DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
US FDA 10903 New Hampshire Ave, Bldg 51,Rm 422 Silver Springs, MD 20993 (301)796-3334 Fax:(301)847-8738 Industry Information: www.fda.gov/oc/industry	05/15-19/2017 FEI NUMBER 3003885745

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Jun Du, Executive Vice President

FIRM NAME	STREET ADDRESS
Zhejiang Huahai Pharmaceutical Co., Ltd.	Coastal Industrial Zone, Chuannan No. 1 Branch
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Duqiao, Linhai 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

Appropriate controls are not implemented over Quality Control instruments to ensure the integrity of analytical testing. Furthermore, anomalies in analytical testing are not investigated.

1. During a review of API testing assay testing is repeated in order to obtain satisfactory/ within specification results:

Standard Operating Procedure (SOP) QC-024-5 requires that replicate samples subject to analysis for assay to exhibit no more than (b)(4)% difference in result. This SOP was utilized to engage in repeat analysis of API in instances of out-of-specification and out-of-trend results without a corresponding investigation. Examples may be found below:

(a) (b)(4) batch (b)(4) exhibited a large differential between replicate sample results, such that one injection yielded an out-of-specification. The initial failing injections were not processed. Due to this large differential, this batch of (b)(4) was retested without conducting an investigation and passing results were reported.

(b) (b)(4) batch (b)(4) exhibited failing assay result for one of the replicate injections ((b)(4) % against a specification of (b)(4) %). Due to a large differential in test results between replicate injections for (b)(4) this batch was retested without conducting an investigation and passing results were reported.

(c) The following batches exhibited out-of-trend results, which were retested without an investigation due to a greater than (b)(4) % differential in replicate assay injections:

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i. (b) (4) batch (b) (4)
ii. batch
iii. batch
iv. (b) (4) batch (b) (4)

Further, due to this repeat testing as a result of discrepancies in replicate assay values, I reviewed repeat analytical testing for (b) (4) (b) (4) exhibited an increased rate of repeat testing. The replicate samples from repeat testing conducted between September 2016 and March 2017 for (b) (4) exhibited an average differential in assay results of approximately (b) (4) % (with the acceptable range of the specification spanning (b) (4) %). The replicate samples from repeat testing conducted between September 2016 and March 2017 for (b) (4) (b) (4) exhibited an average differential in assay results of approximately (b) (4) % (with the acceptable range of the specification spanning (b) (4) %). I asked your firm's Quality Control Director to explain how such routine, large differences in assay values of replicate samples was consistent with assurance that the analytical method is effective and released API indeed met specification. They did not provide a sustentative explanation.

Note: this repeat testing encompassed subjecting the same API batch to repeat testing without investigating the initial test results and the requirement for re-testing.

2. Impurities occurring during analytical testing are not consistently documented/ quantitated.

(a) Testing of (b) (4) content of (b) (4) batch (b) (4) by Liquid Chromatography-Mass Spectrometry yielded an unidentified peak at an approximate retention time of (b) (4) minute. Your firm explained this unknown peak as a "ghost peak" that appears from time to time in chromatograms for undetermined reasons. This peak was substantially larger than that of (b) (4) the subject of the testing. No investigation was conducted.

(b) Testing of (b) (4) content of (b) (4) batches (b) (4) (among others) by Liquid Chromatography-Mass Spectrometry yielded an unidentified peak at an approximate retention time of (b) (4) minute until the end of the chromatogram. This peak was substantially larger than that of (b) (4) the subject of the testing. No investigation was conducted.

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(c) Impurity testing of (b) (4) batches (b) (4) yielded a prominent, coalescing peak with that of the primary (b) (4) peak. Nevertheless, the impurity was quantitated along with the (b) (4) peak as desired API and no investigation was initiated.

OBSERVATION 2

Facilities and equipment are not maintained to ensure quality attributes of drug product.

a) On May 15, 2017, (b) (4) V-305 exhibited particulate matter and (b) (4) paint on the inner face of the gasket to the (b) (4) ((b) (4) b) (4) Further, this gasket was fraying, and loose threads were visible (b) (4) The gasket inside the (b) (4) b) (4) (b) (4) had deteriorated such that the missing portions could not be accounted for. The mass balance of this gasket could not be accounted for. Further, this gasket was discolored brown. Finally, a portion of the interior of this (b) (4) was discolored white. This (b) (4) was utilized in the manufacture of (b) (4) (b) (4) lo (b) (4) intended for the US market. This equipment was in the clean status.

b) On May 15, 2017, the (b) (4) to (b) (4) J09-805 contained screws displaying a reddish-brown discoloration consistent with rust (interior of the (b) (4) . This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market. This equipment was in the clean status and is used in the (b) (4) (b) (4)

c) On May 15, 2017, (b) (4) IX-501-2 exhibited particulate matter and blue paint on the inner face of the gasket to the (b) (4) Particulate matter and paint were falling from the (b) (4) upon opening the (b) (4) Further, this gasket was fraying, and loose threads were visible (b) (4) The gasket inside the (b) (4) had deteriorated such that the missing portions could not be accounted for. The mass balance of this gasket could not be accounted for. Further, this gasket was discolored brown. Finally, the interior of this (b) (4) was discolored brown. This (b) (4) was utilized in the manufacture of (b) (4) lo (b) (4) intended for the US market. This equipment was in the clean status.

d) On May 15, 2017, (b) (4) IX-501-1 exhibited what appeared to be flaking of the surface to the (b) (4) The gasket inside the (b) (4) had deteriorated such that portions of the

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gasket were missing and threads of the gasket were fraying. The mass balance of this gasket could not be accounted for. This(b) (4) was utilized in the manufacture of(b) (4) lot (b) (4) intended for the US market. This equipment was in the clean status.

e) On May 15, 2017, the(b) (4) W02-802-2 exhibited white particulate facing the interior of the(b) (4) that appeared to originate from the gasket to the(b) (4) Further, this(b) (4) (b) (4) appeared heavily scratched. This(b) (4) was utilized in the manufacture(b) (4) lot(b) (4) intended for the US market. This equipment was in the clean status and is used in the(b) (4)

f) On May 16, 2017, (b) (4) III-319 exhibited what appeared to white particulate matter in the interior of the(b) (4) The gasket inside the(b) (4)) had deteriorated such that portions of the gasket were missing and threads of the gasket were fraying. The mass balance of this gasket could not be accounted for. This(b) (4) was utilized in the manufacture of(b) (4) lot(b) (4) intended for the US market. This equipment was in the clean status.

For the aforementioned Observation, the following complaints pertaining to your firm's API were noted:

i. CC-16006 addressing(b) (4) particles,(b) (4) color, yellow rust" in(b) (4) batch(b) (4)
ii. CD-15004 reporting "black metallic particles" in(b) (4) batch(b) (4)
iii. CD-15003 addressing "mixed fragment(b) (4) " in(b) (4) batch(b) (4)
iv. CD-15006 stating "black particles were found in(b) (4) batch(b) (4)
v. CD-15001 reporting "That(b) (4) particles is(b) (4) ". The affected product is(b) (4)

OBSERVATION 3

Invalidation of out-of-specification results lacks adequate scientific justification.

a) Report OOS-CQC15067relating to(b) (4) batch(b) (4) was reported "Unknown impurity peak is appeared under unknown reason". Your firm explained this unknown peak as a "ghost peak" that appears from time to time in chromatograms for undetermined reasons. Without an indication of the cause of the out-of-specification, an attribution of "Lab error was made."

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b) Report OOS-CQC16103 reported out-of-specification of residual solvents in (b) (4) The Phase I laboratory investigation failed to identify a laboratory error. This investigation attributed the failure to "Pollution" from the environment during sample preparation.

c) Report OOS-CQC15103 due to a single impurity in (b) (4) batch (b) (4) (b) (4) % against a specification of no more than (b) (4) %). This was assigned as a "Lab error" due to "possible" residue in the column. When inquiring about why this impurity specifically eluted in the (b) (4) analytical test of the testing sequence, your firm again referenced a "ghost peak".

5/19/17

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