Food and Drug Administration Establishment Inspection Report

Date Assigned: 06/05/2017 **Inspection Start Date:** 05/15/2017 **Inspection End Date:** 05/19/2017

Firm Name & Address: Zhejiang Huahai Pharmaceutical , Coastal Industrial Zone , Chuannan No. 1 Branch Duqiao, Linhai City

Firm Mailing Address: Coastal Industrial Zone, Linhai City, Duqiao ,Zhejiang Province ,317016, China

FEI: 3003885745 **JD/TA:** **County:** **Est Size:** 50,000,000 - and over

Phone: ()8501600 **District:** IOG-MPT **Profiled:** Yes

Conveyance Type: **% Interstate:** 100 **Inspectional Responsibility:**

Endorsement

This pre-announced comprehensive GMP and (b) (4) ((b) (4)) inspection of an active pharmaceutical ingredient (API) manufacturer was issued under eNSpect ID 55134. The inspection was conducted under Compliance Policy Guidance Manual (CPGM) 7346.832 and CPGM 7356.002F and ICH 7 guidelines. The PAC codes covered were 56002F and 46832, and the profile class covered was "CSN".

The previous inspection was conducted between 05/19-23/2014 and concluded with no FDA-483 Inspectional Observations.

The current inspection was a system based approach, with a focus on the Quality, Laboratory Control, Facilities and Equipment and Production Systems. At the conclusion of the inspection, a three-item (3) Form FDA-483 with multiple sub-points, Inspectional Observations, was issued to Mr. Jun Du, Executive Vice President, for the following:
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.
2- Facilities and equipment are not maintained to ensure quality attributes of drug product.
3- Invalidation of out-of-specification results lacks adequate scientific justification.

Discussion Items Include:
1 - Analytical methods pertaining to (b) (4) for (b) (4) are not validated.
2 - Complaints are invalidated without documenting the rationale.

The firm promised a response in writing to CDER/OC/DIDQ within 15 days.

No samples were collected. No refusals or delays were encountered.
Registration is current.

F/U: Field Classification OAI. Refer to CDER, Office of Compliance to initiate WL or other possible action.

Distribution:
O: eNSpect
Original exhibits and C/S: CDER/OC, (HFR-325)-WO -Building 51, Room 4235; 10903 New Hampshire Ave Silver Springs, MD 20993

Endorsement Location:

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
	ET		ET

Food and Drug Administration Establishment Inspection Report

FEI: 3003885745 **Inspection Start Date:** 05/15/2017 **Inspection End Date:** 05/19/2017

Firm Name & Address: Zhejiang Huahai Pharmaceutical , Coastal Industrial Zone , Chuannan No. 1 Branch Duqiao, Linhai City

Related Firm FEI: **Name & Address of Related Firm:**

Registration Type		Registration Dates		
DRG	Drug	10/01/2016	01/26/2011	02/01/2008
GDF	GDUFA Self-Identified Firm	01/01/2017		

Establishment Type		Industry Code	
M	Manufacturer	61	Human and Animal Drugs
M	Manufacturer	62	Human and Animal Drugs
M	Manufacturer	66	Human and Animal Drugs

District Use Code:

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
46832	Manufacturer	(b) (4)				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	07/31/2017	Official Action Indicated (OAI)	Ryan, Brian J	CDER-DIA

Remarks: (b) (4) : Incomplete or unsuccessful method validation or verification.

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/07/2017	Official Action Indicated (OAI)	Glenn, Angela E	IOG-MPT

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/07/2017	Official Action Indicated (OAI)	Motamed, Massoud	IOG-MPT

Remarks: Firm is not ready for manufacture

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PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56002F	Manufacturer	(b) (4)				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	09/15/2017	Voluntary Action Indicated (VAI)	Terrell, Towanda L	CDER-OMQ

Remarks: GMP portion of inspection reclassified to VAI as firm's response is mostly adequate as noted in Center Endorsement text in CMS, and in OMQ reclassification memo dated 09/07/2017.

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/07/2017	Official Action Indicated (OAI)	Glenn, Angela E	IOG-MPT

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/07/2017	Official Action Indicated (OAI)	Motamed, Massoud	IOG-MPT

Remarks: Data integrity, facility condition and OOS handling

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PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56002F	Manufacturer	(b) (4)				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	09/15/2017	Voluntary Action Indicated (VAI)	Terrell, Towanda L	CDER-OMQ

Remarks: GMP portion of inspection reclassified to VAI as firm's response is mostly adequate as noted in Center Endorsement text in CMS, and in OMQ reclassification memo dated 09/07/2017.

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/07/2017	Official Action Indicated (OAI)	Glenn, Angela E	IOG-MPT

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/07/2017	Official Action Indicated (OAI)	Motamed, Massoud	IOG-MPT

Remarks: Data integrity, facility condition and OOS handling

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Food and Drug Administration Establishment Inspection Report

FEI: 3003885745 **Inspection Start Date:** 05/15/2017 **Inspection End Date:** 05/19/2017

Firm Name & Address: Zhejiang Huahai Pharmaceutical , Coastal Industrial Zone , Chuannan No. 1 Branch Duqiao, Linhai City

Products Covered

Product Code	Est Type	Description	Additional Product Description
(b) (4)	Manufacturer	(b) (4) ((b) (4)) Human - Rx/Single Ingredient Active Pharm Ingred/Chems for Further Manuf	
	Manufacturer	(b) (4) ((b) (4)) Human - Rx/Single Ingredient Active Pharm Ingred/Chems for Further Manuf	
	Manufacturer	(b) (4) N.E.C. Human - Rx/Single Ingredient Active Pharm Ingred/Chems for Further Manuf	(b) (4) an advanced intermediate for (b) (4)

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Motamed, Massoud	GDF	PHRM2	46832	Manufacturer	(b) (4)	30
Motamed, Massoud	GDF	PHRM2	56002F	Manufacturer		32
Motamed, Massoud	GDF	PHRM2	56002F	Manufacturer		30
					Total Hours:	92

Food and Drug Administration Establishment Inspection Report

FEI: 3003885745 **Inspection Start Date:** 05/15/2017 **Inspection End Date:** 05/19/2017

Firm Name & Address: Zhejiang Huahai Pharmaceutical , Coastal Industrial Zone , Chuannan No. 1 Branch Duqiao, Linhai City

Inspection Result

EIR Location

Trips Num
2017-218D

Inspection Summary
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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.
2- Facilities and equipment are not maintained to ensure quality attributes of drug product.
3- Invalidation of out-of-specification results lacks adequate scientific justification.

Discussion Items Include:
1 - Analytical methods pertaining to (b) (4) for (b) (4) are not validated.
2 - Complaints are invalidated without documenting the rationale.

The firm promised a response in writing to CDER/OC/DIDQ within 15 days.

No samples were collected. No refusals or delays were encountered.
Registration is current.

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals: No refusal

Samples Collected

Sample Number

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FEI: 3003885745 **Inspection Start Date:** 05/15/2017 **Inspection End Date:** 05/19/2017

Firm Name & Address: Zhejiang Huahai Pharmaceutical , Coastal Industrial Zone , Chuannan No. 1 Branch Duqiao, Linhai City

FDA 483 Responses

483 Issued?: Y **483 Location:**

Response Type	Response Mode	Response Date	Response Summary
Adequate, Requires Verification	Letter	06/12/2017	Firm's response deemed adequate per OMQ reclassification memo OAI to VAI dated 09/07/2017. Firm's corrective actions require verification upon next inspection.

TABLE OF CONTENTS

SUMMARY

This pre-announced comprehensive GMP and (b) (4) ((b) (4)) inspection of an active pharmaceutical ingredient (API) manufacturer was issued under eNSpect ID 55134. The inspection was conducted under Compliance Policy Guidance Manual (CPGM) 7346.832 - Pre-Approval & Post Approval Inspections, and CPGM 7356.002F – "Active Pharmaceutical Ingredient Process Inspections" and ICH 7 guidelines. The PAC codes covered were 56002F and 46832, and the profile class covered was "CSN".

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The firm promised a response in writing to CDER/OC/DIDQ within 15 days.

No samples were collected. No refusals or delays were encountered.

Registration is current.

ADMINISTRATIVE DATA

Inspected firm:	Zhejiang Huahai Pharmaceutical Co., Ltd.
Location:	Coastal Industrial Zone, Chuannan No. 1 Branch Linhai Zhejiang 317016 China
Phone:	+86 576 85016003
Website:	www.huahaipharm.com
Mailing address:	Coastal Industrial Zone, Chuannan No. 1 Branch Linhai Zhejiang 317016 China
Dates of inspection:	05/15-19/2017
Days in the facility:	5
Participants:	**Massoud Motamed, Investigator**

On May 15, 2017 I arrived at the Zhejiang Huahai Pharmaceutical facility in Linhai, China. FDA credentials were shown and a business card was provided to Mr. Jun Du, Executive Vice President, who identified himself as the most responsible individual present at the firm. I informed Mr. Du that I was at the firm to conduct this pre-announced FDA inspection for pharmaceutical products to be offered to the US market. Additionally, I stated I was conducting a Preapproval Inspection pertaining to an advanced intermediate termed "(b) (4)" for manufacture of (b) (4). Business card exchange ensued. After initial pleasantries, the inspection followed. I informed firm management that I would hold an informal discussion to discuss any observed issues as concerns arose, to allow an opportunity for management to clarify their position.

At the conclusion of the inspection, on May 19, 2017 a three-item (3) Form FDA-483, Inspectional Observations, with multiple sub-points, was issued to Mr. Du. Additionally, two items were verbally communicated to the firm. Mr. Du promised to respond to the Agency in writing within fifteen business days of the close of the inspection.

HISTORY

Firm history remains unchanged and may be found in the introductory presentation contained in **Exhibit 2**.

Briefly, the company (Huahai) was founded in 1989, and has (b) (4) (b) (4) and (b) (4) Drug Master Files (DMFs). This Chuannan site of Huahai manufactures APIs and advanced intermediates for the US market. The site is divided into East and West Zones encompassing (b) (4) m^2. Each zone is then further subdivided into Workshops.

The firm currently has (b) (4) personnel. Employee numbers in some key departments are as follows (**Exhibit 2**):

Department	No. of Employees (East)	No. of Employees (West)
Production	(b) (4)	(b) (4)
Quality Assurance	(b) (4)	(b) (4)
Quality Control		(b) (4)

Engineering	(b) (4)		(b) (4)

Office Hours: (b) (4) .

Production Hours: (b) (4)

The official correspondence address for the firm is as follows:

Mr. Jun Du, Executive Vice President
Zhejiang Huahai Pharmaceutical Co., Ltd.
Coastal Industrial Zone, Chuannan No. 1 Branch
Linhai Zhejiang 317016 China

The address of US Agent for this firm is as follows:
Huahai US Inc.
2002 Eastpark Blvd.
Cranbury, NJ 08512
Attn: Dr. Xiaodi Guo
Email: xguo@huahaipharmus.com

INTERSTATE (I.S.) COMMERCE/ JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

The site is registered with the US FDA as an API manufacturing facility for domestic and export (directly or indirectly) to the USA. As such, the firm is subject to the adulteration provisions of section 501(a)(2)(b) of the FD&C Act.

See **Exhibit 3** for a list of APIs manufactured for the US market since the previous FDA inspection. The table below contains information pertaining to APIs that are commercialized for the US market with the corresponding DMF number and building of manufacture:

Product	DMF Number	Workshop	Building Manufactured
(b) (4)			

See **Exhibit 4** for information identifying corresponding associated consignee.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Detailed information pertaining to some key individuals is detailed below:

Mr. Jun Du – Executive Vice President – Mr. Du has been with the firm since 2000. His role includes overseeing operations at the firm in the absence of Mr. Baohua Chen, President / General Manager, who is based in the firm's Headquarters (this was explained as he serves the role as Mr. Chen's Deputy). Mr. Du stated he is responsible for dealing / managing operations in the absence of Mr. Chen. He stated that he is responsible for overseeing all employees and retains the authority to hire/ fire (with approval by HR). Mr. Du was present daily, and provided clarification of the firm's position regarding several concerns, including presenting proposed corrective action. As the most responsible person for the firm, Mr. Du was issued the FDA 483.

Mr. (b) (6) – Vice Manager, Corporate QA (Translator) – Mr. (b) (6) has been with the firm for 3.5 years. Mr. (b) (6) is responsible for coordinating customer and authority audits. Mr. (b) (6) reports to Mr. Baohua Chen and Mr. Cunxiao Ye (Vice President, Quality Assurance, Headquarters). He specified he has (b) (4) direct reports. Mr. (b) (6) was present for the entirety of the inspection providing all necessary translation contained within this report.

Mr. Jie Wang – Vice President, Business Development, Headquarters – Mr. Wang has been with the firm since 2014. He is responsible for overseeing sales and marketing. Mr. Wang oversees (b) (4) direct reports and reports to Mr. Baohua Chen. Mr. Wang was present throughout the inspection and addressed the Preapproval Aspect of this inspection. Further, Mr. Wang is fluent in English and additionally provided clarification to translations provided by Mr. (b) (6) when necessary.

Ms. Jucai Ge – Director, Quality Assurance, API Chuannan site – Ms. Ge has been with the firm for 17 years. Ms. Ge oversees (b) (4) direct reports and reports to Mr. Cunxiao Ye. Ms. Ge stated her responsibilities include establishing and maintaining the quality system, handling complaints and reviewing investigations (complaints, deviations, out-of-specification, etc.). Ms. Ge was present for the entirety of the inspection and provided information pertaining to the firm's operations and quality unit.

Mr. Qiangming Li – Director, Quality Control, API Chuannan site – Mr. Li has been with the firm since 1999 and in his current role for 5 years. Mr. Li is responsible for the Quality Control Department, including resource allocation, providing technical oversight, investigating out-of-specification / out-of-trend events, etc. He oversees (b) (4) direct reports and reports to Dr. Min Li, Analytical Operations Vice President. Mr. Li answered questions pertaining to the Quality Control Laboratory.

Additional information pertaining to the organization may be found in **Exhibit 5**.

FIRM'S TRAINING PROGRAM

Training is dictated by SOP SMP-006.03 titled "Corporate Training System" effective January 10, 2014. (b) (4) training is described. This SOP requires an initial training relating to corporate SOPs, departmental training and on-the-job training. Further, the SOP requires (b) (4) GMP training.

MANUFACTURING/DESIGN OPERATIONS

Preapproval Coverage

Preapproval coverage encompasses manufacture of an advanced intermediate ((b) (4)) under DMF (b) (4) for manufacture pursuant to (b) (4) ((b) (4)).

I perused applicable documentation prior to the inspection and reviewed analytical methods contained in the (b) (4) (**Attachment 1**). A review of the analytical methodology from (b) (4) (b) (4) (**Attachment 1**) states in multiple methods "Sonicate if necessary". As such, I provided my (b) (4) to Huahai and asked for an explanation (**Attachment 1**). Further, I asked Huahai how the method for testing (b) (4) is considered validated or reproducible if sample and standard preparation varies. The firm responded by stating that (b) (4) (b) (4) without their concurrence. I asked for this to be indicated in writing and was provided **Exhibit 6**. This document notes that the firm does not agree with this "sonicate if necessary" statement in analytical methods. Further **Exhibit 6** indicates that Huahai had not agreed with (b) (4) in regards to the method of analysis. Most importantly, Huahia stated (and provided in writing in **Exhibit 6**) that the analytical method validation was "uncompleted". See ***Verbal Item 1***.

No agreement between Huahai and (b) (4) was available / reached.

I reviewed process validation of manufacture of advanced intermediate (b) (4). The manufacturing process schematic follows (adapted from **Exhibit 6**).

(b) (4)

The process validation was governed via protocol PV PVD-14019(P). This protocol was prospective in nature, specifying batches to be utilized in process validation ((b) (4), (b) (4) and (b) (4)). The associated report PV PVD-14019(R) deemed the manufacturing process valid without deviation. Batch Record (b) (4) was reviewed without note.

Facilities and Equipment

The site is dedicated to intermediate and API manufacture. The area of the site is quite large, encompassing approximately (b) (4) square meters. This area is divided into two parallel manufacturing areas termed the East Zone and West Zone. Both areas have manufacturing areas, administrative buildings and laboratories. The manufacturing Zones contain multiple manufacturing buildings termed workshops (note: workshops in the West Zone contain the (b) (4)). Within these workshops there are areas termed synthetic and clean. The synthetic area is where the API is manufactured and is not a classified area. The clean area is a Class D (ISO 8) area where API (b) (4) takes place. The majority of US API is manufactured in the East Zone, so this area was mostly reviewed. During my inspection, production was ongoing, so available, clean equipment (b) (4) of API manufacture was inspected. Additionally, I observed corresponding equipment logs which appeared adequate.

In total, I thoroughly inspected the interior of 9 pieces of equipment with deficiencies noted in 7 (***Observation 2***). **Exhibit 7** depicts the last US batch manufactured on the equipment subject to ***Observation 1***. The following provides specifics:

I began the inspection in Workshop (b) (4). I observed the synthetic area, where the API is made (b) (4) (b) (4). This area contained approximately (b) (4) dedicated to various processes. Equipment was tagged with both equipment IDs and status. (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) (**Exhibit 1** pages 3 -5). Further, this gasket was fraying, and loose threads were visible (b) (4). The gasket inside the (b) (4) ((b) (4) – API contact surface) had deteriorated such that the missing portions could not be accounted for (**Exhibit 1** pages 6 -7). Further, this gasket was discolored brown. Finally, a portion of the interior of this (b) (4) was discolored white (**Exhibit 1** pages 8 -9). This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market (**Exhibit 8**). This equipment was in the clean status (**Exhibit 1** pages 1 -2). Most of the other equipment in this synthetic area was not clean or not in use.

Subsequently, I asked to observe the associated clean area of Workshop (b) (4) (where the API is (b) (4)). I observed (b) (4) J09-805 used in API (b) (4). The (b) (4) to (b) (4) (b) (4) J09-805 contained screws displaying a reddish-brown discoloration consistent with rust (interior of the (b) (4) – where API contacts) (**Exhibit 1** pages 12 -15). This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market (**Exhibit 9**). This equipment was in the clean status and is used in the (b) (4) (**Exhibit 1** pages 10 -11).

Subsequently, I went to Workshop (b) (4). I observed 3 (b) (4) the manufacturing process that were available for inspection. I requested and had (b) (4) IX-501-2 opened (**Exhibit 1** page 18). After opening the (b) (4) particulate matter was released from the (b) (4) soiling the operator (and my) hand (**Exhibit 1** pages 19 -21). Similar particulate matter and (b) (4) paint was observed on the inner face of the gasket to the (b) (4) (b) (4)) (**Exhibit 1** pages 22 -25). Further, this gasket was fraying, and loose threads were visible (b) (4) (**Exhibit 1** page 26). The gasket inside

the (b) (4) had deteriorated such that the missing portions could not be accounted for (**Exhibit 1** pages 28 -29). Further, this gasket was discolored brown. Finally, the interior of this (b) (4) was discolored brown (**Exhibit 1** pages 28 -31). This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market (**Exhibit 10**). This equipment was in the clean status (**Exhibit 1** pages 16 -17).

(b) (4) IX-501exhibited what appeared to be flaking brown material from the surface to the (b) (4) (**Exhibit 1** pages 34 -35). The gasket inside the (b) (4) (b) (4)) was warped and threads of the gasket were fraying (**Exhibit 1** pages 36 -37). This equipment was in the clean status (**Exhibit 1** pages 32 -33).

(b) (4) IX-501-1 exhibited what appeared to be flaking of the surface to the (b) (4) (**Exhibit 1** pages 41 -42). The gasket inside the (b) (4) had deteriorated such that portions of the gasket were missing and threads of the gasket were fraying (**Exhibit 1** page 40). Additionally, the (b) (4) interior of the (b) (4) was discolored in a manner consistent with rust (**Exhibit 1** page 40). This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market (**Exhibit 11**). This equipment was in the clean status.

To gather a more comprehensive assessment, I observed a clean area in the West Zone. (b) (4) (b) (4) (b) (4) -802-2 exhibited white particulates / residue (b) (4) that appeared to originate from the gasket to the (b) (4) (**Exhibit 1** pages 45 -47). Further, this (b) (4) appeared heavily scratched (**Exhibit 1** page 48). Later, the scratching was attributed to (b) (4) . However, evidence supporting this sentiment was not provided during the inspection. This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market (**Exhibit 12**). This equipment was in the clean status and is used in the (b) (4) .

Finally, I evaluated Workshop (b) (4) synthetic area. (b) (4) III-319 exhibited what appeared to be white particulate matter in the interior of the (b) (4) (**Exhibit 1** pages 51 -52). The gasket inside the (b) (4) had deteriorated such that portions of the gasket were missing, and other areas had no observable gasket (**Exhibit 1** pages 53 -58). To fully document this situation, I procured a video demonstrating the interior of the (b) (4) showing all angles of the (b) (4) area (**Exhibit 56**). This (b) (4) was utilized in the manufacture of (b) (4) (b) (4) lot (b) (4) intended for the US market (**Exhibit 13**). This equipment was in the clean status (**Exhibit 1** pages 49 -50).

The following complaints pertain to foreign materials in API that may be associated with the lack of equipment maintenance:

i. CC-16006 addressing "(b) (4) particles, (b) (4) color, yellow rust" in (b) (4) batch (b) (4) (b) (4) (**Exhibit 14**)
ii. CD-15004 reporting "black metallic particles" in (b) (4) batch (b) (4) (**Exhibit 15**)
iii. CD-15003 addressing "mixed fragment of (b) (4) " in (b) (4) batch (b) (4) (**Exhibit 16**)

iv. CD-15006 stating "black particles were found in (b) (4) batch (b) (4)" (**Exhibit 17**)
v. CD-15001 reporting "That (b) (4) particles is (b) (4) (b) (4)" (**Exhibit 18**). The affected product is (b) (4).

Cleaning Validation:

Cleaning validation is covered under SOP TE-001-4 effective November 10, 2016. Section 5.5.2 of this SOP describes the criteria for cleaning validation including a visual assessment and a maximum carryover of (b) (4) ppm. This (b) (4) ppm carryover is assigned to the synthetic area ((b) (4) (b) (4)). With regards to API (b) (4), a maximum carryover of (b) (4) ppm is assigned. This carryover is ascertained by both swabbing and rinse sampling (where applicable). I reviewed the SOP and hardest to clean areas were defined with regards to swabbing. With regards to US APIs, only Workshop (b) (4) is not dedicated, and both (b) (4) and (b) (4) are manufactured in this area. I reviewed the respective cleaning validations and carryover was determined with regards to changeover from (b) (4) to (b) (4), and (b) (4) to (b) (4).

Qualification of Water System:

The firm has (b) (4) based water systems. I reviewed the qualification of (b) (4) Water system 4 termed (b) (4) 4. Initially, I reviewed the associated protocol (EQC-12021(P)). This document requires a (b) (4) sampling plan. (b) (4) (b) (4) (b) (4) The associated report, EQC-13018(R) deemed the water system qualified, including the sampling plan subject to (b) (4) analysis.

Laboratory Control

The firm maintains laboratories on the East and West side administrative buildings. I observed the laboratory in both buildings. The East Side administrative building had microbiological, and research and development areas.

I reviewed the microbiological laboratory on the 3rd floor of the East administration building. Subsequently, I observed the incubators for samples, including 3 incubators at 30-35ºC, 2 incubators at 20-25ºC, and one incubator at (b) (4) -(b) (4) ºC (for endotoxin analysis). The incubators had a log indicating the contents of each incubator. As such, I confirmed that samples (b) (4) (b) (4) were present in the incubator as specified in the log.

Stability chambers were in various rooms within the QC laboratories. I observed Chamber H405037 maintained at 40ºC and 75% RH. This chamber had a log specifying the contents of the chamber. As such, I reviewed the log and confirmed that sample (b) (4) was present.

I reviewed an out-of-specification (OOS) list (**Exhibit 25**) and corresponding SOP (**Exhibit 23**). From a review of these OOSs, I noted that several were product quality related and led to API being reprocessed. Thus, I focused on identifying the reason OOSs had been invalidated. OOS-CQC15067 and OOS-CQC15103 resulted from aberrant, unknown peaks in chromatograms (see **Exhibits 24** and **27**, respectively). Throughout a discussion of the logic for invalidating these OOSs, it was clarified that there was not supporting justification for invalidating the OOSs besides a passing retest result (***Observation 3a*** and ***3c***). OOS-CQC16103 attributes a residual solvent OOS to "Pollution" (**Exhibit 26**). However, upon inquiring about the impact of that attribution on the analytical method and API manufactured in the same environment, the firm disavowed that justification for invalidating the OOS.

I reviewed testing conducted in the firm's Empower 3 based chromatographic system. The folders are subdivided by year, month and product. As such, I asked the firm to copy and paste the injection history into an Excel file for September 2016 until March 2015 for (b) (4), (b) (4), (b) (4), (b) (4) and (b) (4). Retesting of assay for (b) (4) and (b) (4) appeared common. The firm explained that SOP QC-024-5 requires that replicate samples subject to analysis for assay to exhibit no more than (b) (4)% difference in result (**Exhibit 39** form Q/ZHH QC-051-2). This SOP was utilized to engage in repeat analysis of API in instances of out-of-specification and out-of-trend (OOT) results without a corresponding investigation (***Observation 1.1***). Additionally, the need for such extensive repeating of assay testing due to large differentials among replicates may indicate that the analytical method is not effective as intended.

Additionally, a review of raw chromatographic data identified that the appearance of unknown peaks in various testings go uninvestigated (***Observation 1.2***).

Production

The firm routinely engages in reprocessing (see **Exhibit 25** where OOS for designating of product quality issues are subject to reprocessing). A reprocessed batch list may be found in **Exhibit 28**. I subsequently reviewed reprocessing with Ms. Jucai Ge – Director, Quality Assurance, API Chuannan site. She presented SOP SMP-025.02 "Reprocess and Rework Management Procedure" effective June 01, 2016. I asked Ms. Ge how the firm is aware that reprocessing activity does not have an impact on stability. Ms. Ge specified that this is described in section 5.8.3 of the SOP. Upon review, the firm only assesses stability implication in (b) (4) instance of reprocessing of the (b) (4). I asked Ms. Ge if the stability implications based on following the stability of (b) (4) batch and she confirmed. I asked if the firm determines the impact of stability upon reprocessing at other stages in API synthesis. She specified that they review the impurity profile, but no stability studies are conducted.

Subsequently, I covered reprocessing with Ms. Yuelin Hu, Manager, Quality Assurance, API Chuannan site East Zone. I asked Ms. Hu if reprocessing activities are validated and she stated that the reprocessing of batches follows the previously validated manufacturing process. I confirmed that (b) (4) batch (b) (4) was reprocessed to batch (b) (4) following the established manufacturing process. I reviewed the associated DMFs and reprocessing is designated.

I spoke with Ms. Ge regarding establishing hold times and associated deviations. Ms. Ge specified that none of the manufacturing processes have established hold times, as materials are not normally held at any stage of manufacture and therefore there are no deviations specific to hold times. The only evidence I noted for material being held for an extended period was deviation DD-15001 opened July 10, 2015, due to the occurrence of a typhoon (**Exhibit 29**). During the typhoon Workshops (b) (4) and (b) (4) were in operation and processes occurring at the time were subject to an extended hold time.

Process Validation was covered for (b) (4) as a part of the Preapproval aspect of the inspection.

The firm's manufacturing process was manual without the aid of computerized systems.

Quality

The quality unit responsibilities are delegated in SOP CA-006-3 titled "Responsibilities of Quality Unit" effective April 1, 2014. This SOP designates the quality unit as independent with the authority to accept or reject API.

I reviewed various annual product reviews: ARC-16-057 for (b) (4) year 2016 and ARC-16-071 for (b) (4) year 2016. These reviews included complaints, investigations and trends. However, due to the repeat testing noted in ***Observation 2***, it is not clear how the firm ensures the validity of assay testing for (b) (4) and (b) (4) noted in these trends. Further, deficiencies with investigations included in the annual product reviews are discussed in ***Observation 3*** and below.

Mr. (b) (6) stated that the firm has not reworked or rejected US API since the previous US FDA inspection. Reprocessing is discussed as a part of the Production system.

OOS investigations are discussed as a part of the Laboratory Control section.

Complaints are covered under SOP SMP-011.07 titled "Complaint management procedure" (**Exhibit 31**). Additionally, **Exhibit 32** encompasses a list of complaints. I noted reoccurring complaints pertained to particulate matter in API (see ***Observation 2*** for a discussion) and for discrepancies in testing between Huahai and their consignees. The complaints pertaining to particulate matter may be related to equipment maintenance as discussed in ***Observation 2***. To address the firm's handling of complaints describing testing disparities, I had the firm generate a list of such complaints, as well as associated pie charts (**Exhibit 33**). From 2015 until May 2017, 13 complaints related to discrepancies between Huahai's test results and their consignees results. Of these complaints 85% had what the firm termed "Customer has no subsequent feedback or treatment." Specifically, this 85% was further broken down into 3 categories: the batch subject to the complaint was sent to other consignees who did not report a complaint, there is a test method discrepancy and feedback was provided to the consignee without a response and the consignee failed to respond but continued to purchase API from Huahai. Several of these complaints were collected (**Exhibits 34 – 37**). See ***Verbal Item 2***.

MANUFACTURING CODES

Mr. (b) (6) provided a list of (b) (4) codes for US products (**Exhibit 30**):

An example of the batch numbering system is as follows:

(b) (4)

COMPLAINTS

Complaints are discussed under the Quality System section of this report.

RECALL PROCEDURES

Recalls are governed by SOP SMP-013.05 effective January 1, 2014 titled "Product Recall Management System". This SOP addresses the handling of situations that may warrant a recall including requests by the authorities (FDA, etc.), information received externally (i.e. consumer feedback) or internal findings (identification of quality issues by the firm. Ms. Yuelin Hu, Manager, QA, API Chuannan site East Zone, stated that the firm has not engaged in a recall since the previous FDA inspection.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

On May 19th at approximately 1:06 pm, I held a close-out meeting with the following individuals from the firm:

Name of the attendee	Title
Jun Du	Executive Vice President
Cunxiao Ye	Vice President, Quality Assurance, Headquarters
Jie Wang	Vice President, Business Development, Headquarters
Lihong Lin	Director, Regulatory Affairs, Headquarters
Baozhen Chen	Director, Corporate Quality Assurance
Dachuan Zhao	Vice President, Analytical, Shanghai R&D Center
Lijin Jiang	Vice President, API Operation/ Facility Director, API Chuannan site, East Zone
Peng Wang	Facility Director, API Chuannan site, West Zone

Jucai Ge	Director, Quality Assurance, API Chuannan site
Qiangming Li	Director, Quality Control, API Chuannan site
(b) (6)	Deputy Plant Director, Engineering and Maintenance, API Chuannan site East Zone
(b) (6)	Deputy Plant Director, Engineering and Maintenance, API Chuannan site West Zone
Yuelin Hu	Manager, Quality Assurance, API Chuannan site East Zone
(b) (6)	Director Assistant, Quality Assurance, API Chuannan site West Zone
(b) (6)	Director Assistant, Technical, API Chuannan site East Zone
(b) (6)	Director Assistant, Technical, API Chuannan site West Zone
Yinhua Tang	Manager, Quality Control, API Chuannan site
(b) (6)	Vice Manager, Corporate Quality Assurance (Translator)

During the close-out meeting, I verbally communicated two items discussed under the General Discussion with Management section of this report.

Subsequently, I stated that as a result of the inspection, I had three (3) written observations to make as seen on the Form FDA 483 – Inspectional Observations issued to Mr. Jun Du, as the most responsible person for the firm, and listed below. I read the observations to the firm and addressed any questions / concerns.

After reading the FDA 483, Mr. Du stated the firm would respond to the Agency in writing within 15 business days. I stated the observations listed below are not a final agency determination on the firm's compliance. I stated that FDA will further review these observations and if the Agency determines that the observations constitute a violation of the Food Drug and Cosmetic Act, the Agency has the authority to take further regulatory action consistent with foreign inspections. At approximately 2:40 pm I stated that the inspection was concluded.

Observations listed on form FDA 483

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:

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) 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.

(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.

Supporting Evidence and Relevance:

See **Exhibit 55** for a sealed CD of photographs.

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

Specifically, I reviewed testing conducted in the firm's Empower 3 based chromatographic system. The folders are subdivided by year, month and product. As such, I asked the firm to copy and paste the injection history into an Excel file for September 2016 until March 2015 for (b) (4), (b) (4), (b) (4), (b) (4) and (b) (4). Retesting of assay for (b) (4) and (b) (4) appeared common. The following was noted:

SOP QC-024-5 requires that replicate samples subject to analysis for assay to exhibit no more than (b) (4) % difference in result (**Exhibit 39** form Q/ZHH QC-051-2). This SOP was utilized to engage in repeat analysis of API in instances of out-of-specification and out-of-trend (OOT) 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 (see **Exhibit 40** for laboratory notebook documenting the situation, corresponding chromatograms – initial and retest and final CoA). 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) %) (see **Exhibit 41** for laboratory notebook documenting the situation, corresponding chromatograms – initial and retest and final CoA). Due to a greater than (b) (4) % differential in test results between replicate injections for (b) (4), this batch was retested without conducting an investigation and passing results were reported.

SOP QC-024-5 section 5.5.1 does not allow for rounding up of OOS results (see **Exhibit 39** last page for a translation).

(c) I had the firm generate a list of applicable initial and repeat test results stemming from SOP QC-024-5 (**Exhibit 42**). 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:

a. (b) (4) batch (b) (4)
b. batch
c. batch
d. (b) (4) batch (b) (4)

Note OOT limits may be found in **Exhibit 43**.

Due to this repeat testing as a result of discrepancies in replicate assay values, I expanded my review to include analytical testing for (b) (4), (b) (4), (b) (4) and (b) (4). (b) (4) and (b) (4) exhibited an increased rate of repeat testing (see **Exhibit 42** for repeat testing incidents and **Exhibit 44** for a list of the number of batches manufactured). For example, the number of (b) (4) batches was approximately 50% of (b) (4) and 160% of (b) (4). However, only a single batch of (b) (4) was subject to retesting due to a differential in replicate assay testing, while 8 batches of (b) (4) were retested and 16 batches of (b) (4) were retested. Ergo, when normalized to testing rate, (b) (4) and (b) (4) exhibit a higher relative proportion of retesting of assay due to discrepancies in replicates.

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) exhibited an average differential in assay results of approximately (b) (4)% (with the acceptable range of the specification spanning (b)(4)%). I asked Qiangming Li, 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. He did not provide a sustentative explanation. Mr. Li only specified that for (b) (4), this is an analytical method issue (the assay is conducted at the upper end of the linearity), which he claimed had been resolved in March via a change request (changing the method), but ultimately this remedy did not appear effective. I reviewed the change request (SLRC-17002) (**Exhibit 45**) for altering this method and noted continuation of retesting the assay due to a greater than (b)(4)% differential among replicates. Specifically, the change was affected in March 2017, so I reviewed assay testing of (b) (4) since then and noted three instances of where assay was repeated due to a differential in assay replicates (see **Exhibit 46** for the injection history and corresponding lab notebook pages). I asked Mr. Li for an explanation of why the method alteration was considered as resolving the issue, but he did not provide a response.

Given that the firm repeats assay testing due to variation among assay replicates (even in instances of OOSs and OOTs), it is unclear how the firm demonstrates the validity of their assay testing. This situation was further complicated due to the current variation in testing for (b) (4) not being reflected in the original method validation (**Exhibit 47**). Finally, I obtained assay trending from a recent annual product review for (b) (4) (**Exhibit 48**) and (b) (4) (**Exhibit 49**). Given the

wide variability between injection replicates and the widespread rejection and retests seen in this assay method, there is no assurance that the test method as validated, is suitable for its intended use. Additionally, the lack of investigation of rejected injection results casts a cloud of uncertainty over the accuracy of test results used in approval and release of the firm's finished API products.

This variation in testing may relate to ***Verbal Item 2*** which discusses the firm invalidating customer complaints of discrepancies in analytical testing without adequate justification.

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.

An electronic version of the injection history is available in **Exhibit 56**.

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 (see **Exhibit 52** for the CoA and chromatograms). Note the chromatograms include testing of batches (b) (4) and (b) (4), which do not display this peak. The 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) and (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 (see **Exhibit 50** for CoA and chromatograms for batch (b) (4), and **Exhibit 51** for CoA and chromatograms for batch (b) (4)). Note the chromatograms include testing of batches that do not display this peak, demonstrating the peak is not ubiquitous to the test. This peak was substantially larger than that of (b) (4) (b) (4), the subject of the testing. No investigation was conducted.

(c) Impurity testing of (b) (4) batches (b) (4) (b) (4) yielded a prominent, coalescing peak with that of the primary (b) (4) (b) (4) peak (see **Exhibit 53** for CoAs and chromatograms). It is noteworthy that this peak occurs in some but not all chromatograms provided, indicating that it is not ubiquitous to the testing itself. Nevertheless, the impurity was quantitated along with the (b) (4) peak as desired API and no investigation was initiated.

During the inspection, the firm provided a proposed SOP to address laboratory incidents (**Exhibit 54**).

Discussion with Management:

Mr. Jun Du stated that should part 1a and 1b of this Observation truly be OOS, the firm failed to follow their own procedure. I provided the firm time to gather documents for Mr. Du, so he may

confirm the accuracy of the Observation. Upon observing the data, Mr. Du requested that I note that part 1a is an obvious laboratory error due to the high discrepancies between replicates. I stated that I cannot discern what the cause of the original failure had been as there is no investigation, but I will note that there is a large variation between replicates.

Mr. Du promised a written response to the Agency within fifteen business days.

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)). Further, this gasket was fraying, and loose threads were visible (b) (4) (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, a portion of the interior of this (b) (4) was discolored white. 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.

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) .

c) On May 15, 2017, (b) (4) IX-501-2 exhibited particulate matter and (b) (4) paint on the inner face of the gasket to the (b) (4) (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) (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) lot (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) (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.

e) On May 15, 2017, the (b) (4) (b) (4) -802-2 exhibited white particulate facing the interior of the (b) (4) that appeared to originate from the gasket to the (b) (4)

(b) (4)). Further, this (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) (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) (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) (b) (4)
ii. CD-15004 reporting "black metallic particles" in (b) (4) batch (b) (4)
iii. CD-15003 addressing "mixed fragment of (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) (b) (4) ". The affected product is (b) (4) .

Supporting Evidence and Relevance:

In total, I thoroughly inspected the interior of 9 pieces of equipment with deficiencies noted in 7. **Exhibit 7** depicts the last US batch manufactured on the equipment subject to this Observation. The following provides specifics:

a) (b) (4) V-305 exhibited particulate matter and (b) (4) paint on the inner face of the gasket to the (b) (4) (**Exhibit 1** pages 3 -5). Further, this gasket was fraying, and loose threads were visible (b) (4) . The gasket inside the (b) (4) (b) (4) – API contact surface) had deteriorated such that the missing portions could not be accounted for (**Exhibit 1** pages 6 -7). Further, this gasket was discolored brown. Finally, a portion of the interior of this (b) (4) was discolored white (**Exhibit 1** pages 8 -9). This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) (b) (4) intended for the US market (**Exhibit 8**). This equipment was in the clean status (**Exhibit 1** pages 1 -2). Most of the other equipment in this synthetic area were not clean or not in use. The equipment had been painted in April of 2017 (**Exhibit 19**).

b) I observed (b) (4) J09-805 used in API (b) (4) . The (b) (4) to (b) (4) J09-805 contained screws displaying a reddish-brown discoloration consistent with rust (interior of the (b) (4) – where API contacts) (**Exhibit 1** pages 12 -15). This (b) (4) was utilized in the manufacture of (b) (4) lot (b) (4) intended for the US market

(**Exhibit 9**). This equipment was in the clean status and is used in the [(b) (4)] [(b) (4)] (**Exhibit 1** pages 10 -11).

c) I requested and had [(b) (4)] IX-501-2 opened (**Exhibit 1** page 18). After opening the [(b) (4)] particulate matter was released from the [(b) (4)] soiling the operator (and my) hand (**Exhibit 1** pages 19 -21). Similar particulate matter and [(b) (4)] paint was observed on the inner face of the gasket to the [(b) (4)] (**Exhibit 1** pages 22 -25). Further, this gasket was fraying, and loose threads were visible [(b) (4)] [(b) (4)] (**Exhibit 1** page 26). The gasket inside the [(b) (4)] had deteriorated such that the missing portions could not be accounted for (**Exhibit 1** pages 28 -29). Further, this gasket was discolored brown. Finally, the interior of this [(b) (4)] was discolored brown (**Exhibit 1** pages 28 -31). This [(b) (4)] was utilized in the manufacture of [(b) (4)] lot [(b) (4)] intended for the US market (**Exhibit 10**). This equipment was in the clean status (**Exhibit 1** pages 16 -17).

d) [(b) (4)] [(b) (4)] IX-501-1 exhibited what appeared to be flaking of the surface to the [(b) (4)] (**Exhibit 1** pages 41 -42). The gasket inside the [(b) (4)] had deteriorated such that portions of the gasket were missing and threads of the gasket were fraying (**Exhibit 1** page 40). Additionally, the [(b) (4)] interior of the [(b) (4)] was discolored in a manner consistent with rust (**Exhibit 1** page 40). This [(b) (4)] was utilized in the manufacture of [(b) (4)] lot [(b) (4)] intended for the US market (**Exhibit 11**). This equipment was in the clean status.

e) [(b) (4)] [(b) (4)] -802-2 exhibited white particulates / residue facing the interior of the [(b) (4)] that appeared to originate from the gasket to the [(b) (4)] [(b) (4)] (**Exhibit 1** pages 45 -47). Further, this [(b) (4)] appeared heavily scratched (**Exhibit 1** page 48). Later, the scratching was attributed to [(b) (4)]. However, evidence supporting this sentiment was not provided during the inspection. This [(b) (4)] was utilized in the manufacture of [(b) (4)] lot [(b) (4)] intended for the US market (**Exhibit 13**). This equipment was in the clean status and is used in the [(b) (4)] [(b) (4)].

f) [(b) (4)] III-319 exhibited what appeared to white particulate matter in the interior of the [(b) (4)] (**Exhibit 1** pages 51 -52). The gasket inside the [(b) (4)] [(b) (4)] had deteriorated such that portions of the gasket were missing, and other areas had no observable gasket (**Exhibit 1** pages 53 -58). To fully document this situation, I procured a video demonstrating the interior of the [(b) (4)] showing all angles of the gasket area (**Exhibit 56**). This [(b) (4)] was utilized in the manufacture of [(b) (4)] lot [(b) (4)] intended for the US market (**Exhibit 13**). This equipment was in the clean status (**Exhibit 1** pages 49 -50).

Additional Example:

[(b) (4)] IX-501exhibited what appeared to be flaking brown material from the surface to the [(b) (4)] (**Exhibit 1** pages 34 -35). The gasket inside the [(b) (4)]

(b) (4) was warped and threads of the gasket were fraying (**Exhibit 1** pages 36 -37). This equipment was in the clean status (**Exhibit 1** pages 32 -33).

The following complaints pertain to foreign materials in API that may be associated with the lack of equipment maintenance:

i. CC-16006 addressing "(b) (4) particles, (b) (4) color, yellow rust" in (b) (4) batch (b) (4) (b) (4) (**Exhibit 14**). This investigation concludes "Through investigation, no any abnormal situation was occurred during our manufacturing process of (b) (4), so it's not possible to have the foreign matters in the final (b) (4)."

ii. CD-15004 reporting "black metallic particles" in (b) (4) batch (b) (4) (**Exhibit 15**). This investigation concludes "There is a very small possibility of metallic foreign matter introduced into material during (b) (4) production and packaging, but the possibility of metallic foreign matter was generated by clean area equipment can be ruled out." The basis for this sentiment is not discussed; however, the complaint goes on to require "verify equipment integrity".

iii. CD-15003 addressing "mixed fragment of (b) (4)" in (b) (4) (b) (4) batch (b) (4) (**Exhibit 16**). The investigation report for this complaint identifies that "Foreign matters 2 might be the mixed fragment of (b) (4) (b) (4) generated during (b) (4)". The report then goes on to discuss increased maintenance intervals.

iv. CD-15006 stating "black particles were found in (b) (4) batch (b) (4)" (**Exhibit 17**). The conclusion identifies the cause as equipment related.

v. CD-15001 reporting "That (b) (4) particles is (b) (4) (b) (4)" (**Exhibit 18**). The affected product is (b) (4). The report concludes "Above all, during production and packaging of (b) (4), risk for introducing metal particles is relatively low."

Despite these complaints, the condition and maintenance of equipment has not been comprehensively assessed.

Potentially relevant SOPs were noted:

SOP CB-1728-2 titled "Regulation on equipment and pipeline's connections and sealing management" requires the gasket of the (b) (4) to be assessed (b) (4) the equipment is opened (**Exhibit 20**). This SOP is silent regarding the maintenance of the gasket (b) (4) (b) (4). Mr. (b) (6) explained that an SOP does not define the maintenance of that gasket.

SOP CD-080-6 titled "Maintenance procedure of (b) (4)" calls for (b) (4) tests on (b) (4) (b) (4) intervals (**Exhibit 21**).

During the inspection, the firm acknowledged the findings and provided proposed corrective actions (**Exhibit 22**).

Discussion with Management:

During closeout, Mr. Jun Du explained that these issues are associated with the age of the equipment. He called my attention to the firm refurbishing Building (b)(4) documented in change request Q/ZHHJG 163-4 effective December 10, 2015. Mr. (b)(6) had explained this change control as requiring the facilities to be updated due to production demands and equipment / facility age. I noted that the firm continues API manufacture without a comprehensive facility assessment and has consumer complaints potentially stemming from the equipment condition.

Additionally, Mr. Jun Du provided a draft document (**Exhibit 22**) acknowledging the aforementioned Observation and proposing corrective action.

Mr. Du promised a written response to the Agency within fifteen business days.

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."

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".

Supporting Evidence and Relevance:

See **Exhibit 23** for SOP SMP-021.07 governing OOSs.

a) Report OOS-CQC15067 relating to (b)(4) batch (b)(4) was reported "Unknown impurity peak is appeared under unknown reason" (see **Exhibit 24** for the OOS Report with associated CoA and **Exhibit 25** for the OOS summary indicating the attribution). I addressed this OOS with Mr. Qiangming Li – Director, Quality Control, API Chuannan site, as translated by Mr. (b)(6). I noted that the OOS report indicates a laboratory error, so I asked Mr. Li what the exact error was. Mr. Li replied that the firm knew it was a laboratory error because upon retest the sample, the peak was no longer present. He also said that the peak may originate from column contamination, although he was not aware of why the contamination would present in this specific sample. I attempted to delineate why the firm considers the initial OOS result invalid, but a passing retest as valid. Upon inquiry with Mr. Li, Mr. Jun Du clarified that this is a "ghost peak". I indicated that I am not familiar with this concept and Mr. Du explained that this unknown peak causing

the OOS as a "ghost peak" that appears from time to time in chromatograms for undetermined reasons. Thus, without an indication of the cause of the out-of-specification, an attribution of "Lab error was made."

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 (see **Exhibit 26** for the OOS Report with associated CoA and **Exhibit 25** for the OOS summary indicating the attribution). This investigation attributed the failure to "Pollution" from the environment during sample preparation. The corrective action indicates that windows be closed upon testing, along with analysts conducting olfactory examination for possible pollution. I broadly asked the firm that should pollution be causing an OOS result for residual solvents, what are the implications with the reliability of the analytical method and how does the firm ensure the pollution does not contaminate the API which is manufactured in this environment. Mr. Du reiterated that Phase I laboratory investigation failed to identify a laboratory error. He then specified that the retest had passed, so the analysts were "looking for root cause" and made a mistake. He then asked me if I observed poor environmental conditions throughout my 5 day inspection. Mr. Du assured me the root cause of pollution was inaccurate and the analysts had sought to come up for an explanation of the original failure.

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) %) (see **Exhibit 27** for the OOS Report and **Exhibit 25** for the OOS summary indicating the attribution). This was assigned as a "Lab error" due to "possible" residue in the column. I inquired with Mr. Li about why this impurity specifically eluted in the (b) (4) analytical test of the testing sequence (i.e. not the blank or other testing). Additionally, I asked for supporting evidence. Again, the firm referenced a "ghost peak" appearing in chromatograms in an inconsistent matter.

Relevance: For this Observation, it appears that the firm had invalidated OOSs without a logical attribution. Further, when I inquired into the OOSs due to aberrant peaks, the firm referenced "ghost peaks" that appear in no discernable pattern or consistency (Note: a similar attribution was made with regards to ***Observation 1.2***). If this is indeed the case, it is not entirely clear how the firm ensures the integrity of column based analytical testing in general. Additionally, testing that is within specification is considered valid without further review; however, OOS results are invalidated without a scientific justification.

Discussion with Management:

Mr. Jun Du assured me that pollution was not affecting residual solvent of drug product and that he understood the Observation. Mr. Du promised a written response to the Agency within fifteen business days.

GENERAL DISCUSSION WITH MANAGEMENT

Two items were discussed verbally with the firm:

1 - Analytical methods pertaining to (b) (4) for (b) (4) are not validated.

I perused applicable documentation prior to the inspection and reviewed analytical methods contained in the (b) (4) (**Attachment 1**). A review of the analytical methodology from (b) (4) (b) (4) (**Attachment 1**) states in multiple methods "Sonicate if necessary". As such, I provided my (b) (4) to Huahai and asked for an explanation (**Attachment 1**). Further, I asked Huahai how the method for testing (b) (4) is considered validated or reproducible if sample and standard preparation varies. The firm responded by stating that (b) (4) (b) (4) without their concurrence. I asked for this to be indicated in writing and was provided **Exhibit 6**. This document even notes that the firm does not agree with this "sonicate if necessary" statement in analytical methods. Further **Exhibit 6** indicates that Huahai had not agreed with (b) (4) in regards to the method of analysis. Most importantly, Huahia stated (and provided in writing in **Exhibit 6**) that the analytical method validation was "uncompleted".

2 - Complaints are invalidated without documenting the rationale.

Complaints are covered under SOP SMP-011.07 titled "Complaint management procedure" (**Exhibit 31**). Additionally, **Exhibit 32** encompasses a list of complaints. I noted reoccurring complaints pertained to discrepancies in testing between Huahai and their consignees. To address the firm's handling of complaints describing testing disparities, I had the firm generate a list of such complaints, as well as associated pie charts (**Exhibit 33**). From 2015 until May 2017, 13 complaints related to discrepancies between Huahai's test results and their consignees results. Of these complaints 85% had what the firm termed "Customer has no subsequent feedback or treatment." Specifically, this 85% was further broken down into 3 categories: the batch subject to the complaint was sent to other consignees who did not report a complaint, there is a test method discrepancy and feedback was provided to the consignee without a response and the consignee failed to respond but continued to purchase API from Huahai. Several of these complaints were collected (**Exhibits 34 – 37**). Essentially, Huahai presumes that a lack of further communication is indicative of acceptable product quality. I queried how the firm justifies this practice given the discrepancies in their own test results (see ***Observation 1***). I additionally indicated that this was of concern given that many consignees may subject the API solely to identity testing, as required by the GMPs.

For example, complaint CC-16008 (**Exhibit 37**) pertains to a discrepancy in testing of (b) (4) (b) (4) content in (b) (4). This complaint had been dismissed due to a lack of feedback by the customer. However, the firm has had repeated OOS results for this same testing and has attributed it to the sensitivity of the test method (see **Exhibit 25** for the listings in the OOS summary and **Exhibit 38** for copies of such OOS reports).

ADDITIONAL INFORMATION

Note that this facility is a large campus with many buildings that lack readily obtainable access to an elevator. As such, sufficient amount of walking and climbing stairs may be expected.

SAMPLES COLLECTED

No samples were collected during this inspection.

VOLUNTARY CORRECTIONS

Actions taken in response to concerns are discussed in the body of this report where the Observations report the underlying issue.

EXHIBITS COLLECTED

Exhibit 1 - Huahai pics, 58 pages
Exhibit 2 - Introductory Presentation, 18 pages
Exhibit 3 - APIs for the US, 21 pages
Exhibit 4 - US Customers, 2 pages
Exhibit 5 - Organizational Chart, 2 pages
Exhibit 6 - (b) (4) Presentation, 39 pages
Exhibit 7 - Last US batch manufactured on the equipment, 1 page
Exhibit 8 - Lot (b) (4) information, 3 pages
Exhibit 9 - Lot information, 3 pages
Exhibit 10 - Lot (b) (4) information, 3 pages
Exhibit 11 - Lot information, 3 pages
Exhibit 12 - Lot information, 3 pages
Exhibit 13 - Lot information, 3 pages
Exhibit 14 - CC-16006, 3 pages
Exhibit 15 - CD-15004, 9 pages
Exhibit 16 - CD-15003, 26 pages
Exhibit 17 - CD-15006, 6 pages
Exhibit 18 - CD-15001, 6 pages
Exhibit 19 - Painting of (b) (4), 2 pages
Exhibit 20 - SOP CB-1728-2, 5 pages
Exhibit 21 - SOP CD-080-6, 4 pages
Exhibit 22 - Draft report on Equipment, 21 pages
Exhibit 23 - SOP SMP-021.07, 49 pages
Exhibit 24 - OOS-CQC15067, 40 pages
Exhibit 25 - OOS Summary, 27 pages
Exhibit 26 - OOS-CQC16103, 13 pages
Exhibit 27 - OOS-CQC15103, 18 pages
Exhibit 28 - Reprocessed Batches, 9 pages
Exhibit 29 - Deviation List, 2 pages
Exhibit 30 - Batch Coding, 1 page
Exhibit 31 - SOP SMP-011.07, 23 pages
Exhibit 32 - Complaint List, 22 pages
Exhibit 33 - Complaint Trends, 6 pages
Exhibit 34 - CC-15006, 13 pages
Exhibit 35 - CC-16003, 9 pages
Exhibit 36 - CC-16011, 26 pages
Exhibit 37 - CC-16008, 18 pages
Exhibit 38 - OOS Reports, 36 pages
Exhibit 39 - SOP QC-024-5, 17 pages

Exhibit 40 - Batch (b) (4) Testing, 7 pages
Exhibit 41 - Batch (b) (4) Testing, 6 pages
Exhibit 42 - Assay Summary, 2 pages
Exhibit 43 - OOT Limits, 5 pages
Exhibit 44 - Batch Numbers, 1 page
Exhibit 45 - SLRC-17002, 12 pages
Exhibit 46 - (b) (4) Injection History, 13 pages
Exhibit 47 - (b) (4) Validation, 48 pages
Exhibit 48 - (b) (4) APR, 3 pages
Exhibit 49 - (b) (4) APR, 3 pages
Exhibit 50 - Batch (b) (4) Testing, 12 pages
Exhibit 51 - Batch Testing, 12 pages
Exhibit 52 - Batch Testing, 4 pages
Exhibit 53 - (b) (4) Testing, 14 pages
Exhibit 54 - Lab Event Proposal SOP
Exhibit 55 - CD of Photos, 1 page
Exhibit 56 - Electronic Files in a Sealed CD, 1 page

ATTACHMENTS

Upload Issued Form 483
Attachment 1 - (b) (4) Review, 38 pages

6/7/2017

X Massoud Motamed

Signed by: Massoud Motamed -A

X