches (b) (4) and (b) (4) on 11 and 12 August 2023 respectively. The information was rewritten as replacement of (b) (4) tubing with integrity test on 14 August 2023.

Observation 4:

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically,

a) Not all locations on Workshop (b) (4) filling line, used for filling products (b) (4) Injection and (b) (4) Suspension, shows adequate air flow without turbulence during smoke studies.

1) The (b) (4) area next to the Workshop (b) (4) filling line with Grade A airflow is used for opening the LAF (b) (4) retrieving sterilized components prior to placement of sterilized components into the Grade A filling line. The smoke study video at 1:00 minute and 1 minute and 30 seconds shows an up-flow of smoke as the operator opens the HEPA filter (b) (4) to take out sterilized equipment and components for filling line set up. Up to (b) (4) personnel stand in this (b) (4) area during filling line set up.

2) Workshop (b) (4) # 1 is used for filling product intended for US distribution. (b) (4) # 1 is one of (b) (4) ocated the (b) (4) from the point of filling. The smoke study video does not demonstrate airflow without turbulence for the entire pathway to (b) (4) # 1 classified as Grade A.

3) The Workshop (b) (4) smoke study video at times provided only a closeup view of the filling line, which did not demonstrate air flow without turbulence from top (smoke source) to the filling line location.

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a) On 25 August 2023, while observing filling operations in Workshop (b) (4) the filling line was set up with a (b) (4) that was (b) (4) in color, and not consistent with the color of (b) (4) (b) (4) available for use on this filling line. Filling in Workshop (b) (4) is used to fill (b) (4) product (b) (4) Suspension. A review of Workshop (b) (4) smoke study video that was filmed in February 2023 shows that the (b) (4) was also (b) (4) in color at that time.

b) On 25 August 2023, the filling line in Workshop (b) (4) was observed with deep groves in the (b) (4) surfaces near the (b) (4)

Observation 5:

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.
Specifically,

a) Filling of (b) (4) Suspension in Workshop (b) (4) uses dedicated, (b) (4) product contact (b) (4) tubing during filling operations. The (b) (4) tubings are required to be replaced (b) (4) (b) (4) Media simulation studies in Workshop (b) (4) s performed with (b) (4) tubing, instead of (b) (4) tubing used to manufacture (b) (4) Suspension.

b) Operators are not required to disinfect their gloved hands prior to each removal of sterilized components from the LAF (b) (4) and installed into Workshop (b) (4) and (b) (4) filling lines. The sterilized components used for filling setup are taken out of the (b) (4) unwrapped and transported to the filling line (b) (4) LAF (b) (4)

Observation 6:

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically,

a) Operators performing critical (b) (4) interventions on aseptic filling lines in Workshops (b) (4) and (b) (4) are not monitored after completing the intervention on the Grade A filling line. For example,
   1) SOP # PO-3 112 005-012, SOP for Filling Operations of Workshop (b) (4) does not require monitoring of gloved hands after each allowed (b) (4) corrective interventions.
   2) SOP # PO-3 115 005-012, SOP for Filling Operations of Workshop (b) (4) does not require monitoring of gloved hands after each allowed (b) (4) corrective interventions.

b) The Grade A filling line in Workshop (b) (4) room (b) (4) used for filling product distributed to the U.S. market, (b) (4) Injection, is not monitored in the location where (b) (4) are exposed to the

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environment before filling. The location where an operator removes the [(b) (4)] of sterile [(b) (4)] and removes the [(b) (4)] from the [(b) (4)] for loading onto the filling machine, is not monitored by settle plates, [(b) (4)] air sampling, or nonviable particle monitoring.

c) The Grade A area where sterile stoppers are bagged by personnel in Workshop [(b) (4)] has settle plate and nonviable air monitoring which do not monitor the activity as the area is physically separated from the operations by [(b) (4)]

d) [(b) (4)] samples are not obtained at points of use.

1) [(b) (4)] used in [(b) (4)] Suspension compounding operations in Workshop [(b) (4)] is sampled from port # [(b) (4)] for testing [(b) (4)] microbial limit and bacterial endotoxin. The points of use for production of [(b) (4)] Suspension is Tanks # [(b) (4)] which are on a different pipe line. In addition, a section of the transport pipe to [(b) (4)] are made of [(b) (4)] tubing, whereas the path to the sample port is made of [(b) (4)]

2) [(b) (4)] used in compounding operations for [(b) (4)] Suspension in Workshop [(b) (4)] is sampled from port # [(b) (4)] and not at the point of use for tank [(b) (4)] approximately 14 feet from the sample site.

Observation 7:

Established test procedures are not documented at the time of performance.
Specifically, after incubation is completed of environmental monitoring samples and bioburden test samples, the first microbiologist performs the reads of all [(b) (4)] plates without documenting the results. Only after the second microbiologist performs review of the [(b) (4)] plates and an agreement is reach on the read result, is the results documented by the first microbiologist.

Observation 8:

All compounding and storage containers used during the production of a batch of drug product is not properly identified at all times to indicate contents or the phase of processing of the batch. Specifically,

a) Compounding tanks in Workshop [(b) (4)] used to manufacture [(b) (4)] Injection for U.S. distribution [(b) (4)] were not correctly labeled on 15 August 2023. The Compounding Tank [(b) (4)] in Workshop [(b) (4)] all had status labels dated 10 August 2023, which represented

cleaning that had occurred on the exterior of the tanks. The (b) (4) tanks did not have status label indicating clean status of the interior of the tanks.

b) The Grade A filling line in Workshop (b) (4) used for filling (b) (4) Injection, utilizes product dedicated (b) (4) tubing attached to . The tubing sets can be used for (b) (4) filling operations or within (b) (4) On 15 August 2023, two sets of dedicated filling tubes were found not uniquely identified as two sets were found with the same tubing identification, both coming from the same master tube roll.

Observation 9:

The batch production and control records are deficient in that they do not include documentation of the accomplishment of each significant step in manufacturing, processing, and holding.
Specifically,

a) Workshop (b) (4) tanks used for holding in-process sterile drug solutions (b) (4) have (b) (4) used for (b) (4) into the tanks. The (b) (4) had labels that documented number of uses, (b) (4) installation, (b) (4) model, batch number, replacement date, sterilization frequency, operator, and reviewer. After each use of the tank, the identification card on the (b) (4) with the above information is discarded and not documented elsewhere.

b) Workshop (b) (4) used for manufacturing (b) (4) Tablets has a tablet compression machine (Model (b) (4) that has no printing function for the electronic data generated during (b) (4) operations. The electronic data is backed up (b) (4) with potential to lose up to (b) (4) of data.

c) Workshop (b) (4) used for manufacturing (b) (4) Tablets has a (b) (4) used for (b) (4) solid drug (b) (4) The (b) (4) does not have automatic documentation of (b) (4) are documented (b) (4) Qualification by way of (b) (4) mapping is performed (b) (4) and calibration of (b) (4) probe is conducted (b) (4)