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 Industry Information: www.fda.gov/oc/industry	January 16-17, and 20-24, 2025
	FEI NUMBER 3003999190

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Lihong Lin, Corporate Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Xunqiao
CITY, STATE AND ZIP CODE Linhai, Zhejiang 317024, China	TYPE OF ESTABLISHMENT INSPECTED Drug Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION #1

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

1. Cleaning of non-dedicated (b) (4) used to manufacture US market products was not effective. There are (b) (4) non-dedicated (b) (4) used for US market products. The following was observed on cleaned equipment:

a. The non-dedicated GJC100-01 (b) (4) was not clean on January 16, 2025, immediately before it was intended to be used to manufacture batch (b) (4) of (b) (4) and (b) (4) Tablets USP (b) (4) mg (US market). The non-dedicated piece of equipment is used to manufacture (b) (4) different US market products.

Prior to batch (b) (4) the equipment had undergone "Type C" changeover cleaning on January 15, 2025, that should have removed all product from the previous batch. On the morning of January 16, 2025, a production operator had visually inspected the equipment for cleanliness and approved the cleaning without identifying any (b) (4) residues.

When the equipment was inspected later in the morning, after initial (b) (4) for batch (b) (4) had already started, visible residues were observed in the following locations:

i. (b) (4) and (b) (4) residues were observed in the (b) (4) duct and on the valve of the (b) (4) duct. Swab sampling detected the presence of (b) (4) and (b) (4) in this area.

(b) (4) was last manufactured December 21, 2024. Since that time, batches of (b) (4) Tablets, (b) (4) Tablets, (b) (4) Tablets, and (b) (4) and (b) (4) Tablets had been manufactured on this

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equipment.

This site was previously cited on an FDA 483 for failing to appropriately clean the (b) (4) ducts of the (b) (4) (b) (4)

ii. (b) (4) and (b) (4) residues were observed on equipment surfaces on the underside of the (b) (4) at the bottom of the product container. No sampling of this area was conducted before the equipment was cleaned.

iii. (b) (4) was observed on surfaces in the (b) (4) No sampling of this area was conducted before the equipment was cleaned.

iv. (b) (4) were observed on the surface of the (b) (4) zone. Swab sampling of this area detected (b) (4)

v. (b) (4) were observed in the chute that transfers product from (b) (4) to the (b) (4) Swab sampling of this area detected (b) (4)

vi. (b) (4) residues were observed on the rim of the product container. Swab sampling identified (b) (4) and (b) (4)

vii. (b) (4) residues were observed on the gasket between the product container and (b) (4) zone. Swab sampling identified (b) (4) and (b) (4)

viii. (b) (4) was observed on external surfaces of the equipment. No sampling of this area was conducted before the equipment was cleaned.

ix. During additional inspection of the equipment on January 20, 2025, the (b) (4) duct and valve were observed to have (b) (4) build-up on them.

b. On January 16, 2025, (b) (4) was observed on the (b) (4) valve on the (b) (4) of the cleaned (b) (4) GJC349-05. The investigation conducted by quality personnel was not going to include sampling of this visible

[redacted] or the area behind the [redacted] valve on the [redacted] duct. These areas were only swabbed after discussions during the inspection. When swab sampling of the [redacted] residues was conducted and tested against the previous product, no peak was identified.

On January 20, 2025, a buildup of [redacted] was observed on the [redacted] duct and valve for this piece of equipment.

c. On January 20, 2025, [redacted] residues were observed on the [redacted] valve on the [redacted] of [redacted] GJC348-05. The investigation conducted by quality personnel was not going to include sampling of this area. These areas were only swabbed after discussions during the inspection. When sampling was performed, the APIs [redacted] and [redacted] were detected.

There was also stagnant liquid in the [redacted] duct.

A buildup of [redacted] was observed on the [redacted] duct and valve.

Equipment surfaces on the top of the [redacted] also appeared to have [redacted] residues.

d. On January 20, 2025, [redacted] was observed on the surfaces of the [redacted] duct and valve of the [redacted] GJC350-05.

The [redacted] duct and valve was not sampled as part of the quality investigation before it was cleaned.

e. On January 20, 2025, [redacted] was observed on the surfaces of the [redacted] duct and valve on [redacted] GJC101-01.

During investigation sampling by quality personnel, [redacted] was detected in the [redacted] duct and valve.

2. Cleaning of non-dedicated [redacted] equipment used to manufacture US market products was not effective. There are [redacted] non-dedicated [redacted] used for US market products. On January 21, 2025, the following was observed on cleaned equipment:

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a. There appeared to be residues where the [(b) (4)] connect to the product bowl on [(b) (4)] GJC104, GJC105, and GJC106.

b. There appeared to be residues on the [(b) (4)] equipment and on the gasket of the door with the [(b) (4)] equipment on [(b) (4)] GJC105.

c. There were residues on equipment surfaces inside the [(b) (4)] equipment that surrounds the product drum on [(b) (4)] GJC104, GJC105, and GJC106.

d. There was buildup of unidentified material in the [(b) (4)] duct in [(b) (4)] GJC104, GJC105, GJC106, and GJC201.

e. It appeared that pieces of unidentified material from the [(b) (4)] duct had fallen onto the [(b) (4)] that attaches to the [(b) (4)] bowl on [(b) (4)] GJC104, GJC105, and GJC106.

3. Cleaning validation studies did not identify the hardest to clean areas of equipment. For example:

a. Cleaning validation for [(b) (4)] in Workshop [(b) (4)] Unit [(b) (4)] did not include sampling of difficult to clean areas like the bottom of the product [(b) (4)] surfaces in the [(b) (4)] gaskets, areas at the top of the [(b) (4)] or [(b) (4)] ducts to evaluate cleaning effectiveness.

b. Cleaning validation for the Workshop [(b) (4)] Unit [(b) (4)] was limited to two sampling points, including the product bowl and a [(b) (4)] It did not consider other difficult to clean areas including the [(b) (4)] the door of the [(b) (4)] surfaces within the equipment outside of the product bowl, or [(b) (4)] ducts.

OBSERVATION #2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

1. Smoke studies regarding Workshop [(b) (4)] used for aseptically filling [(b) (4)] Injection, USP

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(b) (4) mg, (b) (4) mL and (b) (4) mg (b) (4) mL vials for the US Market:

a. Air turbulence was observed for the following interventions:

i. Installation of (b) (4) for Stoppers

ii. Installation of Stopper Bowl into Line

b. The following dynamic interventions were not evaluated in the smoke studies:

i. The (b) (4) of stopper bags from Grade B onto the Grade A filling line platform, which occurs routinely during filling operations and up to (b) (4) bags at a time.

ii. The (b) (4) of stoppers into the (b) (4) with the remaining bags of previously (b) (4) stopper bags on the filling line platform. Stoppers are (b) (4) (b) (4) Smoke studies did not evaluate this entire intervention and how the airflow during stopper (b) (4) might be impacted by the remaining bags stored on the platform.

c. Smoke studies for dynamic (b) (4) intervention of (b) (4) Disassemble and Installation was performed with the smoke generator pointing down, in the same direction as the airflow. It was not performed with the smoke generated pointing perpendicular to the airflow.

2. Smoke studies regarding Workshop (b) (4) used for aseptically filling (b) (4) Injection, USP (b) (4) mg vial for the US market:

a. The dynamic (b) (4) loading of the (b) (4) vials into the (b) (4) was not evaluated as part of smoke studies.

b. Smoke studies for dynamic (b) (4) interventions were performed with the smoke generator pointing down, in the same direction as the airflow. It was not performed with the smoke generated pointing perpendicular to the

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airflow. These include:

i. Calibration of Scale prior to filling
ii. Calibration of Scale after being filled
iii. Adjustment of (b) (4)
iv. Adjustment of (b) (4)
v. (b) (4) Removing Vials at (b) (4)
vi. (b) (4) adjustment leading to (b) (4)

3. Smoke studies for Workshop (b) (4) and (b) (4) were performed using (b) (4) generated from (b) (4) There has been no evaluation of whether this produces neutrally buoyant smoke.

OBSERVATION #3
There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

1. The visual inspection qualification process for 100% manual visual inspection is deficient in the following ways:

a. The visual inspection kits for liquid vials do not contain glass, metal, elastomer material, and fiber of known size.

b. The visual inspection kits for liquid vials do not contain defect for precipitate (critical defect), group of particles (critical defect), smoke like particle deposit (critical defect), protein floccule (critical defect), appearance defect with impact on container closure system (critical), and significant appearance (b) (4) (major defect), which are defect categories listed in the visual inspection record of each batch. There is no assurance operators can adequately identify these type of defects, where applicable, during manual visual inspection process.

c. The visual inspection kits for (b) (4) vials do not contain defect vials for (b) (4) (critical defect), (b) (4) (b) (4) (major defect), and (b) (4) (major defect), which are defect categories listed in the visual inspection record of each batch.

d. There is no complete defect library containing all defects for the liquid and (b) (4) vials.

e. Visual inspectors are required to be able to identify the defect vials during qualification and record the vial number in the corresponding defect row (such as critical, major, minor). The qualification records do not indicate what specific defect (such as glass, metal, etc.) was observed for each of these vials.

f. There is no answer key for the current set of liquid test kits used to qualify operators for 100% visual inspection. After the most recent visual inspection qualification, the vial numbers were changed, but there is no record identifying which vial contains what defect after the change.

2. The (b) (4) used during visual inspection of sterile liquid drug products distributed to the US market in workshop (b) (4) is not qualified. The original qualification performed in 2018 required a two-stage qualification. The second stage of the qualification has never been performed, and to date, there is no active protocol or schedule to complete Stage 2.

Additionally, prior to use of this equipment for commercial batches, a pre- and post- rejection test, using standard vials, is required to be performed. These standard vials do not contain glass, metal, elastomer material, and fiber of known size.

3. Acceptable ranges have not been established for operating the tablet compression machines. Examples include, but are not limited to (b) (4) Tablets and (b) (4) Tablets for the US market:

a. Studies have not been completed to establish the reject rates used during compression of tablets. There are no limits set in batch records and there is no process for setting the reject limits described in procedures used by the compression operators. Additionally, the operators have the ability to change the values for reject limits for each batch and to make changes during the batch. There has been no review of the electronic data to see what values were used during US market batches and to evaluate whether these values would have appropriately rejected non-conforming tablets.

b. Acceptable ranges for compression machine parameters that the operators can change have not been established. For example: feeder speed, fill depth, or target main compression force.

4. During process validation, sampling plans have not been established that would allow for evaluation of variation that could be caused by different parameters used to operate equipment or evaluate variability within a batch. For example:

a. Different compression speeds were used during process validation studies for (b) (4) Tablets and (b) (4) Tablets to establish acceptable ranges for commercial batches. Tablets manufactured at the different speeds were not separately sampled and tested to evaluate whether the different speeds led to variability within the batch.

b. During (b) (4) Tablets process validation, (b) (4) sampling was used for (b) (4) during the (b) (4) compression, (b) (4) and finished product testing stages (b) (4) content testing during (b) (4) Tablets process validation was based on (b) (4) sampling.

OBSERVATION #4
There is a failure to thoroughly review any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

1. Deviation DF-23012 was opened when foreign matter was observed in (b) (4) of batch (b) (4) of (b) (4) Tablet (b) (4) mg (US Market). The batch was rejected. The investigation failed to perform any identification of the foreign matter or take any pictures. During the investigation, foreign matter similar in appearance was observed in the (b) (4) duct of the (b) (4) GZ5029. The area was cleaned without any analytical evaluation of the observed residues and no pictures were taken.

The investigation did not thoroughly assess whether contamination in this area could have impacted other batches made on this equipment. Additional batches made as part of the same campaign were not thoroughly inspected for the presence of foreign particles.

The investigation was not expanded to inspect the (b) (4) ducts and document findings in other (b) (4) (b) (4) used for the US market products.

The cleaning procedures were not reevaluated to consider cleaning of this area during changeover between

products. The area is cleaned during maintenance [(b) (4)] but there is no requirement for the maintenance personnel to document if they observe residues during maintenance activities.

2. Complaint investigation CF-23274 was opened when a customer obtained an OOS for dissolution on [(b) (4)] and [(b) (4)] Tablet [(b) (4)] mg batch [(b) (4)] (EU market). The OOS was confirmed during testing of retain samples. The investigation identified higher main compression force during tableting, which had no established limits, as well as increased disintegration times during storage. The cause of the higher compression force was identified in the investigation as batch to batch variation, without further investigation of causes for the variation.

The investigation was not extended to US market tablet products, which similarly had no established ranges for main compression force, to determine whether portions of batches were subject to variation leading to higher compression forces that could have produced non-conforming tablets.

3. Investigation OOT-FQC22020 was opened during stability testing of process validation batches of [(b) (4)] Tablets for the US market at the [(b) (4)] timepoint. The product is labeled with a [(b) (4)] expiration date and has a specification for unknown impurities of not more than [(b) (4)]%. Batch [(b) (4)] had a result of [(b) (4)]% and batch [(b) (4)] had a result of [(b) (4)]% for unknown impurities. The production investigation identified inter-batch variability as the result of higher impurities in these batches, but failed to understand what was causing this variation or what caused the impurity to form. The investigation did not thoroughly evaluate whether a [(b) (4)] expiration date was appropriate for ongoing commercial manufacturing given this data and the lack of understanding of the cause of variability that generated this impurity.

A different unknown peak has been detected in some [(b) (4)] Tablets stability batches. For example, batches [(b) (4)] and [(b) (4)] each had a result of [(b) (4)]% at [(b) (4)] compared to a specification of not more that [(b) (4)]%. The peak was attributed to an excipient, but the specific excipient was not identified. No investigation evaluated why this peak is not detected in all stability batches if it is coming from an excipient, which should be present in all batches.

4. Investigation OOS-FQC23008 was opened for a content uniformity OOS result for batch [(b) (4)] of [(b) (4)] Tablets (US market). The batch was rejected. The investigation concluded the operators did not properly

reject tablets at the end of the batch, resulting in lower assay results for tablets at the end of the batch, which caused the failure. No confirmatory testing of tablets from the end of the batch was conducted to support this conclusion. The investigation concluded the incident was isolated to this batch.

Another batch in the campaign (b) (4) had a content uniformity stage one AV of (b) (4) and stage two of (b) (4) compared to an AV limit not more than (b) (4) This was higher than historical data. The investigation included additional (b) (4) testing for this batch, but no testing specific to the end of the batch to evaluate whether a similar incident had occurred.

OBSERVATION #5

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

On 16-Jan-2025, a 2 x 126 cm piece of non-sterile tape was observed between (b) (4) sharing (b) (4) These sit below the HEPA filters and above where empty vials enter the line from the (b) (4) (b) (4) before being aseptically filled within Workshop (b) (4) The tape was placed between these (b) (4) to seal an approximate 3mm gap, which was observed sometime after the HEPA filters had been replaced around April 2024. This aseptic filling line is used to fill (b) (4) Injection (b) (4) mg) for the US Market.

1. There is no record documenting when the gap was observed, who it was observed by, and if the gap was reported to the appropriate department including the Quality Unit. No investigation and subsequent CAPA plan into the cause of the gap has been made.

2. There is no record documenting the approval and use of the non-sterile tape to seal the gap within the Grade A filling line, and there is no workorder or documentation detailing the installation, and subsequent replacement (if performed) of the tape.

3. An assessment was not performed to evaluate how the gap between the HEPA filter (b) (4) in the aseptic filling line and the use of the non-sterile tape within the area might impact airflow, cleaning, environmental monitoring, and product quality.

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OBSERVATION #6

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.

Analytical method validation studies have not included forced degradation studies for methods used for stability testing. For example, the US market products: (b) (4) Tablets (b) (4) and (b) (4) Tablets, (b) (4) and (b) (4) Tablets, (b) (4) Tablets, and (b) (4) Tablets.

OBSERVATION #7

The quality control unit lacks authority to review production records to assure that no errors have occurred.

1. Procedures for audit trail reviews for production equipment have not been established:

a. Production operators can make changes to compression settings. Quality personnel do not review audit trails that document parameters and changes.

b. Production personnel can make changes to recipes for production and (b) (4) in the Workshop (b) (4) Quality personnel do not review audit trails that document this information.

2. (b) (4) GJC100-01 and GJC101-01 do not have an audit trail, do not save data, and requires personnel to manually input operating parameters for production and (b) (4) There is no quality unit verification of the manually entered information.

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