DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Use this check box to generate the required 483 statement on page 1 for medical device observations. ☐

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	11/12-20/2024
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Ms. Lihong (Linda) Lin, Vice President of Quality

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Taizhou Zhejiang, 317016, China	API 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 (I) (WE) OBSERVED:

OBSERVATION 1

Laboratory records do not include complete test data derived from all tests.

Specifically,

A. There is no documentation of raw test data relating to equipment cleaning samples (swab and rinse) test solution preparation. For example,

Your analytical test procedures for detection of residual active components by UV Spectroscopy and TOC has series of steps such as (b) (4) for the preparation of cleaning samples test solution, however your Quality Unit has not established any system in the form of logbook or worksheet for documenting cleaning test solution preparation. Thereby, your QC Engineers (Analysts) have never documented cleaning test solution preparation pertaining to all APIs and intermediates tested in your QC laboratory.

According to your Quality Assurance Manager, about (b) (4) % of cleaning samples are tested using UV Spectroscopy and about (b) (4) % of cleaning samples are tested by TOC method for which there is no documentation relating to cleaning samples test solution preparation. Thereby, there is no assurance over reliability of cleaning samples test result and laboratory OOS investigations relating to cleaning samples failures. There is a potential for carryover and cross-contamination of residual actives, impurities, and degradants between APIs and intermediates that are manufactured using shared (non-dedicated) equipment at your site. This issue is applicable to all APIs and intermediates that are manufactured at your site including the ones for the U.S. market.

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Your Quality Unit has deviated from the following procedures for not documenting the test solution preparation:

SOP No.: SOP QC-021-19, Titled: "Recording and Review Procedure for Laboratory's Record", Version:19, Effective date: June 30, 2024, Section 3.1 relating to QC Analyst responsibilities to "Ensure that the test records are written in a timely, accurate manner". Additionally, your QC Reviewers, Supervisors/Chemist, Laboratory Manager and QA also deviated from their responsibilities (sections 3.2 to 3.5) to ensure reliability of test results in the absence of raw test data. Furthermore, other sections but not limited to sections 5.2 – regarding general requirement for record writing, 5.3.7 – regarding documentation requirement for reference standards, 5.3.9 – regarding documentation requirement for test solutions (liquid, solution and samples) preparation, 5.3.11 – regarding documentation requirement for calculations, 5.4 – regarding review of the testing.

SOP No.: SMP-035.05, Titled: Data Integrity Management System, Version: 05, Effective date: November 30, 2023, section 3.1 relating to ALCOA++ General principle for Data Integrity.

B. There is no documented test procedure established to include details pertaining to diluent preparation, stepwise instructions for cleaning samples (swab and rinse) test solution preparation, and reference standard preparation for (b) (4) and (b) (4) APIs that are commercialized into the U.S. market. Similarly, there are no cleaning solution test procedures established for (b) (4) and (b) (4) APIs that were manufactured using non-dedicated equipment for registration purpose into the U.S. market.

OBSERVATION 2

Deviations from analytical test procedures are not investigated.

Specifically,

A. Your Quality Control Unit deviated from equipment cleaning samples (swab and rinse) test procedures for APIs and intermediates by not preparing and testing reference standard solutions to ensure system suitability

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and linearity for UV Spectroscopy and TOC prior to testing cleaning test sample solutions. This deficiency is applicable to testing of cleaning samples of all APIs and intermediates using UV Spectrometry and TOC for the U.S. market.

B. Your Quality Unit deviated from equipment cleaning samples (swab and rinse) test procedure by utilizing "E value" (UV extinction coefficient) method to calculate test results instead of linear equation calculation which is required per your analytical cleaning samples test procedures. For example,

Per your Test Procedures QS-C054, and QS-C006 for [redacted] (b) (4) API and its intermediate for equipment cleaning solution, linear equation calculation should be used to calculate cleaning solution test results by UV Spectroscopy. However, your QC Engineers (Analysts and Reviewers) utilized general procedure SOP QC-048, titled: "API production cleaning solution testing practices" to calculate test results by "E value" calculation. Per your QC Deputy Director, results calculated through "E value" and linear equation would not be the same.

Moreover, your QC Engineers bypassed testing [redacted] (b) (4) different concentrations reference standard preparations to establish linearity plot of UV Spectroscopy system prior to testing cleaning samples. In the absence of linearity value, your QC Engineers used E value that was established through linearity plot based on [redacted] (b) (4) different concentration reference standard during analytical test method validation corresponding to each API several years ago. Thereby, cleaning sample test results calculated for all APIs and intermediates are unreliable due to not establishing UV Spectroscopy performance and linearity to ensure accuracy of UV Spectroscopy measurement. This deficiency is applicable to all APIs and intermediates for the U.S. market.

OBSERVATION 3

Laboratory investigations are not adequately conducted to determine the root cause.

Specifically,

Your Out-of-Specification (OOS) investigations for equipment cleaning samples (rinse and swab) failures does not include scientific justification supported with documented evidence for the probable root cause based on which the

investigations were closed. For example,

A. OOS investigation numbers: OOS-CQC 22149, OOS-CQC 150, and OOS-CQC 151, date initiated: December 13, 2022, description of OOS event: (b) (4) cleaning solution batch were not within acceptance limit criteria for TOC test. The following results were obtained:

- For OOS-CQC 22149, Batch number (b) (4) Result: (b) (4) mg/L, Acceptance Limit: < (b) (4) mg/L, Sample type: Rinse sample, Equipment detail: (b) (4) ID: (b) (4)
- For OOS-CQC 22150, Batch number: (b) (4) Result: (b) (4) µg/cm2, Acceptance Limit: < (b) (4) µg/cm2, Sample type: Swab sample, Equipment detail: (b) (4) ID: (b) (4)
- For OOS-CQC 22151, Batch number: (b) (4) Result: (b) (4) µg/cm2, Acceptance Limit: < (b) (4) mg/L, Sample type: Swab sample, Equipment detail: (b) (4) ID: (b) (4)

Your Quality Unit determined the probable root cause for failing test result was due to the use of new TOC sample bottle. We observed the following deficiencies in these OOS investigations:

1) There were (b) (4) cleaning samples (swab and rinse) analyzed using TOC. During your Phase I (laboratory) investigation, your firm failed to determine that the raw test data pertaining to cleaning sample solution preparation, along with calculations used for calculating test results were not documented for all samples tested using TOC. In the lack of documented raw test data, there is no assurance over the reliability of reported test results for all samples.
2) There was no simulation experiment conducted to scientifically prove whether the above three (3) cleaning samples failed to meet acceptance limit was due to the use of new TOC sample bottle.

As a result of the deficiencies mentioned above and categorizing the root cause due to laboratory error, your firm did not reclean equipment (b) (4) and (b) (4) and continued to use them in the manufacturing of APIs.

B. OOS investigation number: OOS-COC 24011, date initiated: January 30, 2024, description of OOS event: (b) (4) cleaning solution batch (b) (4) was not within acceptance limit criteria for TOC test.

Result: (b) (4) mg/L, Acceptance Limit: ≤ (b) (4) mg/L. Sample type: Rinse sample.

Your Quality Unit determined the probable root caused was due to production operator kept stopper of sampling flask on the ground before sampling and thereby contaminated cleaning solution from the stopper. We observed the following deficiencies:

1) During your Phase I (laboratory) investigation, your firm failed to determine that the raw test data pertaining to cleaning sample solution preparation, along with calculations used for calculating test results were not documented for all samples tested using TOC. In the lack of documented raw test data, there is no assurance over the reliability of reported test results for all samples.
2) There is no documentation of total number of samples collected by the operator and impact of his sample collection technique on other cleaning samples test result reliability.

As a result of the deficiencies mentioned above and categorizing the root cause to production operator's sample collection technique, your firm did not reclean the equipment and continued to use them in the manufacturing.

OBSERVATION 4

Deviation investigation relating to facility, equipment and production are not always investigated.

Specifically,

On November 12, 2024, we observed a total of about 101 issues documented on 2 separate spreadsheets stored on the local drive of your IT Supervisor's laptop for the issues related to rusted, leaking and disrepair state of some of manufacturing equipment along with documentation of potentially raw data relating to (b) (4) stage on a piece of yellow colored uncontrolled paper among some other issues which were reflective of the lack of Good Documentation Practices and Data Integrity concerns. Most of these issues were supported with pictures taken by your IT Supervisor.

On November 12, 2024, your IT Supervisor stated that upon discovering significant GMP issues during his visit of production workshops on September 23, 26, 27 and October 18, 2024, he took pictures and documented the issues on two (2) separate uncontrolled spreadsheets. Further, according to him the issues were reported to the respective production workshop management personnel. However, your production unit did not communicate any of the

observed issues to QA department and there was no deviation investigation conducted.

Upon discussing the observation, your firm initiated deviation investigation (DC-24144) on November 12, 2024 and closed this investigation on November 14, 2024 without determining the root cause for each of the issues reported by IT Supervisor. There was no documented interview of the personnel involved and there was no risk and impact assessment was performed. Additionally, there was no corrective action and preventative action (CAPA) taken by your firm to ensure employees are trained and adequate procedures as required are established.

On November 19, 2024, we evaluated some of the issues from the pictures (taken by your IT Supervisor) and observed integrity of your manufacturing data is not always maintained. For example,

Your production operator potentially recorded (b) (4) step raw data in the form of numbers on a piece of yellow colored uncontrolled paper and placed it between pages inside a batch manufacturing record (BMR), page 53 of 57 relating to the process validation of (b) (4) API in workshop (b) (4) batch number: (b) (4) The information on page 53 of 57 was found not written in respective columns when it was observed by IT personnel on September 23, 2024. However, the verification of BMR on November 19, 2024 revealed the information documented in BMR was on September 24, 2024. This is reflective of the inconsistencies in contemporaneously documenting the information.

Furthermore, raw data handwritten in black color ink pen on a piece of scrap paper varied from the raw data handwritten in black color ink pen on this BMR. Six (6) out of seven (7) numbers on a piece of scrap paper appeared to be (b) (4) whereas the numbers found handwritten in black color ink pen on BMR were (b) (4) and (b) (4)

OBSERVATION 5

Lack of Quality Unit oversight to ensure integrity of test data and document management.

Specifically,

A. On November 14, 2024, we observed (b) (4) cleaning samples (rinse and swab) mainly relating to product changeover and cleaning validation were pending for testing in your QC laboratory. These equipment

cleaning samples were received in your QC laboratory for testing between October 29 to November 14, 2024. Even after repetitively discussing observations and expressing concerns over the lack of test data reliability in the absence of raw test data relating to documentation of cleaning test solution preparation along with not verifying the UV Spectroscopy and TOC equipment performance through reference standards (refer to Observations 1A and 2A), on November 18, 2024, we observed your QC Deputy Director and QA Senior Director allowed your QC Engineers (Analysts) to keep on testing cleaning test samples without documenting diluent preparation, test solution preparation, and without establishing linearity curve through series of different concentration reference standards to evaluate system suitability and performance of UV Spectroscopy and TOC.

Further, the Production Unit of your firm continued to keep manufacturing APIs and intermediates utilizing most of equipment without confirming if the (b) (4) cleaning test samples would meet the acceptance limit or not.

B. Your Quality Unit lacked oversight on destruction of documents using shredder. For example, on November 12 and 13, 2024, we observed white shredded pieces of documents inside the shredder located in QC documentation room of your west direction QC building. Your firm identified type of documents destroyed using shredder were GMP and non-GMP documents. Your firm maintains similar shredding machine inside production, technical, and process engineering departments among other non-GMP areas (administrative and finance department) of your facility. There is no oversight from your Quality Assurance department on controlling and management of GMP documents that are potentially shredded using the shredders located inside these departments.

OBSERVATION 6

The master batch production record lacks an established time limits and detailed production instructions to ensure the quality of intermediates and APIs are met for individual processing steps and/or total process.

Specifically,

Your firm failed to establish and document a specific speed range in the Batch Manufacturing Record (BMR) for

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the (b) (4) steps in the manufacturing process of (b) (4) and (b) (4). Your firm has minimum time requirements for (b) (4) and (b) (4) steps during the manufacturing process, but failed to document at what (b) (4) speed these steps were occurring, even when the speed could be manually adjusted by your operator through knobs and buttons. A total of (b) (4) located in workshops (b) (4) and (b) (4) were observed with speed adjustment capabilities, and all were adjusted by the operators at random operational speeds. Since the (b) (4) speed can be changed and it is not being documented on the BMR this can cause variability from batch to batch. Since July 2021 a total of (b) (4) lots of (b) (4) lots of (b) (4) and (b) (4) lots of (b) (4) were manufactured with no (b) (4) speed documented in the BMR. All lots are within their retest period.

Similarly, your firm failed to establish a minimum (b) (4) time and record the speed and time in which the (b) (4) process for (b) (4) and (b) (4) in the Batch Manufacturing Record. Your firm established that (b) (4) or all these products will continue until a visual inspection by the operator determines that no more solvent is being removed by (b) (4) This can cause variability from batch to batch since the time of (b) (4) can be arbitrary.

On November 13, 2024, while performing an inspectional walkthrough during the (b) (4) step of (b) (4) Batch Number (b) (4) we asked the operator to inspect the (b) (4) step and to informed us how much time the (b) (4) had to be continued before finishing the step, and he responded (b) (4) At the same time, we asked the workshop director to inform us how much more time the (b) (4) needed to continue, and he responded (b) (4) Your firm (b) (4) process end time is subjective to the operator discretion and not by a scientifically measurable limit or range established on your BMRs. Your BMRs documents the start of the (b) (4) process but does not record the (b) (4) end time for the (b) (4) and (b) (4) manufacturing process.

Furthermore, (b) (4) has (b) (4) operational speeds (b) (4) used in (b) (4) purification step, (b) (4) purification step and (b) (4) step. The speed in which the (b) (4) operates is not documented even when it can be changed by the operator. Since July 2021 a total of (b) (4) lots of (b) (4) and (b) (4) lots of (b) (4) were manufactured with no minimum (b) (4) time and no end time or speed recorded in the BMRs. Since July 2021 a total of (b) (4) lots of (b) (4) were manufactured with no minimum (b) (4) time requirement or speed recorded in the BMRs. All

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lots are withing their retest period.

These issues pertaining to not establishing control for speed (b) (4) and minimum time requirements is applicable for all manufacturing equipment throughout your facility thereby there is no assurance over your process validation to ensure safe and effective APIs and intermediates are manufactured consistently each time.

OBSERVATION 7

Equipment used in the manufacture of intermediates and APIs should be maintained in a good state of repair to prevent contamination that would alter the safety, identity, strength, quality and purity of the drug product.

Specifically,

During the inspectional walkthrough, on November 12, 2024 we observed that your firm failed to maintain equipment used in the manufacturing of APIs and intermediates in a good state of repair. For example, your (b) (4) located inside workshop (b) (4) and used in the manufacture of (b) (4) and (b) (4) had (b) (4) material flaking out with some missing pieces of (b) (4) at the (b) (4) piping. Your firm's equipment preventive maintenance records (PMs) show that a preventive maintenance check was performed on (b) (4) and (b) (4) for (b) (4) respectively and this deficiency was not addressed. The condition of the (b) (4) material is not inspected as part of your firm's preventive maintenance record. Since November 2023, a total of (b) (4) lots of (b) (4) lots of (b) (4) and (b) (4) lots of (b) (4) were manufactured using this equipment and all U.S. marketed lots are currently within their respective retest date.

OBSERVATION 8

The procedure for collecting cleaning samples from the manufacturing equipment is deficient.

Specifically,

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While performing an inspectional walkthrough of Workshop (b) (4) Building (b) (4) on November 19, 2024 your firm officials explained that for the Cleaning Validation of (b) (4) (ID: XVII-204) and (b) (4) (XVII-309) swab samples were collected by production operators going physically inside of the equipment due to the distance of the swabbing locations from the equipment access point (b) (4) Upon review of (b) (4) Cleaning Validation Protocol in Workshop (b) (4) Document Number: CVC-20036(P) we observed that there is no documented protocol on how your operators will physically enter this equipment without compromising the integrity of the equipment cleaning and its qualification. Your cleaning validation does not describe if there is a gowning requirement for the operators or provide sufficient detailed instructions to determine the specific swabbing location once inside the equipment.

Your firm cleaning validation protocol is deficient on identifying a potential cross contamination by the operator during the sampling process. Your operators are entering inside the equipment from a room that has not been evaluated for cleanliness and this practice can potentially further contaminate the cleaned equipment that will be sampled and then used in the manufacturing process of your APIs. Since January 2023, a total of (b) (4) lots of (b) (4) were manufactured using both the (b) (4) (ID: XVII-204) and (b) (4) (XVII-309). All lots are currently within their respective retest date in the U.S. market.

N/A PSU 11/20/2024

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."