DURING AN INSPECTION OF YOUR FIRM 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 ±5% 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) batch 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 was retested without conducting an investigation and passing results were reported.

   (b) batch exhibited failing assay result for one of the replicate injections against a specification of ±5%. Due to a large differential in test results between replicate injections for 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 ±5% differential in replicate assay injections:

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Further, due to this repeat testing as a result of discrepancies in replicate assay values, I reviewed repeat analytical testing for repeat testing. The replicate samples from repeat testing conducted between September 2016 and March 2017 for exhibits an increased rate of exhibited an average differential in assay results of approximately (with the acceptable range of the specification spanning (4)%). The replicate samples from repeat testing conducted between September 2016 and March 2017 for exhibits an average differential in assay results of approximately (with the acceptable range of the specification spanning (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 substantiative 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 content of by Liquid Chromatography-Mass Spectrometry yielded an unidentified peak at an approximate retention time of 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 the subject of the testing. No investigation was conducted.

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

District Address and Phone Number:
US FDA
10902 New Hampshire Ave, Bldg 51, Rm 422
Silver Spring, MD 20993
(301) 796-3334 Fax (301) 847-8738
Industry Information: www.fda.gov/oc/industry

Name and Title of Individual to Whom Report Issued:
To: Mr. Jun Du, Executive Vice President

 Firm Name: Zhejiang Huahai Pharmaceutical Co., Ltd.
Street Address: Coastal Industrial Zone, Chuannan No. 1 Branch
City, State, Zip Code, Country: Duqiao, Linhai Zhejiang 317016 China
Type of Establishment Inspected: API Manufacturer

(c) Impurity testing of [redacted] batches yielded a prominent coalescing peak with that of the primary peak. Nevertheless, the impurity was quantitated along with the [redacted] 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, V-305 exhibited particulate matter and paint on the inner face of the gasket to the [redacted]. Further, this gasket was fraying, and loose threads were visible. The gasket inside the [redacted] 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 lot was discolored white. This lot was utilized in the manufacture of [redacted] intended for the US market. This equipment was in the clean status.

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

c) On May 15, 2017, IX-501-2 exhibited particulate matter and blue paint on the inner face of the gasket to the [redacted]. Particulate matter and paint were falling from the [redacted] upon opening the [redacted]. Further, this gasket was fraying, and loose threads were visible. The gasket inside the [redacted] 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 lot was discolored brown. This lot was utilized in the manufacture of [redacted]. This equipment was in the clean status.

d) On May 15, 2017, IX-501-1 exhibited what appeared to be flakes of the surface to the [redacted]. The gasket inside the [redacted] 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 was utilized in the manufacture lot intended for the US market. This equipment was in the clean status.

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

f) On May 16, 2017, III-319 exhibited what appeared to white particulate matter in the interior of the 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 was utilized in the manufacture lot 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 particles color, yellow rust in batch

ii. CD-15004 reporting "black metallic particles" in batch

iii. CD-15003 addressing "mixed fragment" in batch

iv. CD-15006 stating "black particles were found in batch" particles is	 The affected product is

v. CD-15001 reporting "That batch was reported as "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."

OBSERVATION 3

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

a) Report OOS-CQC15067 relating to batch 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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Massoud Motamed, Investigator

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b) Report OOS-CQC16103 reported out-of-specification of residual solvents in (0.04) 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 (0.04) batch (0.04) against a specification of no more than (0.06). This was assigned as a "Lab error" due to "possible" residue in the column. When inquiring about why this impurity specifically eluted in the analytical test of the testing sequence, your firm again referenced a "ghost peak".

5/19/17