DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	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:

QUALITY SYSTEM

OBSERVATION 1

The change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate. Specifically,

a) you do not always conduct a formal risk assessment for critical changes to evaluate the potential impact of proposed changes on the quality of intermediates or APIs. Critical Change Request PCRC-11025 was initiated November 27, 2011 and closed November 29, 2011, for the stated purpose of making changes to the (b) (4) manufacturing process to (b) (4) the current (b) (4) ((b) (4) % - (b) (4) %) of the known isomer impurity (b) (4) (b) (4) in the final API and (b) (4) batch yields (current batch yield (b) (4) - (b) (4) per batch).

i) you did not conduct and document a formal risk assessment for Change Request PCRC-11025 to evaluate the potential impact of proposed changes on the quality of the intermediates or the final API for this critical change to your validated manufacturing process prior to your quality unit approving the change.

ii) you hired an outside laboratory to conduct a small lab scale research project. Based on the results of a lab scale research project you initiated validation on a commercial scale to change your validated manufacturing process without conducting pilot scale or other small scale batches. Your Deputy Director of Manufacturing stated you have commercial experience and since you only changed the (b) (4) there was no need to conduct pilot scale trial batches before instituting critical changes on a commercial scale.

You initiated validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to your validated manufacturing process on the quality of intermediates and APIs. You do not have a quality agreement with the outside laboratory you used to perform a lab scale research project requiring (prior to initiating testing and reporting results): qualification of all instruments used to conduct tests; validation of all software used with qualified instruments to conduct tests; calibration of all applicable measurement devices against traceable standards prior to use; use of official standards as appropriate; if applicable, establishing system suitability prior to testing samples and processing data; and validation of all test methods used for testing.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Cheryl Clausen	Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018 FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

b) you do not have an adequate change control system requiring scientific judgement to determine what additional testing and validation studies are appropriate to justify changes to a validated manufacturing process. You do not always have data to support approval of changes to validated processes.

i) You did not identify specific parameters and specify acceptance criteria for those parameters prior to implementing changes, as part of critical Change Request PCRC-11025, to use to evaluate if the implemented changes (b) (4) the isomer (b) (4) of (b) (4) and (b) (4) the batch yield.

ii) Additional testing requirements associated with critical changes are not always based on sound scientific judgement. Change Request PCRC-11025 included changing (b) (4) in your validated manufacturing process. Additional testing requirements associated with these changes were limited to three validation batches and a commitment to conduct additional testing on (b) (4) batches a (b) (4)

c) you do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process. You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File (b) (4) USP (Process (b) (4) DMF# (b) (4) dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File (b) (4) USP (Process (b) (4)) DMF# (b) (4) contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change.

d) written change control procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit. Your quality unit does not always follow your written procedure for change control. Your written procedure Change Control System SMP-018.05 effective December 30, 2017 section 5.3.6 (3) specifies QA shall reject the change if the action cannot meet predetermined expectations. Critical Change Request PCRC-11025 did not include acceptance criteria with predetermined expectations. (b) (4) Product Development Report-01 dated April 13, 2012 Table 8 includes (b) (4) isomer impurity (specification < (b) (4) %) from three batches manufactured according to the validated manufacturing process (results range from (b) (4) % - (b) (4) %) and Table 10 includes (b) (4) isomer impurity from the three

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

validation batches manufactured using a different (b) (4) (results range from (b) (4) % - (b) (4) %). The product development report is silent regarding evaluation of the ability of the implemented changes to (b) (4) isomer (b) (4) (b) (4) Product Development Report-01 did not compare the batch weights from batches manufactured immediately before the change to the validated manufacturing process and the first batches manufactured after implementing changes to the manufacturing process.

OBSERVATION 2

Validation of production processes, cleaning procedures, analytical methods, and in-process control test procedures are not always adequate. Specifically,

a) your manufacturing processes are not always capable of consistently producing final products meeting all product quality specifications. Deviation No. DCB18-17017 was initiated for OOS genotoxic impurity (b) (4) (b) (4) ppm (specification < (b) (4) ppm) in (b) (4) batch (b) (4) Repeat test results included OOS results. As a corrective action you reprocessed (b) (4) batch (b) (4) by (b) (4) the (b) (4) step in your manufacturing process. You did not investigate corrective actions to your manufacturing process or to the manufacturing batch record to improve product consistency and manufacturing reproducibility, and to reduce the level of (b) (4) in the (b) (4) intermediate crude. You did not develop a prevent action plan to prevent future OOS (b) (4) levels in the intermediate crude and final API.

Between December 16, 2016 and August 22, 2017 you initiated 17 OOS investigations for (b) (4) impurity in (b) (4) Of the 17 OOS investigations initiated for (b) (4) impurity in (b) (4) you attributed 13 OOS results to lab related errors, 5 OOS results to production errors, and 2 OOS results to a combination of lab and production errors. You reprocessed all 17 (b) (4) batches you investigated for OOS (b) (4) impurity.

b) written validation protocols are not always adequate.

i) Your Process Validation Protocol for (b) (4) Process (b) (4) Workshop (b) (4) CNVP-11-075 and Process Validation Protocol for Crude (b) (4) Step (b) (4) PVC-18012(P) do not include the specific parameters with acceptance criteria to establish your manufacturing process is not only consistent and reproducible but able to fulfill the purpose for changing your validated manufacturing process.

ii) Neither Process Validation Protocol for (b) (4) Process (b) (4) Workshop (b) (4) CNVP-11-075 nor

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018 FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	**TYPE OF ESTABLISHMENT INSPECTED**
Linhai, Zhejiang Province 317016 China	manufacturer

Process Validation Protocol for Crude (b) (4) Step (b) (4) PVC-18012(P) specified the number of manufacturing batches to be manufactured as part of validation of your manufacturing process or discussed the number of validation batches to manufacture based on the complexity of the process or the magnitude of the process change.

iii) Neither Process Validation Protocol for (b) (4) Process (b) (4) Workshop (b) (4) CNVP-11-075 nor Process Validation Protocol for Crude (b) (4) Step (b) (4) PVC-18012(P) included a sampling plan designed to demonstrate the consistency and reproducibility of your manufacturing process through batch uniformity data.

c) you do not always initiate investigations during process validation. (b) (4) process validation batch (b) (4) est results for Diastereo-isomer (b) (4) % (specification < (b) (4) %) were OOT (Out-of-Trend) compared to the other (b) (4) validation batches with Diasterio-isomer results ranging from (b) (4) % to (b) (4) %. You did not initiate an investigation to identify the CPP(s) (Critical Process Parameter), non-critical process parameter(s), raw material(s), or other influences which could impact Diastereo-isomer results in an effort to improve the quality and consistency of (b) (4) (the product from the (b) (4) synthesis step in the manufacture of (b) (4) .

d) you do not have sufficient data to demonstrate your in-house test methods, used for Assay and Related Substance testing of (b) (4) are at least equivalent to USP Monograph test methods. (b) (4) USP Method and In-house Method Qualification Comparison Research Report VLDor-10-099 (R) version 2 effective August 29, 2014 does not include data showing you tested known concentrations of (b) (4) and spiked (b) (4) samples and then compared the results from your in-house test method with results from tested known concentrations of (b) (4) and spiked (b) (4) samples using the USP method to verify your in-house test results at least meet the acceptance criteria of the USP methods.

e) you do not have validated cleaning procedures. Cleaning procedures for (b) (4) -203-1 and (b) (4) 204-3 in workshop (b) (4) used in the manufacture of crude (b) (4) are not validated in that you do not have data to demonstrate the cleaning procedure is effective following manufacture of (b) (4) consecutive batches. The most recent cleaning validation study, CVD-18015 (R), approved in July 2018, is based on (b) (4) consecutive batches. The 2016 equipment use log for (b) (4) -203-1 shows (b) (4) consecutive batches were manufactured before cleaning. The 2016 equipment use log for (b) (4) -204-3 shows (b) (4) consecutive batches were manufactured before cleaning. Your Quality Assurance Director verbally confirmed no rinse samples were analyzed following either of these cleanings.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	CAC	Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

OBSERVATION 3

The system for managing quality to ensure confidence that the API will meet its intended specifications for quality and purity is not adequate in that your quality unit lacks written procedures and the authority and responsibility to ensure all critical deviations are thoroughly investigated. Specifically,

a) you release finished APIs manufactured from crude intermediates with OOS levels of genotoxic impurities without conducting a thorough investigation. Deviation No. DCB18-17025 initiated December 13, 2017 and closed April 16, 2018 was initiated for OOS (b) (4) impurity (b) (4) ppm (specification < (b) (4) ppm) in (b) (4) batch (b) (4) You identified the root cause as an equipment failure which impacted intermediate crude (b) (4) batch (b) (4) during (b) (4) You reprocessed (b) (4) batch (b) (4) Intermediate crude (b) (4) batch (b) (4) was also used in (b) (4) API final batch (b) (4) You did not reprocess batch (b) (4) made from OOS intermediate crude (b) (4) batch (b) (4) . You did not open an investigation, or conduct additional testing on batch (b) (4) Your QA Director stated batch (b) (4) met the product release specification for Related Substance (b) (4)

b) major Deviation DD (b) (4) 17003 was initiated August 2, 2017 and closed September 11, 2017 for (b) (4) batches (b) (4) and (4) with OOS results for a single unknown impurity (specification < (b) (4) %). You confirmed OOS results for (b) (4) batches (b) (4) single unknown impurity (b) (4) %, and (b) (4) single unknown impurity (b) (4) %.

i) you did not identify a root cause for the single unknown impurity results in batches (b) (4) and (b) (4) You stated the root cause was probably due to occasional fluctuation in your manufacturing process. You did not attempt to identify this single unknown impurity. You did not attempt to identify the source of fluctuations in your manufacturing process for (b) (4) .

ii) you did not develop an adequate Corrective Action and Preventive Action (CAPA) plan. The CAPA you listed on Deviation Investigation Report Form for Deviation DD (b) (4) 17003 included: discarding both batches, and following-up on the next (b) (4) batches to see if a similar issue occurs. You did not review your manufacturing process and manufacturing batch records to determine if your manufacturing process and manufacturing batch records could be revised to reduce process variation. You did not interview employees to determine if employees consistently and reproducibly follow your manufacturing instructions.

iii) you did not conduct a thorough risk assessment. Your risk assessment consisted of answering (b) (4) generic

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
		Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

questions: yes, no, or NA (Not Applicable). Deviation DD(b) (4) 17003 investigation did not include documentation showing a more thorough risk assessment was conducted by your risk management team. Your written procedure for Quality Risk Management SMP-023.03 effective November 1, 2017 section 7.1.3 specifies a risk management team should be established when solving major risk issues, and section 7.1.5 of the same procedure specifies to select different tools according to the risk category. Quality Risk Management SMP-023.03 section 8.3 specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not specify which risk management methods and tools to use in association with specific deviation categories.

c) you do not always thoroughly document investigations. your written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018 section 6.4.2 specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP-17.04 effective May 30, 2016). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

d) you do not always thoroughly investigate deviations before closing the deviation. Deviation DCB02-17002 was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification (b) (4) %) (b) (4) intermediate (b) (4) batches (b) (4) (b) (4) %) and (b) (4) (b) (4) %). The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) (b) (4) is an in-process impurity observed in other batches but at levels not more than (b) (4) %. You did not identify a root cause. Your corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity. You did not develop a preventive action plan. You did not identify the single unknown impurity. You reprocessed (b) (4) intermediate (b) (4) batches (b) (4) and (b) (4) and assigned the reprocessed batches final API batch numbers (b) (4) and (b) (4) You then closed the investigation without identifying the single unknown impurity.

e) you do not always follow your written procedures. Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature. You classified Return No. RC-18006 as not quality related for (b) (4) batches (b) (4) and (b) (4) returned for not complying with customer PSD specifications, a

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	CAC	Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018 FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

physical feature. The Treatment Record section and closure date on Return No. RC-18006 were left blank.

OBSERVATION 4

The quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs. Specifically, (b) (4) batch (b) (4) ((b) (4) designates the batch was (b) (4)) did not meet your customer's specification for PSD (Particle Size Distribution (b) (4) – (b) (4) µm). The actual PSD values were not reported on the CoA (Certificate Analysis for the batch. The quality unit did not complete a Product Release Form rejecting the batch for not meeting the customer's PSD specification with instructions for handling the batch.

(b) (4) batch (b) (4) was (b) (4) a (b) (4) time and the batch number was changed to batch (b) (4) ((b) (4) µm). The quality unit completed a Product Release Form and identified the batch as released without further instructions for handling the batch. Yet (b) (4) batch (b) (4) was (b) (4) a (b) (4) time. After (b) (4) batch (b) (4) was (b) (4) a (b) (4) time PSD results were (b) (4) µm. The quality unit completed a Product Release Form releasing the batch a second time.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 5

Cleaning procedures do not contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Specifically, your cleaning procedures are inadequate in that three of the three (b) (4) examined during the inspection contained visible residue or apparent foreign material. (b) (4) (b) (4) 102-1 contained apparent white particulate matter and what appeared to be a red-colored metallic particle. (b) (4) 102-2 contained apparent white residue. (b) (4) II-250 also contained apparent white residue along the length of the (b) (4)

OBSERVATION 6

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, and maintenance. This is a repeat observation. Specifically, a) you do not maintain equipment in a good state of repair. The end of the (b) (4) in (b) (4) II-250 is not adequately repaired. The repaired area on the (b) (4) consists of (b) (4) different colored unidentified materials: (b) (4) Your Engineering Supervisor stated the (b) (4) material is the (b) (4) repair material and the (b) (4) material is the (b) (4) of the same repair material.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	CK	Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

Only a small portion of the (b) (4) covered the repaired area. The durability of the (b) (4) in the absence of the (b) (4) is unknown. The (b) (4) material is unknown.

b) you do not have adequate lighting in (b) (4) to inspect (b) (4) after cleaning to ensure no visible residue remains.

c) you do not have an adequate (b) (4) sealing machine to seal (b) (4) API (b) (4) bags. (b) (4) sealing machine (b) (4) -811 does not have sufficient controls for pressure and time to ensure proper sealing. You do not conduct leak tests to check bag seals prior to final product approval and release.

OBSERVATION 7
Schedules and procedures for preventive maintenance of equipment are not adequate or do not exist. Specifically,

a) you do not have a written procedure describing how to conduct a (b) (4) test to verify the integrity of the interior surface of the (b) (4) in your manufacturing workshops. (b) ( ) are used in the manufacture of crude (b) ( ) in workshops (b) (4) and (b) (4).

b) you do not have a written procedure describing how to perform repairs to the interior surfaces of (b) (4) (b) (4) Repairs to interior surfaces of (b) (4) are made by your employees without written instructions for how to make those repairs.

c) you do not have a record showing a (b) (4) test was performed immediately following a repair to the (b) (4) of the (b) (4) in (b) (4) II-250. (b) (4) II-250 is used in the manufacture of crude (b) (4)

OBSERVATION 8
Substances associated with the operation of equipment, such as lubricants, heating fluids or coolants are not always food grade lubricants and oils. Specifically, you use (b) (4) in all of your (b) (4) reactors in Workshop (b) (4) You do not test (b) (4) prior to release for use for (b) (4) a potential toxic contaminant. Rather than preventing potential finished API contamination from (b) (4) by testing (b) (4) for (b) (4) prior to approval and release, your QA Director stated you periodically monitor your finished product APIs for (b) (4) contamination.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
		Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018
	FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Linhai, Zhejiang Province 317016 China	manufacturer

LABORATORY SYSTEM

OBSERVATION 9

Sampling plans, and test procedures are not always scientifically sound and appropriate to ensure raw materials, intermediates and APIs conform to established standards of quality.

a) you do not always have scientifically sound reasons for invalidating OOS results for lab related reasons. This is a repeat observation. Complaint No. CC-16008 received September 13, 2016 for (b) (4) batches (b) (4) ((b) (4) ppm (b) (4) impurity) and (b) (4) ((b) (4) ppm (b) (4) impurity) failing to meet (b) (4) impurity specification < (b) (4) ppm identifies the complaint as a quality complaint for product quality attribute. Your Vice President of Analytical Operations stated a Single Quadrupole LC-MS is not as sensitive as a Triple Quadrupole LC-MS and sometimes it gives false positive results. Your customer tested (b) (4) batches (b) (4) and (b) (4) using a Triple Quadrupole LC-MS. You sent samples of (b) (4) and (b) (4) to an outside laboratory to test using a Triple Quadrupole LC-MS. Your customer provided you with their LC-MS test method. The outside laboratory used a Triple Quadrupole LC-MS but did not follow the test method provided by your customer.

You do not have a quality agreement with this outside laboratory requiring all equipment used for testing is qualified, any software used with the instrument is validated, and the test method used is validated prior to reporting results. You used results from this outside laboratory for (b) (4) batches (b) (4) and (b) (4) to invalidate the OOS results reported by your customer. After your customer returned (b) (4) batches (b) (4) and (b) (4) you reprocessed the batches and assigned the reprocessed batches new batch numbers (b) (4) and (b) (4) Finished API batches (b) (4) and (b) (4) were then sold to other customers.

b) you do not have scientifically sound sampling plans.

i) Sampling Procedure for API Raw Material QC-026-9 effective September 30, 2017 includes sampling instructions designed to obscure non-homogenous raw material batches. As an example, section 5.6 specifies to sample the (b) (4) of (b) (4) compartment in the tanker and (b) (4) the compartment sample and then (b) (4) the (b) (4) samples from (b) (4) the compartments. You do not have data establishing inter-batch and intra-batch homogeneity for key starting materials.

ii) Sampling procedures lack sufficient details describing how to collect samples to ensure the sampling

procedure is consistently and reproducibly followed. Sampling Procedure for APIs QA-005-5 effective August 30, 2017 is silent regarding which drums to sample or how to collect samples from the sampled drums.

c) you do not have data to support reduced testing for genotoxic and other impurities. During process validation for (b) (4) you committed to testing the final API validation batches for elemental impurities and residual solvents, (b) (4) After the three (b) (4) validation batches you test (b) (4) batches (b) (4) for elemental impurities and residual solvents. During process validation for (b) (4) you tested the finished API validation batches for potential genotoxic impurity (b) (4) After the validation batches you test (b) (4) batches (b) (4) for potential genotoxic impurity (b) (4)

OBSERVATION 10

Your on-going testing program to monitor the stability characteristics of APIs to confirm appropriate storage conditions and retest dates is not adequate. Specifically,

a) you subjected (b) (4) API samples to conditions expected to cause degradation (forced degradation). You did not conduct full product release testing on those forced degradation samples, using validated test methods, to identify the specific product release test(s) that are stability indicating. Instead you included forced degradation samples in three HPLC test method validations for Related Substance, Assay and (b) (4) impurity. Not all potential product degradants can be identified by HPLC test methods. Product release tests for (b) (4) include tests for identification of Residual Solvents by GC-FID. You did not test forced degradation samples for Residual Solvents by GC-FID.

b) you do not always appropriately add stability study samples to your stability study program. Deviation investigation DCB02-17002 was initiated for (b) (4) intermediate (b) (4) batches (b) (4) single unknown impurity (b) (4) % (specification < (b) (4) %) and (b) (4) single unknown impurity (b) (4) %. You reprocessed the batches. You assigned the following batch numbers to the finished APIs made from the aforementioned (b) (4) intermediate (b) (4) batches: (b) (4) and (b) (4) You did not add batches (b) (4) and (b) (4) to your stability study program.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Food and Drug Administration, ORA OPQO HQ 12420 Parklawn Drive, RM 2032 Rockville, MD 20857 Industry Information: www.fda.gov/oc/industry	07/23/2018 - 07/28/2018, 07/30/2018-08/03/2018 FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Jun Dun, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE AND ZIP CODE	**TYPE OF ESTABLISHMENT INSPECTED**
Linhai, Zhejiang Province 317016 China	manufacturer

PRODUCTION SYSTEM

OBSERVATION 11

Production deviations are not always reported and evaluated and critical deviations are not always investigated and the conclusions recorded. Specifically,

a) your production operators do not always follow batch production instructions for critical processing parameters. At approximately (b) (4) on July 24, 2018, the temperature monitor for (b) (4) II-201 used in the manufacture of (b) (4) crude (b) (4) batch (b) (4) displayed (b) (4) degrees C. The manufacturing batch record for (b) (4) crude (b) (4) showed the manufacturing process for intermediate (b) (4) from chemical synthesis (b) (4) step was at step (b) (4) in the manufacturing process. The batch record identifies the parameters for this step as (b) (4) °C - (b) (4) °C maintained for (b) (4) The batch record also identifies this (b) (4) time duration as critical. The previous batch record entry recorded at (b) (4) lists a temperature of (b) (4) °C. The temperature for step (b) (4) is controlled by a manual (b) (4)

b) on July 25, 2018 in workshop (b) (4) a production employee was observed recording a value of (b) (4) liters for the amount of (b) (4) at step (b) (4) in the batch manufacturing record during the production of crude (b) (4) batch (b) (4) The flowmeter for the (b) (4) displayed a value of (b) (4) A production operator in Workshop (b) (4) stated (b) (4) equates to (b) (4) liters. The specification for (b) (4) at step (b) (4) in the batch manufacturing record for crude (b) (4) is (b) (4) +/- (b) (4) L.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	Cheryl Clausen	Cheryl Clausen, Investigator Joel Hustedt, Investigator	08/03/2018