Food and Drug Administration Establishment Inspection Report

Date Assigned: 12/20/2016 **Inspection Start Date:** 02/27/2017 **Inspection End Date:** 03/08/2017

Firm Name & Address: Dr. Reddy's Laboratories Ltd. , P1 - P9 V Sez , Phase Iii Duvvada

Firm Mailing Address: P1 - P9 V Sez, Phase Iii, Duvvada ,Andhra Pradesh ,530046, India

FEI: 3006549835 **JD/TA:** **County:** **Est Size:** 1,000,000 - 4,999,999

Phone: ()91 891 270234 **District:** IOG **Profiled:** Yes

Conveyance Type: **% Interstate:** 100 **Inspectional Responsibility:** Center/Field

Endorsement

Continued from inspection summary

The current inspection found the firm continues to manufacture sterile injectable and tablet products for the US market. At the conclusion of the inspection a 13-item FDA 483 was issued including observations for: investigations into discrepancies were not thorough; inadequate procedures for the qualification of visual inspection operators; failure to maintain and evaluate complete data; production records do not contain complete and accurate information; procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed; aseptic processing areas are deficient regarding the system for monitoring environmental conditions; procedures for the preparation of master production and control records are not followed; appropriate controls are not exercised over computer or related systems; data is not documented contemporaneously; thorough review of documents is not performed; procedures for maintenance of equipment had not been established and followed; samples taken for process validation are not scientifically justified; and samples collected to evaluate conformance of a batch are not representative. In addition, repeated instances of employees providing false or misleading statements was discussed with firm management.

Firm management promised corrections to all observations and committed to providing an initial written response within 15 business days. No samples were collected and there were no refusals. The facility has a current drug registration.

Initial Classification: OAI
Final Classification: CDER/OC

Distribution:
O: CDER/OC
EIR in OSAR- DMPTI via eNSpect

Endorsement Location:

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

Food and Drug Administration Establishment Inspection Report

FEI: 3006549835 **Inspection Start Date:** 02/27/2017 **Inspection End Date:** 03/08/2017

Firm Name & Address: Dr. Reddy's Laboratories Ltd. , P1 - P9 V Sez , Phase Iii Duvvada

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

Registration Type		Registration Dates		
DRG	Drug	01/01/2018	11/01/2016	04/01/2016
GDF	GDUFA Self-Identified Firm	01/01/2017		

Establishment Type		Industry Code	
M	Manufacturer	60	Human and Animal Drugs
M	Manufacturer	61	Human and Animal Drugs
M	Manufacturer	62	Human and Animal Drugs
M	Manufacturer	64	Human and Animal Drugs

District Use Code:

FEI: 3006549835 **Inspection Start Date:** 02/27/2017 **Inspection End Date:** 03/08/2017

Firm Name & Address: Dr. Reddy's Laboratories Ltd. , P1 - P9 V Sez , Phase Iii Duvvada

Inspection Basis: F/U to Warning Letter

Inspected Processes & District Decisions

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

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	10/12/2017	Official Action Indicated (OAI)	Plucinski, Carrie-Ann	CDER-OMQ

Remarks: Regulatory Meeting held with firm on 7-19-17.

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	04/04/2017	Official Action Indicated (OAI)	Boyd, Justin A	IOG

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	04/04/2017	Official Action Indicated (OAI)	Bous, Sherry G	IOG

Remarks:

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

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	10/12/2017	Official Action Indicated (OAI)	Plucinski, Carrie-Ann	CDER-OMQ

Remarks: Regulatory Meeting held with firm on 7-19-17

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
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Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
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Remarks:

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Remarks:

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Food and Drug Administration Establishment Inspection Report

FEI: 3006549835 **Inspection Start Date:** 02/27/2017 **Inspection End Date:** 03/08/2017

Firm Name & Address: Dr. Reddy's Laboratories Ltd. , P1 - P9 V Sez , Phase Iii Duvvada

Products Covered

Product Code	Est Type	Description	Additional Product Description
(b) (4)	Manufacturer	(b) (4) N.E.C. Human - Rx/Single Ingredient Small Volume Parenteral <100ml	(b) (4)
	Manufacturer	(b) (4) Human - Rx/Single Ingredient Small Volume Parenteral <100ml	
	Manufacturer	(b) (4) N.E.C. Human - Rx/Single Ingredient (b) (4) Tablets	(b) (4) Tablets

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Boyd, Justin A	DDC	ORAHQ	56002	Manufacturer	(b) (4)	25
Oladimeji, Toyin B	INV	BLT-DO	56002	Manufacturer		25
Boyd, Justin A	DDC	ORAHQ	56002A	Manufacturer		50
Oladimeji, Toyin B	INV	BLT-DO	56002A	Manufacturer		50
Boyd, Justin A	DDC	ORAHQ	56002A	Manufacturer		50
Oladimeji, Toyin B	INV	BLT-DO	56002A	Manufacturer		50
					Total Hours:	250

Food and Drug Administration Establishment Inspection Report

FEI: 3006549835 **Inspection Start Date:** 02/27/2017 **Inspection End Date:** 03/08/2017

Firm Name & Address: Dr. Reddy's Laboratories Ltd. , P1 - P9 V Sez , Phase Iii Duvvada

Inspection Result

EIR Location	Trips Num
	2017-149D

Inspection Summary

A for cause inspection and Warning Letter follow-up of this foreign pharmaceutical finished dosage manufacturer was conducted per FY17 work plans and assignment #11696932. The inspection covered corrective actions to a corporate Warning Letter 320-16-02 dated November 5, 2015. The firm manufactures profile class SVL, SVS, and TCM. Coverage was given to compliance program 7356.002, Drug Manufacturing Inspections, and compliance program 7356.002A, Sterile Drug Process Inspections. The Quality, Facilities & Equipment, Production, and Laboratory systems received coverage.

The previous FDA inspection was conducted 2/26/2015-3/06/2015 and classified OAI. The inspection resulted in a Warning Letter dated 05 November 2015. There was a 20-item FDA 483, Inspectional Observations, issued that included observations for: use of malfunctioning equipment to manufacture product, failure to initiate an investigation, equipment with difficult to clean surfaces, observation of poor aseptic techniques, no smoke studies supporting the use of equipment, dirty facility surfaces; process validation protocols failed to include acceptance criteria and a lack of statistical sampling representing the manufacturing process; media fills that did not meet the established acceptance criteria, no established rationale for media fill interventions and not including observed interventions in media fills, batch records fail to identify the operators performing operations, no rationale for the placement of temperature probes for monitoring of the media fill incubators, lack of investigation or identification of fibers found in media fill vials; there is no raw data for the internal (b) (4) temperatures for (b) (4) , aeration phase (b) (4) fan speed, no documented rationale for the placement of CIs for the (b) (4) processing, no established system administrator, former employees computer system accounts are still active; smoke studies that do not demonstrate unidirectional airflow during interventions and manipulations; no evaluation of airflow for manual aseptic connections performed in ISO 5 environments; failure to monitoring of non-viable particles for portions of filling operations and failure to monitor non-viable particles during operations; there is no protocol or document to describe the manner with which the integrity test parameters were developed and established; no scientific rationale for the placement of the (b) (4) and biological indicators during their (b) (4) re-qualification of (b) (4) lack of assessment of the alarm events; failure to document the manufacture of visual inspector defect kits used for the qualification of finished product visual inspectors; use of vial defect photos not representative of product at the facility for visual-aids; production unit performing quality unit functions; failure of a laboratory analyst to correctly identify a failing endotoxin test result; the data does not support their current environmental monitoring program; failure to conduct personnel monitoring post sterility testing; use of an unapproved vendor; a lack of review of qualification documents by the current quality assurance department personnel; and the failure of the quality unit to identify and correct problems. Corrective actions for the previously cited observations were evaluated during the current inspection. It was found that numerous items had not been corrected.

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals:

Samples Collected	Recall Numbers	Related Complaints

Food and Drug Administration Establishment Inspection Report

FEI: 3006549835 **Inspection Start Date:** 02/27/2017 **Inspection End Date:** 03/08/2017

Firm Name & Address: Dr. Reddy's Laboratories Ltd. , P1 - P9 V Sez , Phase Iii Duvvada

Sample Number **Recall Number** **Consumer Complaint Number**

FDA 483 Responses

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

Response Type	Response Mode	Response Date	Response Summary

TABLE OF CONTENTS

SUMMARY

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The current inspection found the firm continues to manufacture sterile injectable and tablet products for the US market. At the conclusion of the inspection a 13-item FDA 483 was issued including observations for: investigations into discrepancies were not thorough; inadequate procedures for the qualification of visual inspection operators; failure to maintain and evaluate complete data; production records do not contain complete and accurate information; procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed; aseptic processing areas are deficient regarding the system for monitoring environmental conditions; procedures for the preparation of master production and control records are not followed; appropriate controls are not exercised over computer or related systems; data is not documented contemporaneously; thorough review of documents is not performed; procedures for maintenance of equipment had not been established and followed; samples taken for process validation are not scientifically justified; and samples collected to evaluate conformance of a batch are not representative. In addition, repeated instances of employees providing false or misleading statements was discussed with firm management.

Firm management promised corrections to all observations and committed to providing an initial written response within 15 business days. No samples were collected and there were no refusals. The facility has a current drug registration.

ADMINISTRATIVE DATA

Inspected firm:	Dr. Reddy's Laboratories Ltd.

Location:	Plot No. P1 to P9, Phase III Duvvada, VSEZ Visakhapatnam, India
Phone:	91 891 270234
Mailing address:	Plot No. P1 to P9, Phase III Duvvada, VSEZ Visakhapatnam, India
Dates of inspection:	2/27/2017, 2/28/2017, 3/1/2017, 3/2/2017, 3/3/2017, 3/6/2017, 3/7/2017, 3/8/2017
Days in the facility:	8
Participants:	Justin A. Boyd, Investigator Toyin B. Oladimeji, Investigator

This was a joint inspection conducted by Investigator Boyd and Investigator Oladimeji. Investigator Boyd served as the lead investigator. Portions of this report written by Investigator Oladimeji are identified with the initials "TBO". Portions of the report written by Investigator Boyd are identified "JAB".

HISTORY

(JAB)

Dr. Reddy's Laboratories was established in 1984 by Dr. K Anji Reddy. In 1987 the formulations business started. In 1993 Dr. Reddy's Laboratories entered Research and development by establishing Dr. Reddy's Research Foundation. In 1997 first ANDA with FDA for Ranitidine was filed. In 2001 Dr. Reddy's launched its first generic product (Ranitidine) in the US. Dr. Reddy's is headquartered at Hyderabad, India. Dr. Reddy's has manufacturing locations located in India, United States, Mexico, and United Kingdom. A list of these locations is included as **Exhibit JAB #1.**

This manufacturing site is located at Duvvada, Visakhapatnam Special Economic Zone, which is about 30 km south of Visakhapatnam city (VIZAG), A.P State in India. This site has two manufacturing units, Formulation Technical Operation VII (FTO Unit - 7) and Formulation Technical Operation IX (FTO Unit - 9).

FTO Unit -7

FTO-7 facility is designed to manufacture, process, pack, hold, release and stability monitoring of drug products of (b) (4) category & potent drugs using (b) (4) technology. This plant was commissioned in the year 2006. Unit FTO-7 was covered during this inspection.

FTO Unit- 9

FTO-9 facility is designed to manufacture, process, pack, hold, release and stability monitoring of drug products of general injectable, (b) (4) using (b) (4) and form fill seal

technology. This Block was constructed and qualified in 2014. There has been no commercial manufacturing at this site at the time of the inspection. Unit FTO-9 was not covered during this inspection.

Previous FDA inspections of Unit VII were conducted January 2013 (NAI), November 2009 (NAI), and February 2008 (OAI). The February 2008 inspection resulted in the issuance of an Untitled Letter which cited discrepancies between used and reported number of Biological Indicators (BI) and periodic leak testing or dynamic monitoring of the (b) (4) for non-viable particles was not conducted.

The most recent FDA inspection was conducted 2/26/2015-3/06/2015 and classified OAI. There was a 20-item FDA 483, Inspectional Observations, issued that included observations for: use of malfunctioning equipment to manufacture product, failure to initiate an investigation, equipment with difficult to clean surfaces, observation of poor aseptic techniques, no smoke studies supporting the use of equipment, dirty facility surfaces; process validation protocols failed to include acceptance criteria and a lack of statistical sampling representing the manufacturing process; media fills that did not meet the established acceptance criteria, no established rationale for media fill interventions and not including observed interventions in media fills, batch records fail to identify the operators performing operations, no rationale for the placement of temperature probes for monitoring of the media fill incubators, lack of investigation or identification of fibers found in media fill vials; there is no raw data for the internal (b) (4) temperatures for (b) (4) aeration phase (b) (4) fan speed, no documented rationale for the placement of CIs for the (b) (4) processing, no established system administrator, former employees computer system accounts are still active; smoke studies that do not demonstrate unidirectional airflow during interventions and manipulations; no evaluation of airflow for manual aseptic connections performed in ISO 5 environments; failure to monitoring of non-viable particles for portions of filling operations and failure to monitor non-viable particles during operations; there is no protocol or document to describe the manner with which the integrity test parameters were developed and established; no scientific rationale for the placement of the (b) (4) (b) (4) and biological indicators during their (b) (4) re-qualification of (b) (4) lack of assessment of the alarm events; failure to document the manufacture of visual inspector defect kits used for the qualification of finished product visual inspectors; use of vial defect photos not representative of product at the facility for visual-aids; production unit performing quality unit functions; failure of a laboratory analyst to correctly identify a failing endotoxin test result; the firm's data does not support their current environmental monitoring program; failure to conduct personnel monitoring post sterility testing; use of an unapproved vendor; a lack of review of qualification documents by the current quality assurance department personnel; and the failure of the quality unit to identify and correct problems.

Dr. Reddy's received a corporate Warning Letter 320-16-02 dated November 5, 2015. The Warning Letter cited three Dr. Reddy sites Unit V, Unit VI, and this inspected site, which is Unit VII. Unit V and VI manufacture API while Unit VII manufactures finished drug products. The Warning Letter included cites related to data integrity at Unit VI such as the presence of unreported data, software lacked access controls, missing data was entered into batch records at a later date, and inadequate

document control. Cites at Unit V included failure to conduct out-of-specification (OOS) investigations, unauthorized photocopying of labels, analysts were permitted to release product without quality unit approval, and storage containers were not identified to prevent mix-ups. Specific to this inspected site, Unit VII, the Warning Letter cited failure to thoroughly investigate equipment malfunctions of the filling line, media fill units were rejected without justification, and the process to qualify visual inspectors was not adequate.

Official FDA correspondence should be addressed to:
Mr. Satish Reddy, Chairman
Dr. Reddy's Laboratories Limited,
8-2-337, Road No.3
Banjara Hills, Hyderabad
Telangana- 500034, India
Tel: +91-40-49002900
Fax: +91-40-49002999

FMD-145 correspondence to the most responsible individual onsite should be addressed to:
Mr. Vikramkumar B Shukla
Vice President: Head Injectable and Vizag Cluster (Site Head)
Tel: +91-891-2702349
Fax: +91-891-2514650
E-mail: vikramshukla@drreddys.com

The firm's US Agent is:
Srinivasa Rao, Vice President and Head, Regulatory Affairs-North America
Dr. Reddy's Laboratories Inc.
107, College Road East, 2nd Floor
Princeton, New Jersey 08540
Tel: (908)- 635- 7180
Fax: (908)-450-1476
E-mail: srao@drreddys.com

The manufacturing, laboratory, warehouse, and quality department operate (b) (4) (b) (4) Normal business hours for the administrative departments are (b) (4) (b) (4) There are (b) (4) employees at this facility. The facility has a current drug registration.

INTERSTATE COMMERCE

A list of all of the batches that have been shipped to the US market from January 2015-February 2017 is included as **Exhibit JAB #2.**

JURISDICTION

This facility manufactures sterile injectable products including aseptically filled small volume liquid vials, terminally sterilized liquid vials, and (b) (4) vials. The campus also manufactures (b) (4) (b) (4) dosage products for the US market. A list of all products for the US market from Unit VII is included as **Exhibit JAB #3.** A list of all products for the US market intended to be manufactured in Unit IX is included as **Exhibit JAB #4.** A list of all products manufactured on this campus, including those for other markets is included as **Exhibit JAB #5.**

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

At the initiation of this inspection, we presented our FDA credentials and exchanged business cards with the most responsible person for this facility, Vikramkumar B Shukla, Vice President Operations. The personnel present for the initiation of the inspection is included as **Exhibit JAB #6.**

Top management personnel and their duties include:

Name	Job Title	Duties	Reports to
Mr. Satish Reddy	Chairman	Overall the most responsible person for this company.	Board of Directors
Mr. G V Prasad	Co-Chairman & Chief Executive Officer	Chief executive officer of the organization. All employees ultimately report to Mr. GV Prasad. Responsible for hiring or firing Senior Management. Approves capital budgets	Board of Directors
Mr. Ganadhish Kamat	Executive Vice President & Global Head of Quality	Overall responsible for Global Quality. Responsible for hiring or firing Senior Management.	Mr. G V Prasad, Chief Executive Officer
Mr. Vikramkumar B Shukla	Vice President - Head Injectable & Head FTO, Vizag Cluster: Operations	Overall responsible for operation of Vizag cluster including FTO 7 and FTO 9. Responsible for hiring or firing of managers.	Mr Prabhakaran Nair, Sr. Vice President & Head Mfg. FTO-India & EU
Mr. Manish Kumar Choube	Vice President-Head Injectable Quality	Over all responsible for Injectable Quality including FTO 7 and FTO 9. Responsible for hiring or firing of managers.	Mr. Ganadhish Kamat, Executive Vice President & Global Head of Quality
Mr. Debashish Panda	Director - Head Quality Assurance	Head of Quality Assurance for FTO 7 and FTO 9.	Mr. Manish Kumar Choube, Vice President - Head Injectable Quality
Mr. Laxmikant D Tiwari	Director - Head Operations	Overall responsible for Operations related activity and decision at FTO 7.	Mr. Vikramkumar B Shukla, Vice President - Head Injectable & Head FTO, Vizag Cluster: Operations
Mr. Pralhad Nehe	Director - Head Operations	Overall responsible for Operations related activity and decision at FTO 9.	Mr. Vikramkumar B Shukla, Vice President - Head Injectable & Head FTO, Vizag Cluster: Operations

Name	Job Title	Duties	Reports to
Mr. S Karunakaran	Director - Head Quality Control	Head of Quality Control for FTO 7 and FTO 9.	Mr. Manish Kumar Choube, Vice President - Head Injectable Quality
Mr. Ch V V Satyanarayana	Associate Director, Plant QA Head FTO 7	Overall responsible for Quality Assurance related activity and decision at FTO 7.	Mr. Debashish Panda , Director - Head Quality Assurance,
Mr. Nayab Rasool Dudekula	Associate Director and Head QA, Quality Assurance	Overall responsible for Quality Assurance related activity and decision at FTO 9.	Mr. Debashish Panda , Director - Head Quality Assurance,
Mr. Sanjay Patil	Associate Director and Head Microbiology	Head of Microbiology for FTO 7 and FTO 9.	Mr. Manish Kumar Choube , Vice President - Head Injectable Quality

The organizational charts are included as **Exhibit JAB #7.**

FIRM'S TRAINING PROGRAM

(JAB)

I reviewed the training program, which includes GMP training and job specific training. I reviewed training files from selected employees and did not note any significant discrepancies. During review of investigations we found repeated instances that had identified employee errors. The corrective action was to perform additional training. However, the training was not effective in eliminating the repeated employee errors. This is discussed further in **Observation #1.**

MANUFACTURING/DESIGN OPERATIONS

Quality

(JAB)

I reviewed the written procedure for complaints and their complaint list. I chose examples of complaint investigations to review. I did not note any significant discrepancies in the records that I reviewed.

I reviewed the written procedure and the log for Incident investigations. I chose examples of Incidents to review. I found that the Incidents did not include thorough root cause evaluations with appropriate follow-up corrective and preventative actions. This is discussed further in **Observation #1.**

(TBO)

OOSs are investigated per SOP FTCQA058-07, Investigation of Out of Specification Results. I reviewed the following OOSs initiated for the products listed below and observed that thorough investigations were not performed and appropriate corrective action and preventive action was not implemented. **See FDA-483 Observation #1**

(b) (4) Injection

- 310007380, February 05, 2015
- 310007615, March 12, 2015
- 310007627, March 19, 2015
- 310009348, March 18, 2015
- 310010150, August 6, 2015
- 310011171, November 24, 2015

(b) (4) Injection

- 310007275, January 9, 2015
- 310008334, September 5, 2015
- 310010420, September 8, 2015
- 310010591, September 23, 2015
- 310011071, November 14, 2015

(b) (4) Injection

- 310007780, April 18, 2015
- 310008815, November, 10, 2015

(b) (4) Injection

- 310009250, February 16, 2016
- 310009622, May 1, 2016
- 310009706, May 16, 2016
- 310008552, September 22, 2016
- 310009298, February 25, 2016
- 310010270, August 24, 2016

(b) (4) Injection

- 310009719, February 25, 2016
- 310009812, June 20, 2016
- 310009929, July 14, 2016

(b) (4) Injection

- 310010238, August 26, 2016

(b) (4) Injection

- 310011681 – date not recorded

Change Control

Change controls are managed per SOP QM-P02-05. I reviewed the following initiated change controls:

- 200146793, September 4, 2015 – added new specification for (b) (4) injection (b) (4) mg/mL for Russia and Ukraine Market
- 200147414, September 9, 2015 – new batch record for (b) (4) njection to increase batch size from (b) (4) to (b) (4)
- 200152148, October 16, 2015 – addition of new product (b) (4) Injection)
- 200156130, November 18, 2015 – tightening of total impurities for (b) (4) Capsules
- 200159998, December 17, 2015 – temporary change to conduct media fill prior to getting environmental monitoring results
- 200166672, February 9, 2016 – fill volume revision for (b) (4) injection
- 200169776, March 2, 2016 – tightening of yield specification for (b) (4)
- 200212332, December 7, 2016 – modification of privileges in the automatic loading and unloading system (ALUS)

No discrepancies were noted with the change controls reviewed.

Rejects

The firm does not have a procedure that specifically governs handling of rejects. Mr. Rama Krishna, Manager, Quality Assurance, stated that finished products and/or materials are rejected via SAP. I reviewed logbooks that identified rejected raw materials, intermediates, and finished products such as container closures, filters, and garments. A review of the garment inspection record revealed that the rejected garment (Code No.10012017-07 OG) is currently in use. The gown inspector (b) (6) also confirmed that the gown was inspected on 28 February 2017. There is no evidence to show whether this garment is in use or discarded. **See FDA-483 Observation #4.**

Incidents

Incidents are investigated per SOP GQA032-00. I reviewed the initiated incidents listed below. Objectionable observations were noted for failure to thoroughly investigate the incidents related to product leakage to ensure that true root causes have been identified and appropriate corrective actions are implemented. **See FDA-483 Observation #1.**

- 200217386, January 6, 2017 - one broken media fill vial
- 200210831, November 11, 2016 – power failure for continuous particle monitoring system (CPMS)
- 200207627, November 10, 2016 – two incubated vials from media fill was missing

- 200194896, August 26, 2016 – alarms observed in the filling (b) (4)
- 200224221, February 14, 2017 – liquid droplets observed on vials after (b) (4) cycle, investigation is still open
- 200188375, July 19, 2016 – impurity peak was not integrated for (b) (4) injection (b) (4) ng/vial
- 200168017, February 17, 2016 – product leakage during filling of (b) (4) injection
- 200168685, February 22, 2016 – product leakage during filling of (b) (4) injection
- 200193210, August 17, 2016 – product leakage during filling of (b) (4) injection
- 200215055, December 23, 2016 – product leakage during filling of (b) (4) injection
- 200225061, February 19, 2017 – product leakage during filling of (b) (4) injection
- 200198319, September 16, 2016 – product leakage during filling of (b) (4) injection

Facilities and Equipment

(JAB)

During the inspection we conducted a walkthrough inspection of the production facilities. These included Block (b) (4) of Unit VII. The manufacturing campus has two units, identified as Unit VII and Unit IX. Unit IX does not yet produce commercial product and was not covered during this inspection. Unit VII has (b) (4) blocks:

(b) (4)

I found the production facilities appeared to be adequate in size and design to perform necessary operations. The facilities appeared to be maintained in an acceptable manner. The facility does not handle penicillin or beta-lactams.

We observed that the equipment was labeled with its status, identification number, and calibration/qualification dates where applicable. There were associated use logs. We noted deficiencies in the maintenance of (b) (4) surfaces and HEPA filter covers as well as deficient maintenance procedures for (b) (4) This is discussed further in **Observation #11.**

We inspected the (b) (4) system. Each unit has its own (b) (4) system. There is one Unit VII system that has separate loops for Block (b) (4) I did not note any significant discrepancies during inspection of the system. Review of the monitoring indicated that the (b) (4) system has had findings of objectionable organisms, which were not investigated in a rough manner, see **Observation #1.**

(TBO)

Filter Validation

I reviewed the following filter validation reports for the (b) (4) µm filter and no discrepancies were noted:

- Bacterial Retention – (b) (4) µm (b) (4) report # V&Q00808BI-BRR, date: August 27, 2009
- Compatibility – (b) (4) µm µm (b) (4)
- Extractables - (b) (4) µm µm (b) (4) report # V&Q00808131-EXTS, date: March 25, 2010

(b) (4) *Integrity*

I reviewed (b) (4) test reports on the (b) (4) Integrity Unit (PRE-346) and noted that (b) (4) were not replaced after (b) (4) integrity test failures as instructed in SOP OPR519-00, Operation of (b) (4) Integrity Tester. **See FDA-483 Observation #1.**

Equipment/System Controls

I reviewed the controls applied over the support equipment used in production such as (b) (4) (b) (4) filter integrity tester and (b) (4) integrity tested. I noted that the supervisor has access to change the time on the (b) (4) and test results can be deleted from the filter and (b) (4) integrity testers. **See FDA-483 Observation #8.**

Cleaning Validation

I reviewed the cleaning validation reports for (b) (4) Injection, report # FT7PECVR040-00, date: April 12, 2012; and (b) (4) Injection (b) (4) ng/mL, report # FT7PICVR059-00, date: February 16, 2016. No discrepancies were noted in the records I reviewed.

Production

(JAB)

A description of the manufacturing process for the (b) (4) products can be summarized as follows. (b) (4) (b) (4) (b) (4) They are visually inspected manually, labeled, and packaged. There have been no significant changes to this manufacturing process since the previous inspection.

During the inspection we observed the production activities as they were occurring. While we watched production we verified the steps and documentation in the batch records. Review of the entry records for the area indicated the records were not being documented contemporaneously, see **Observation #4.**

We inspected the visual inspection area. Visual inspection is done manually. We reviewed the qualification of visual inspectors and found that it did not thoroughly cover common defects found in (b) (4) products. This was cited in **Observation #2.**

I reviewed the media fill protocols, batch records, and reports for the media fills. I found discrepancies that are described in **Observation #5** for defining how an individual is qualified and inadequate documentation of the activities performed.

(TBO)

Process Validation

I reviewed the process performance qualification (PPQ) for (b) (4) Injection (b) (4) mg/vial, batch (b) (4) and noted that samples collected for finished product testing is not representative of batch size. **See FDA-483 Observation #12.**

Hold Time Study

Hold time study conducted for (b) (4) Injection was summarized under report # FHHTR200016476C. (b) (4) was held for (b) (4) in a (b) (4) mL tank. Chemical and microbial samples were collected (b) (4) for analysis. The study was conducted on 3 batches.

Visual Inspection

Visual inspection is conducted according to SOP OPR012-15, Procedure for Visual Inspection of Filled, Sealed and Over Coded Vials by Using Visual Inspection Hood. The procedure describes evaluation of the particulate matter observed during visual inspection for its color, size, and shape. I

observed that characteristics of fibers were not evaluated for the source on the batches selected for review. **See FDA-483 Observation #1.**

Batch Record Review

A review of (b) (4) Injection, batch (b) (4) batch record was performed. I observed that verification of process steps are not documented contemporaneously in the batch record. According to the Biometric Access System, the employee who verified and signed the "Checked by" column for completion of process step was not present at the time the activity occurred. **See FDA-483 Observation #4.**

Batch Production

I viewed the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) and (b) (4) Injection, batch (b) (4) and observed the following:

- Packaged materials that includes clamps, forceps, twist ties, filters, plastics etc. were stacked in front of the (b) (4) exhaust blocking airflow
- Product leakage was observed on the (b) (4) filter in the (b) (4) during the filling of (b) (4)
- The (b) (4) sealant used to seal the lower bottom area of the (b) (4) appears to be cracking
- The (b) (4) covering the HEPA filters inside the (b) (4) had tears with exposed fibers above open and unstoppered vials

See FDA-483 Observation #1 & 11.

Laboratory

The Unit VII QC chemical lab was expanded and a new microbiology lab was added in 2016. We inspected both of these labs. We found that the that the QC chemistry lab appeared to have the necessary equipment to perform specified analyses, including HPLC, GC, UV, and IR was in place. I found the equipment to be identified and within their calibration/qualification periods. There were log books for laboratory equipment and I verified the log books matched with the sample analysis that I reviewed. There were written methods for tests. System suitability was performed for chromatographic systems.

I reviewed raw data from the analytical records for selected batches. I found the presence of unreported injections that appeared to be samples, even though they had been labeled as system suitability injections. The retrospective data integrity review for the chromatography systems covered Empower, but did not cover Chromeleon. This is described in **Observation #3.**

We inspected the microbiology laboratory. We performed reconciliation of samples and examined the condition of the (b) (4) used. We inspected equipment that included the incubators, sterility testing area, endotoxin test equipment, and microbiology identification equipment. We did not note any significant discrepancies in the equipment we reviewed.

MANUFACTURING CODES

(JAB)

The batch numbering system consists of (b) (4)

(b) (4)

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

At the conclusion of this inspection a FDA 483, Inspectional Observations, was issued to the most responsible individual for this site Vikramkumar B Shukla, Vice President Operations. Firm management committed to correcting the observations and responding in writing to the observations within 15 business days. In addition to Mr. Shukla, a list of the personnel that were present for the closeout discussions is included as **Exhibit JAB #8.**

Observations listed on form FDA 483

OBSERVATION 1

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has already been distributed.

1. On 27 February 2017, during the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) product was observed to have leaked onto the (b) (4) below the (b) (4) filter. This was pointed out to firm management by the FDA investigators. A thorough investigation of the source of this leakage was not performed before dismantling the filter. An investigation was performed and then approved on 02 March 2017. It concluded the observed leakage was from filter (b) (4) before filling started.

This conclusion did not consider that the spilled product was observed at the end of the batch and product from the (b) (4) would have likely evaporated during the filling. Follow-up studies were then conducted as part of the investigation that showed intentionally spilled product evaporated in approximately (b) (4) The amount of time between (b) (4) and the observation of unevaporated spilled product was approximately (b) (4) The updated investigation had been reviewed and signed by Manufacturing and Science Technology, Production, and Quality Assurance concluded "there was no subsequent leakage after (b) (4) of the filter and the spill was most likely from the (b) (4) ", even though the evaporation data did not support this conclusion.

Previous investigations into leakage incidents that occurred during manufacturing have not been thoroughly investigated to ensure true root causes have been identified and appropriate corrective actions are implemented. Despite repeated

investigations, these incidents continue to occur. This was noted during the review of the following quality impacting incident reports:

a. Incident 200168017 was initiated due to product leakage observed on the (b) (4) on the manufacturing vessel before the (b) (4) filter during filling and (b) (4) loading of (b) (4) Injection, (b) (4) mg/vial, batch (b) (4) The incident report indicated that the (b) (4) was not tightened properly. The loss or product resulted into the batch yield not conforming to specification. The procedure was revised to add precautionary steps during connection as preventive action.

b. Incident 200168685 was initiated due to product leakage observed on the (b) (4) connected to the (b) (4) filter prior to filtration during filling of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) The incident report indicated that improper connection as the root cause and the SOP was revised to incorporate instructions and precautions on filtration connections.

c. Incident 200193210 was initiated due to product leakage observed on the (b) (4) gasket of the filtration vessel during filling of (b) (4) Injection, batch (b) (4) The loss of product resulted into batch yield not conforming to specification. Preventive Maintenance Plan (PMP) task checklist was revised to verify all (b) (4) gaskets during scheduled maintenance as preventive action.

d. Incident 200225061 was initiated due to product leakage observed on the (b) (4) filtration filter during filling of (b) (4) Injection, USP (b) mL, batch (b) (4) No assignable root cause has been identified.

e. Incident 200198319 was initiated due to product leakage observed on the (b) (4) connected to the (b) (4) filter prior to filtration during filling of (b) (4) Injection, batch (b) (4) The incident report indicated that improper connection as the root cause. Due to the loss of product, the batch did not conform to yield specification.

f. Incident 200215055 was initiated due to product leakage observed on the (b) (4) connected to the (b) (4) filter prior to filtration during filling of (b) (4) Injection, batch (b) (4) The incident report indicated that the (b) (4) dislodged from the filter causing the product to leak. Awareness training was provided for the operator involved, and line clearance procedure was revised to incorporate pressure verification in the batch record.

2. Collection of trending data for documentation errors, such as GDP errors, calculation errors, missing signatures, or incomplete documentation, began in May of 2016. It identified 314 errors in 22 Batch Manufacturing Records reviewed in May 2016. No critical evaluation of this data was performed to evaluate root causes these errors. These errors repeated in subsequent months. For example:

June 2016 there were 258 errors identified in 15 Batch Manufacturing Records
July 2016 there were 224 errors identified in 17 Batch Manufacturing Records
August 2016 there were 128 errors identified in 21 Batch Manufacturing Records
September 2016 there were 143 errors identified in 22 Batch Manufacturing Records
October 2016 there were 200 errors identified in 21 Batch Manufacturing Records

No evaluation was performed to determine root causes or evaluate why localized training of the affected personnel was ineffective in eliminating errors.

3. Investigations into observations of objectionable organisms in the (b) (4) system were not thorough.

a. (b) (4) identification of isolates from the (b) (4) system identified the objectionable organism Burkholderia cepacia from point (b) (4) for sampling performed 01 August 2014. No root cause was determined and no corrective

actions were performed. No additional identification was conducted to determine if other recovered organisms in subsequent samples were also Burkholderia cepacia.

b. Subsequent[(b) (4)] identification from samples collected on 30 August 2014 (points[(b) (4)] and samples collected 21 September 2014 (point[(b) (4)] identified the objectionable organism Acenitobacter baumanii. No root cause was determined and no corrective actions were performed. No additional identification was conducted to determine if other recovered organisms were also Acenitobacter baumanii.

c. Incident 200135364 was opened when[(b) (4)] identifications of isolates from the[(b) (4)] system identified the objectionable organism Burkholderia cepacia from point[(b) (4)] for sampling perfo 2015. No definitive root cause was determined. The report did not describe historical data, which had previously identified this organism. A potential root cause was identified to be the sampling hose touching a nearby drain. No sampling of the drain was performed to further confirm this root cause. No expanded identification of recovered microbial growth from[(b) (4)] [(b) (4)] sampling was conducted to verify if this organism was present in subsequent sampling.

d. Incident 200142186 was opened when[(b) (4)] identifications of isolates from the[(b) (4)] system identified the objectionable organism Vibrio vulnificus from point[(b) (4)] for sampling performed 23 July 2015. The result was reported 30 July 2015. On 31 July 2015 use of the system was suspended and the system was sanitized. Sampling was repeated on 01 August 2015 and identifications were performed. Vibrio vulnificus was not identified, but other objectionable microorganisms were found: Burkholderia cepacia (4 use points) and Acinetobacter haemolyticus (1 use point).

Sanitization was again repeated on 11 August 2015 followed by sampling and isolate identification. This follow-up sampling again identified the objectionable organisms Burkholderia cepacia (2 use points) as well as Pseudomonas and Acinetobacter organisms.

Sanitization was again repeated on 20 August 2015 and 21 August 2015 followed by sampling and isolate identification. Follow-up sampling again identified the objectionable organisms Burkholderia cepacia (1 use point) on 07 September 2015 from a sample collected 28 August 2015. The[(b) (4)] system had already been cleared for use on 04 September 2015. This is prior to implementation of corrective actions identified in the investigation. No additional actions were specified after the additional finding on 07 September 2015.

The report justified release of[(b) (4)] Tablets batch[(b) (4)] manufactured at the time the original Vibrio vulnificus was detected, based on microbial limits and specified organisms testing. No studies were performed to show the objectionable organisms identified in the[(b) (4)] system during this investigation and previous investigations identified in 3a, 3b, and 3c could be reliably detected by the existing microbial test methods.

The final investigation report evaluated historical trending of objectionable organisms in the[(b) (4)] system. Those instances described in points 3a, 3b, and 3c of this observation were not included in th aluation.

4. Incident 200166175 was opened when Staphylococcus aureus was identified during active air monitoring of the[(b) (4)] Block[(b) (4)] dispensing laminar flow hood point[(b) (4)] on 25 January 2016. The investigation identified the likely root cause as improper gowning and hygiene of employees. The corrective action was identified to be training of personnel when the investigation was closed on 16 February 2016. The first training was not held until 22 March 2016 and some personnel were not trained until 20 April 2016. Additionally, there was no expanded follow-up sampling or identification of isolates to evaluate whether training had been effective.

5. The[(b) (4)] Integrity Test Unit (HSPG-4) equipment #PRE-346 is used to perform an integrity test of the [(b) (4)] that are used for the[(b) (4)] SOP OPR519-00, "Operation of[(b) (4)] Integrity Tester", states in part "In case of failure of[(b) (4)] integrity test, write justification for the failure and repeat the test only for that particular failed[(b) (4)] …and if the[(b) (4)] integrity passes, then proceed for the next routine activity. If integrity failure is confirmed, then immediately inform the superior and replace the faulty[(b) (4)] with new[(b) (4)] and perform the[(b) (4)] integrity test before the start of the[(b) (4)] leak test". A[(b) (4)] replacement was not performed after[(b) (4)] integrity test failed twice,

superior was not notified per instructions in the SOP, and investigations were not initiated. This was evidenced on the following instances:

a [redacted] Number [redacted]-18, Batch Report 1062 for batch [redacted] post-fill)
b [redacted] Number [redacted]-11, Batch Report 1078 for batch [redacted] pre-fill)
c [redacted] Number [redacted]-15, Batch Report 1158, not batch related
d [redacted] Number [redacted]-13, Batch Report 1158, not batch related
e [redacted] Number [redacted]-08, Batch Report 1165, for batch [redacted] pre-fill)
f. [redacted] Number [redacted] 25, Batch Report 1171, for batch [redacted] post-fill)

6. Thorough investigations with scientifically justifiable conclusions to incidents of out-of-specification (OOS) were not performed and/or failed to implement appropriate corrective actions for the root cause determination. The corrective action and preventive action (CAPA) state that training awareness should be conducted; however due to the number of repeated analyst errors identified as the root cause, there is no assurance that the CAPAs are effective in addressing the actual causes as the incidences attributed to analyst errors still continue. The deficiencies are evidenced in the following:

a. OOS 310009438 was initiated due to OOS result obtained during stability testing of [redacted] Injection [redacted] mg/vial, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated that analyst error attributed to the failure. However, the investigation did not identify the specific analyst error even though the procedures stipulated in the test method were followed. No actual or probable root cause was identified. The samples were reanalyzed and passing result was reported.

b. OOS 310007780 was initiated due to OOS obtained during analysis of [redacted] Injection [redacted] mg/vial, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated analyst error was attributed to the failure. However, a specific analyst error was not identified. The samples were reanalyzed and passing result was reported.

c. OOS 310008334 was initiated due to OOS obtained during analysis of [redacted] Injection USP [redacted] mg [redacted] mL, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated analyst error was attributed to the failure. The samples were reanalyzed and passing result was reported.

d. OOS 310009250 was initiated due to OOS obtained during analysis of [redacted] Injection [redacted] mg/vial, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated analyst error was attributed to the failure. The samples were reanalyzed and passing result was reported.

e. OOS 310009706 was initiated due to OOS obtained during analysis of [redacted] Injection [redacted] mg/vial, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated transient equipment error was root cause and awareness training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

f. OOS 310009622 was initiated due to OOS obtained during analysis of [redacted] Injection [redacted] mg/vial [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated unknown analytical error attributed to the root cause – there was a delay in injecting the samples. Training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

g. OOS 310010270 was initiated due to OOS obtained during analysis of [redacted] Injection [redacted] mg/vial, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated analyst error was root cause – there was a delay in injecting the samples. Awareness training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

h. OOS 310008552 was initiated due to OOS obtained during analysis of [redacted] Injection [redacted] mg/vial, batch [redacted] Assay result yielded a failing result of [redacted] % against a specification of [redacted] % - [redacted] %. The investigation report indicated that sampling error by the analyst was the root cause and the quality assurance manager stated that there was

also a delay in receiving samples. Training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

i. OOS 310009929 was initiated due to OOS obtained during particulate matter test of stability sample of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Test results obtained did not meet specification of ≥(b) (4) µ: NMT (b) (4) and ≥(b) (4) µ NMT (b) (4) Analyst error was identified as the root cause and no corrective action was initiated. The samples were reanalyzed and passing result was reported.

j. OOS 310010238 was initiated due to OOS obtained during particulate matter test of (b) (4) Injection (b) (4) mg, batch (b) (4) Test results obtained did not meet specification of ≥(b) (4) µ: NMT (b) (4) and ≥(b) (4) µ NMT (b) (4) No assignable root cause was identified. The analyst involved was trained as a corrective action. The samples were reanalyzed and passing result was reported.

7. There was a failure to identify the characteristics of the fiber/particle rejects, or determine the source of the fibers/particulates in injectable products. SOP OPR012-15, Procedure for Visual Inspection of Filled, Sealed and Over Coded Vials by Using Visual Inspection Hood, describes evaluation of the particulate matter observed during visual inspection for its color, size, and shape. The drug products listed below had rejected vials with (b) (4) fibers that were not characterized or evaluated for a source:

a. (b) (4) Injection, batch (b) (4)

b. (b) (4) Injection, batch (b) (4)

c. (b) (4) Injection, USP (b) (4) mg/vial, batch (b) (4)

Failure to perform thorough investigations is a REPEAT OBSERVATION from the 05 November 2015 FDA WARNING LETTER.

Supporting Evidence and Relevance:

The 05 November 2015 FDA Warning Letter cited the firm for performing inadequate investigations.

1. (JAB) On 27 February 2017 we observed the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) At approximately 11:30am, we observed liquid, on the (b) (4) (b) (4) below the (b) (4) filter. We did not immediately point this out to management and production staff, but did inform them 10-15 minutes later as no actions had been taken by the personnel working in this area. We asked for a camera to be brought into this area. A picture was taken at approximately 12:00pm. The picture is included as **Exhibit JAB #9.**

   After we had pointed out the leak to the operators, we remained in the area to watch post filling activities. We noticed that by (b) (4) pm, the product had evaporated and left a (b) (4) residue. At a later time Mr. Tiwari, Director of Operations for FTO7, informed me the liquid was from the (b) (4) of the filter and they were not concerned that the (b) (4) filter was leaking. I asked when the (b) (4) had occurred and he told me at the beginning of the batch, at approximately (b) (4) am. I explained that based on how quickly the liquid evaporated that it seemed improbable the liquid we observed was from the (b) (4) of the filter. The liquid was present in an area with laminar flow and once evaporated, it left (b) (4) residue. When we

first observed the liquid, there was no (b) (4) residue to indicate the evaporation had occurred. Mr. Tiwari told me they would investigate further. At this time the filter was still assembled the same as it was during filling and could have been further evaluated.

On 02 March 2017 I asked to see the investigation into this incident. I was told it had been completed, approved, and the signed investigation was provided to me, see **Exhibit JAB #10.** The investigation included taking swab samples of the dried residue after the liquid had evaporated. This confirmed the residue to be the product (b) (4) The investigation findings state this liquid was the result of (b) (4) of the (b) (4) at the start of the filling process. During (b) (4) droplets would exit the (b) (4) filter.

This same explanation had been given to me on the date of occurrence and I had specifically pointed out to Mr. Tiwari, Director of Operations for FTO7, that this appeared improbable due to the evaporation of the product leaving visible residue. This was not addressed in the investigation. Further, I confirmed that the filter and connections were not checked prior to dismantling on 27 February 2017 even though Mr. Tiwari had informed me they would investigate.

After I expressed my concerns about the lack of a thorough investigation, Mr. Choube, Vice President- Head Injectable Quality, informed me additional investigation would be conducted.

A follow-up study was conducted that included setting up a new filter and varying the pump pressure and checking for leakage, see **Exhibit JAB #11**. No leakage other than during (b) (4) was observed. However, this is not ensured to be the same as the set-up on 27 February 2017, which they could have evaluated prior to dismantling, but did not.

The study also included purposely spilling a vial of (b) (4) onto the surface of the (b) (4) to evaluate how quickly it would evaporate. This study starts on page #5 of **Exhibit JAB #11.** After pouring the product on the surface in a similar location to where we had observed the liquid, pictures were taken every 10 minutes. The study found that after (b) (4) minutes, the product had started to evaporate leaving crystallization. After (b) (4) minutes the boundaries had dried up leaving (b) (4) crystals and there was some liquid still in the center. After (b) (4) minutes the product was completely evaporated leaving (b) (4) crystals.

This is consistent with what we observed on 27 March 2017. We did not observe the leakage actually occur so do not know how long it had already been present. However, we first observed the liquid in an unevaporated state at approximately 11:30am and took a picture around 12:00pm, in which liquid was still present. Around (b) (4) pm we observed the product had evaporated leaving (b) (4) residues.

I confirmed in the batch record, as is documented in the investigation included as **Exhibit JAB #11**, that (b) (4) occurred on 27 March 2017 at 9:48am. The investigation incorrectly states that (b) (4) residue was observed at 11:40 am. The picture taken as **Exhibit JAB #9** was not taken until approximately 12:00 pm and was still in a liquid state. Additionally, the camera used to take the picture was provided by management and they had a copy of the same picture that is included as **Exhibit JAB #9.**

Nonetheless the investigation concludes *"...it is confirmed that there was no subsequent leakage after* (b) (4) *of the filter and the spill was mostly likely from* (b) (4) This statement suggests that from the times documented in their investigation, 9:48am to 11:40am (112 minutes), the product did not evaporate. In reality the times were even longer, but even 112 minutes is inconsistent with the data in the same report. If complete evaporation occurred in (b) (4) minutes in the study, observing unevaporated liquid after 112 minutes would suggest the leakage did not come from the (b) (4) I asked the personnel responsible for this investigation, which had been signed off as "Reviewed By" representatives from "Manufacturing Science and Technology", "Production" and "Quality Assurance" to explain this conclusion that is inconsistent with the data that was gathered. I was provided no further explanation.

Investigator Oladimeji reviewed examples of other deviation investigations that described leakage events. The investigations showed repeated instances in which leakage occurred. They repeatedly identified human error, but corrective actions were ineffective to ensure that leakage did not continue to occur.

a. (TBO) Incident 200168017 **(Exhibit TBO1)**, dated February 17, 2016, was initiated because product leakage occurred during the filling and (b) (4) loading of (b) (4) injection (b) (4) mg/vial, batch (b) (4) The leakage was attributed to the (b) (4) that was not tightened appropriately, and consequently resulted in product in loss. Approximately (b) (4) L of product was lost. As a corrective action and preventive action, the firm revised the SOP for filtration of bulk solution to add precautionary steps during filtration connections.

b. (TBO) Incident 200168685 **(Exhibit TBO2)**, dated February 22, 2016, was initiated because product leakage was observed during filling and (b) (4) loading of (b) (4) injection (b) (4) mg/vial, batch (b) (4) The leakage was caused by improper connection of the (b) (4) to the filter (b) (4) As a corrective action and preventive action, the firm revised the SOP for filtration of bulk solution to add precautionary steps during filtration connections.

c. (TBO) Incident 200193210 **(Exhibit TBO3)**, dated August 17, 2016, was initiated for product leakage that occurred during filling of (b) (4) injection, batch (b) (4) The leakage was observed on the (b) (4) gasket of the filtration vessel. The loss of

product resulted into the batch not meeting the yield specification. The preventive maintenance plan task checklist was revised to verify all gaskets during scheduled maintenance.

d. (TBO) Incident 200225061 **(Exhibit TBO4)**, dated February 19, 2017, was initiated for product leakage that occurred during filling of (b) (4) Injection USP (b) (4) mL. The leakage was observed on the (b) (4) filter connection. No root cause was assigned and no CAPA was implemented

e. (TBO) Incident 200198319 **(Exhibit TBO5)**, dated September 16, 2016, was initiated for product leakage that occurred during filling of (b) (4) injection. The leakage was observed at the (b) (4) connected to the (b) (4) filter. As a result of the leakage, the batch did not meet the yield specification. The incident was attributed to improper connection by the operator.

f. (TBO) Incident 200215055 **(Exhibit TBO6)**, dated December 23, 2016, was initiated for product leakage that occurred during the filling of (b) (4) injection, batch (b) (4) The leakage was observed at the (b) (4) connected to the (b) (4) filter. The report indicated that improper connection was the root cause, and awareness training was provided as a correction action.

I discussed with the firm management that due to repeated investigations into product leakage during product filling, there is no assurance that the actual root cause has been identified and appropriate corrective action has been implemented to prevent reoccurrence.

2. (JAB) During review of the batch records the in-process QA records any errors such as deviations from Good Documentation Practice (GDP), calculation errors, missing signatures, or incomplete documentation. The person responsible for errors must make corrections, although I found this was not always done in accordance with established GDP procedures, see point #3 of **Observation #9.**

   In May of 2016 management began trending the frequencies of these types of errors. The first review documented 314 errors in 22 Batch Manufacturing Records from May 2016, see **Exhibit JAB #12**. This data was presented to management. Mr. Choube confirmed there was no critical evaluation of this data to identify root causes for these errors or address any additional corrective actions. He reported that personnel responsible for errors were trained by their local supervisors. These errors repeated in subsequent months. For example:

   - June 2016 there were 258 errors identified in 15 Batch Manufacturing Records, see **Exhibit JAB #13.**

- July 2016 there were 224 errors identified in 17 Batch Manufacturing Records, see **Exhibit JAB #14.**
- August 2016 there were 128 errors identified in 21 Batch Manufacturing Records, see **Exhibit JAB #15.**
- September 2016 there were 143 errors identified in 22 Batch Manufacturing Records, see **Exhibit JAB #15.**
- October 2016 there were 200 errors identified in 21 Batch Manufacturing Records, see **Exhibit JAB #15.**

Each month this data was presented to management. Although the data showed that these types of errors continued, no evaluation was performed to determine root causes or evaluate why continued localized training of the affected personnel was ineffective in eliminating errors.

In November 2016 they changed how they did trending. Prior to November 2016, they counted all errors recognized by the in-process QA. The in-process QA notified production personnel of errors or missing documentation and corrections were made. Mr. Choube confirmed these were all deviations from the established procedures that were recognized by the in-process QA. Beginning in November 2016, they started only counting errors found during the final review for release. This does not allow for a comparison of trending before and after November 2016. It also does not represent the numbers of errors that are actually occurring and what number of corrections need to be made at a later time. This new way of trending made it appear corrections were made without addressing the root cause of the errors and making corrections. The trending for November is included as **Exhibit JAB #16.**

3. (JAB) I reviewed investigations related to findings of objectionable organisms in the (b) (4) (b) (4) system. I found these investigations were not thorough to identify root causes and address them in a timely manner to prevent recurrences. As a result the (b) (4) identifications continued to identify the same objectionable organisms.

   The established procedures require investigations to be opened if an objectionable organism is identified. Identification occurs if the sample exceeds the action limit. Additionally (b) (4) (b) (4) any growth is identified, even if the counts are below the action limits for the return loop sample point and generation sample point. This is described in procedure FTCQC017 "Microbial Identification Program" and the accompanying annexures, see **Exhibit JAB #17**. There is (b) (4) generation system that supplies (b) (4) to separate loops in the Block (b) (4) areas. The (b) (4) is used in the (b) (4) dosage plant during (b) (4) steps and for preparation of tablet (b) (4) It is also used as the (b) (4) rinse during cleaning of manufacturing equipment.

a. (b) (4) identification of isolates from the (b) (4) system identified the objectionable organism *Burkholderia cepacia* from point (b) (4) for sampling performed 01 August 2014. The investigation was opened because *Burkholderia cepacia* was determined to be an objectionable organism. The investigation is included as **Exhibit JAB #18.** No root cause was determined and no corrective actions were performed. No additional identification was conducted to determine if other recovered organisms in subsequent samples were also *Burkholderia cepacia*.

b. The next (b) (4) identification is described in **Exhibit JAB #19**. It shows the organism *Acinetobacter baumanii* was identified from samples collected on 30 August 2014 (points (b) (4) and samples collected 21 September 2014 (point (b) (4) This organism was identified as an opportunistic pathogen. Similarly, no root cause was determined and no corrective actions were taken. Again, no additional identification was conducted to determine if other recovered organisms at subsequent testing were also *Acinetobacter baumanii*.

c. Incident 200135364 was opened when (b) (4) identifications of isolates from the (b) (4) system identified the objectionable organism *Burkholderia cepacia* from point (b) (4) for sampling performed 29 May 2015. The investigation report is included as **Exhibit JAB #20.** No definitive root cause was determined. The report did not describe historical data, which had previously identified this organism as described in point "a" of this observation.

A potential root cause was identified to be the sampling hose touching a nearby drain. No sampling of the drain was performed to further confirm this root cause. No expanded identification of recovered microbial growth from (b) (4) sampling was conducted to verify if this organism was present in subsequent sampling. Trending of organisms for the (b) (4) is included as **Exhibit JAB #21.** None of these were identified as part of the investigation.

d. Incident 200142186 was opened when (b) (4) identifications of isolates from the (b) (4) system identified the objectionable organism *Vibrio vulnificus* from point (b) (4) for sampling performed 23 July 2015. The result was reported 30 July 2015. The initial investigation is included as **Exhibit JAB #22** and it did not identify and laboratory errors.

On 31 July 2015 use of the system was suspended and the system was sanitized. This is documented in Addendum I to the Incident 200142186, see **Exhibit JAB #23.** Sampling was repeated on 01 August 2015 and identifications were performed for all organisms recovered. This expanded sampling was not routine and not part of previous investigations. *Vibrio vulnificus* was not identified, but other objectionable microorganisms were found: *Burkholderia cepacia* (4 use points) and *Acinetobacter*

haemolyticus (1 use point). These were similar types of organisms that had been identified before (points a-c of this observation), but no corrective actions or expanded identifications had been done to evaluate whether they continued to be present in the (b) (4) system.

As a result of the additional identification of objectionable organisms, sanitization was again repeated on 11 August 2015 followed by sampling and isolate identification. The follow-up sampling resulted in a TNTC result from point (b) (4) for the organism *Pseudomonas fluorescens.* This was documented in Addendum III of investigation 200142186, see **Exhibit JAB #24**. The follow-up sampling also identified the objectionable organisms *Burkholderia cepacia* (2 use points) and *Acinetobacter* organisms. These are documented in Addendum IV of investigation 200142186, see **Exhibit JAB #25**. These findings after sanitization on 31 July 2015 and 11 August 2015 showed that the sanitization did not appear to be effective to eliminate these organisms.

Sanitization was repeated two more times, on 20 August 2015 and 21 August 2015, followed by sampling and isolate identification of all growth. Follow-up sampling again identified the objectionable organisms *Burkholderia cepacia* (1 use point) on 07 September 2015 from a sample collected 28 August 2015. This is documented in Addendum V of investigation 200142186, see **Exhibit JAB #26.** The (b) (4) system had already been cleared for use on 04 September 2015. This is prior to implementation of corrective actions identified in the overall investigation and impact assessment, see **Exhibit JAB #27**. No additional actions were specified after the additional finding on 07 September 2015. After the (b) (4) system was released, the increased frequency of identifying the organisms recovered did not continue. They continue to perform identifications (b) (4) from the generation and return points.

The final investigation report justified release of (b) (4) Tablets batch (b) (4) This product was manufactured for the Australian market and used (b) (4) in the preparation of the (b) (4) on 28 July 2015, see **Exhibit JAB #28**. The original finding of *Vibrio vulnificus* was from samples 23 July 2015. The investigation justified the release of the product based on microbial limits and specified organisms testing performed on samples from the batch. No studies were performed to show these existing microbial limits and specified organisms test methods could identify *Vibrio vulnificus* if it was present and no samples were submitted for extra testing specific to this organism.

Further, the same justification of passing microbial limits and specified organisms tests was used to justify release of other products. However no studies were

performed to show that *Burkholderia cepacia* or *Acinetobacter* species could be reliably detected by the existing methods.

The final investigation report included as **Exhibit JAB #27** evaluated historical trending of objectionable organisms in the (b) (4) system. Those instances described in points 3a, 3b, and 3c of this observation were not included in the historical evaluation. An overall summary of the Burkholderia cepacia identifications is included as **Exhibit JAB #29.**

4. (JAB) I reviewed Incident 200166175 which is included as **Exhibit JAB #30.** It was opened when *Staphylococcus aureus* was identified during active air monitoring of the OSD Block (b) (4) dispensing laminar flow hood point (b) (4) on 25 January 2016. The investigation is required when pathogenic organisms are identified, even if they are below the action levels. This sampling was conducted during a re-qualification of the area. During the re-qualification identification of all recovered organisms recovered was required.

   The investigation identified the likely root cause as improper gowning and hygiene of employees. The corrective action was identified to be training of personnel when the investigation was closed on 16 February 2016. The first training related to this investigation was not held until 22 March 2016 and some personnel were not trained until 20 April 2016, see page #15-18 **Exhibit JAB #30**.

   There was no expanded follow-up sampling or identification of isolates from subsequent sampling to evaluate whether there was no other source and whether the training had been effective. Follow-up routine environmental monitoring identified growth below the action/alert levels, see **Exhibit JAB #31.** Since they were below the limits, no identifications were performed.

5. (TBO) On February 27, 2017, Mr. Mahesh Nerkar, Associate Director, Production discussed the operating procedure of the (b) (4) integrity tester (PRE-346), which is used to test the integrity of the (b) (4) on the (b) (4) According to SOP OPR519-00, Operation of (b) (4) Integrity Tester **(Exhibit TBO7)**, "*in case of failure of* (b) (4) *integrity test, write justification for the failure and repeat the test only for that particular failed* (b) (4) *...and if the* (b) (4) *integrity passes, then proceed for the next routine activity. If integrity failure is confirmed, then immediately inform the superior and replace the faulty* (b) (4) *with new* (b) (4) *and perform the* (b) (4) *integrity test before the start of the* (b) (4) *leak test*". I reviewed test results on the (b) (4) tester and noted (b) (4) replacement was not performed after (b) (4) integrity test failed twice, a superior was not notified per instructions in the SOP, and investigations were not initiated for the instances listed below:

(b) (4) Number	Batch Report Number	Product Batch Number

(b) (4) -18	1062	(b) (4) post media fill)
-11	1078	(pre media fill)
-15	1158	Not batch related
-13	1158	Not batch related
-08	1165	(b) (4) pre media fill)
-25	1171	(post media fill)

A review of the logbook (**Exhibit TBO27)** also showed that the (b) (4) were not replaced after test failures. The above mentioned failed test results are attached as **Exhibit TBO8.**

6. (TBO) On March 2, 2017, I reviewed initiated out of specification (OOS) investigations pertaining to the drug products (b) (4) Injection, (b) (4) Injection, (b) (4) (b) (4) Injection, (b) (4) Injection, and (b) (4) Injection. I noted that thorough investigations were not performed, and subsequently appropriate corrective actions were not implemented. I observed repeated OOS results, which were attributed to analyst errors. The most often implemented corrective action is awareness training. I explained to the firm management that it appeared the actual root cause is not being identified; therefore proper corrective actions have not been implemented to prevent reoccurrence. The OOS investigations reviewed are listed below.

   a. OOS 310009438 **(Exhibit TBO9)** was initiated due to OOS result obtained during stability testing of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated that analyst error attributed to the failure. However, the investigation did not identify the specific analyst error even though the procedures stipulated in the test method were followed. No actual or probable root cause was identified. The samples were reanalyzed and passing result was reported.

   b. OOS 310007780 **(Exhibit TBO10)** was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was attributed to the failure. However, a specific analyst error was not identified. The samples were reanalyzed and passing result was reported.

   c. OOS 310008334 **(Exhibit TBO11)** was initiated due to OOS obtained during analysis of (b) (4) Injection USP (b) (4) mg (b) (4) mL, batch (b) (4) Assay result yielded a

failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was attributed to the failure. The samples were reanalyzed and passing result was reported.

d. OOS 310009250 **(Exhibit TBO12)** was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was attributed to the failure. The samples were reanalyzed and passing result was reported.

e. OOS 310009706 **(Exhibit TBO13)** was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated transient equipment error was root cause and awareness training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

f. OOS 310009622 **(Exhibit TBO14)** was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial. (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated unknown analytical error attributed to the root cause – there was a delay in injecting the samples. Training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

g. OOS 310010270 **(Exhibit TBO15)** was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated analyst error was root cause – there was a delay in injecting the samples. Awareness training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

h. OOS 310008552 **(Exhibit TBO16)** was initiated due to OOS obtained during analysis of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Assay result yielded a failing result of (b) (4) % against a specification of (b) (4) % - (b) (4) %. The investigation report indicated that sampling error by the analyst was the root cause and the quality assurance manager stated that there was also a delay in receiving samples. Training was provided for the analyst as a corrective action. The samples were reanalyzed and passing result was reported.

i. OOS 310009929 **(Exhibit TBO17)** was initiated due to OOS obtained during particulate matter test of stability sample of (b) (4) Injection (b) (4) mg/vial, batch (b) (4) Test results obtained did not meet specification of ≥ (b) (4) µ: NMT (b) (4)

and ≥(b)(4) µ NMT(b)(4) Analyst error was identified as the root cause and no corrective action was initiated. The samples were reanalyzed and passing result was reported.

j. OOS 310010238 **(Exhibit TBO18)** was initiated due to OOS obtained during particulate matter test of(b)(4) Injection(b)(4) mg, batch(b)(4) Test results obtained did not meet specification of ≥(b)(4) µ: NMT(b)(4) and ≥(b)(4) µ NMT(b)(4) No assignable root cause was identified. The analyst involved was trained as a corrective action. The samples were reanalyzed and passing result was reported.

7. (TBO) On March 6, 2017, I reviewed the SOP OPR012-15, Procedure for Visual Inspection of Filled, Sealed and Over Coded Vials by Using Visual Inspection Hood **(Exhibit TBO19)**. According to section 5.2.11 of the SOP, during visual inspection, if any particulate matter rejects is observed, it shall be evaluated on the basis of its color, size, and shape considering the reject. I asked Mr. Nerkar if particulate matter identified during visual inspection is evaluated for its source. He replied no, they haven't performed particulate matter evaluation. A review of the batch records listed below identified(b)(4) fibers categorized as a "major" reject observed during visual inspection that were not evaluated:

   a. (b)(4) Injection, batch(b)(4) **(Exhibit TBO20)** – 53(b)(4) fibers were identified

   b. (b)(4) Injection, batch(b)(4) **(Exhibit TBO21)** – 41(b)(4) fibers were identified

   c. (b)(4) Injection, USP(b)(4) mg/vial, batch(b)(4) **(Exhibit TBO22) –** 12(b)(4) fibers were identified

Discussion with Management:

Firm management understood this observation. They explained that they have made progress in investigations since the Warning Letter was issued.

OBSERVATION 2

Written procedures for production and process controls designed to assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess have not been established and followed.

1. The defect library used to train the visual inspectors did not include any examples of "black particles" for(b)(4) products until 09 February 2017. During qualification of the operators vials with "black vials" were not included in any of the three(b)(4) products in clear vial challenge kits. Review of trending for(b)(4) batches manufactured in 2016 of the(b)(4) product(b)(4) Injection showed that 18 batches had at least one vial rejected for black particles.

2. Of the three challenge kits for (b) (4) product in clear vials, there is only one example of the critical defect "glass particle". This vial was prepared in-house. The size of the glass particle was not measured and no criteria were established when creating the challenge vial.

Unacceptable procedures for qualification of visual inspectors is a REPEAT OBSERVATION from the 05 November 2015 FDA WARNING LETTER.

Supporting Evidence and Relevance:

The 05 November 2015 FDA Warning Letter cited the firm for unacceptable procedures for qualification of visual inspectors. This included not documenting how the challenge kits were created.

We found that corrections had been made related to the liquid products, but this had not been extended to the visual inspection procedures for the (b) (4) products.

1. (JAB) I observed that "black particles" was a common defect detected during visual inspection of (b) (4) vials. I reviewed trending for (b) (4) batches manufactured in 2016 of the (b) (4) product (b) (4) Injection, see **Exhibit JAB #32.** It showed that 18 batches had at least one vial rejected for black particles.

   Although this defect was routinely found, the operators were not trained to detect it. I reviewed the defect library used to train the visual inspectors prior to conducting qualification. I found that it did not include any examples of "black particles" for (b) (4) products until 09 February 2017. A description of the defect library is included as **Exhibit JAB #33.** Kit #1, #8, and #9 contained (b) (4) product in clear vials as described in **Exhibit JAB #34.**

   During qualification, the operators were not challenged with vials that contained "black particles". A description of the three challenge kits for (b) (4) products in clear vials is included for kit #1 as **Exhibit JAB #35,** kit #8 as **Exhibit JAB #36**, and kit #9 as **Exhibit JAB #37.** The black particle defect was found routinely as documented in **Exhibit JAB #32,** but the rejected vials were not included in the challenge kits.

2. (JAB) I reviewed the three challenge kits for (b) (4) product in clear vials, see **Exhibit JAB #35-37.** These kits are used to qualify visual inspectors. There is only one example of the critical defect "glass particle" and it is in kit #9. This vial was prepared in-house. The size of the glass particle was not measured and no criteria were established when creating the challenge vial to ensure the vial was a representative challenge.

Discussion with Management:

Firm management understood this observation. They acknowledged that the follow-up to the Warning Letter had focused on the liquid products, but had missed similar controls for visual inspection of the (b) (4) products.

OBSERVATION 3

Failure to maintain complete data to ensure compliance with established specifications and standards.

1. Reported analysis of (b) (4) API lot (b) (4) was conducted on 18 April 2014. On 17 April 2014 there was an unreported sequence of the same method and analytical reference number. The injections included samples identified as "Blank" and "Systemsuitability". The "Systemsuitability" chromatograms on 17 April 2014 had a similar peak profile to the samples injected in the reported analysis on 18 April 2014, but a different peak profile than the "Systemsuitability" injections from 18 April 2014.

There was no incident investigation initiated for this test and there is no explanation in the analytical records for the unreported sequence. At the time there was no requirement for review of the sequence audit trails from the Chromeleon software and no retrospective review of previously generated data was performed when review of the sequence audit trails was started in April of 2015.

The corporate FDA Warning Letter issued to Dr. Reddy's on 05 November 2015 identified similar data integrity concerns at another site. Investigation and retrospective review for data integrity was not extended to the Chromeleon chromatography data generated at this site.

2. Video recordings of the media fill are required to be made per the media fill protocols and must be reviewed by QA. These video recordings for media fill batches (b) (4) have since been destroyed.

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Supporting Evidence and Relevance:

1. (JAB) The corporate FDA Warning Letter issued to Dr. Reddy's on 05 November 2015 identified data integrity concerns at other Dr. Reddy sites. This included unreported extra analysis. As part of the response to the Warning Letter, a commitment was made to investigate and conduct retrospective reviews for data integrity. This review was not extended to the Chromeleon chromatography data generated at this site.

   We reviewed the Chromeleon chromatography data. Most samples are currently tested using the Empower systems, but one Chromeleon system remains in use. During our review of the analysis of (b) (4) API lot (b) (4) we observed what appeared to be unreported sample analysis prior to the official analysis.

   On 17 April 2014 there sequence 057023_RS_002 included a series of injections identified with the sample name "Systemsuitability" and "Blank". This sequence is included as **Exhibit JAB #38.** It identifies that all of the "Systemsuitability" samples came from the same vial position, (b) (4) The chromatograms are included as **Exhibit JAB #39.** The area counts for the primary peak are as follows:

Injection Time	Area of the Main (b) (4) Peak
4/17/14 14:21	(b) (4)
4/17/14 14:52	
4/17/14 15:50	
4/17/14 16:11	
4/17/14 16:41	
4/17/14 (b) (4)	
4/18/14 10:32	
4/18/14 11:11	

This sequence had unexplained delays between injections. Further, the last injection, which came from the same vial position (b) (4) had a significantly lower area count for the main peak.

The reported run for (b) (4) API lot (b) (4) occurred on 18 April 2014 under sequence 057023_RS_003. It started just after the end of the last injection in 057023 RS 002. The record of analysis, including all chromatograms for (b) (4) API lot (b) (4) is included as **Exhibit JAB #40.** The area counts for the primary peak are as follows:

Injection Time	Name	Area of the Main (b) (4) Peak
4/18/14 11:41	Blank	(b) (4)
4/18/14 12:12	Blank	
4/18/14 12:42	Systemsuitability	
4/18/14 13:13	Blank	
4/18/14 16:11	Sample	
4/18/14 16:42	Blank	
4/18/14 (b) (4)	Sample	
4/18/14 (b) (4)	Blank	
4/18/14 (b) (4)	B_Systemsuitability	

Although the chromatograms for the sample injected at (b) (4) and the Systemsuitability injected at (b) (4) were not included in the copies we requested, I observed during my review that the sample injection had an area of approximately (b) (4) and the Systemsuitability injection had an area of approximately (b) (4)

These areas appeared to indicate that the injections of 057023_RS_002 labeled as system suitability appeared to be sample injections and not standards, with the exception of the last injection. The chromatograms associated with 057023_RS_002 were never reported or reviewed. There was no explanation in any record to explain what their purpose was. The analyst that performed the analysis was reported to no longer work at this company.

2. (JAB) Video recordings of the media fill are required to be made per the media fill protocols and must be reviewed by QA. I requested to review these video recordings for media fill batches (b) (4) to verify activities performed, including those described in point #1 of **Observation #4** and point #1/#2 of **Observation #5.** I was told the videos had been destroyed once the media fill results were found to be successful. I was provided the video review checklist for (b) (4) see **Exhibit JAB #41.**

Discussion with Management:

Firm management understood this observation. They explained that the procedure for media fills had been revised to ensure that the videos are maintained.

OBSERVATION 4

Production records do not contain complete and accurate information.

1. Review of Biometric entry data, which uses fingerprints to track and grant employee access to the facility, indicated that personnel signing for steps in production records were not actually present at the time of the steps indicated in the records.

a. During the filling of media fill batch (b) (4) (b) (6) " signed for the "checked by" portions of the batch record when biometric and card reading entries indicate he was in other areas of the facility. Examples include, but are not limited to:

i. Page #36, documentation of differential pressures, temperatures, and speeds of the (b) (4) at (b) (4) and (b) (4) Page #34, in-process checks for the (b) (4) performed at (b) (4) However, the biometric entry data showed the employee entering the (b) (4) block from outside at (b) (4)

ii. Page #66, intervention for fallen/rejected vial removal from 16:39 to 16:40. Biometric entry shows the operator entering the changing room at 16:41:56.

iii. Page #65, sterilized seals addition at 16:49 to 16:50, however this employee was entering the Block (b) (4) building from the outside at 16:54:35.

iv. The biometric entry data does not show the employee entering the change room to enter the "Filling Area (b) (4) Block" until 08:34:43 on 25 October 2016. However, the employee performs many activities from approximately (b) (4) on 24 October 2016 until 08:30 on 26 October 2016.

Additionally, when this employee was asked questions about what had occurred, he provided false and misleading statements before later admitting he may not always present at the time the activity occurs.

b. Review of (b) (4) Injection, batch (b) (4) manufacturing batch record showed that the operator who verified and signed the "Checked by" column for completion of process step (b) (4) of the batch record (process instructions) was not present at the time of performance. Step (b) (4) was performed between 14:00 to 14:10. However, according to the

Biometric Access System, the operator was at the exterior entrance to the (b)(4) block at 14:04, and entered the change room for the critical area at 14:21. The operator (b)(6) was interviewed and confirmed he did not witness the operation. He signed the batch record after the process step was completed.

2. In media fill batch record (b)(4) page #14 includes the step #(b)(4) for cleaning of LAF and step #(b)(4) for switching the LAF on and recording the reading on the magnehelic gauge. These steps were documented to done by (b)(6)" and then checked by "(b)(6) on 23 October 2016. Neither of these operators were present in the facility at that time. Further investigation found that these entries had been copied out of a LAF logbook. The entry was then signed and backdated by these individuals that had not performed or been present for these steps.

3. Gown inspection records show that FTO7 critical area gown #10012017-07 was inspected and found acceptable on 27 February 2017 and 28 February 2017. On 27 February 2017 a gown with this number was observed in the FTO7 waste area in a bag that identified these FTO7 critical area gowns had been rejected on 23 February 2017.

4. Visual inspection records for (b)(4) show that there were only two vials rejected for "Black Particles". However, the defect library identifies one vial from batch (b)(4) with black particles is part of the library and analytical request records show two additional vials from batch (b)(4) were submitted for identification of black particles.

Supporting Evidence and Relevance:

1. (JAB) Access to the manufacturing blocks and specific production areas is controlled with Biometric entry barriers. These require an employee to use their fingerprint to access the area. All entries are tracked in a centralized system. Established procedures require each employee to individually use their finger to enter the area. We observed signs at each one of these biometric access areas reminding employees not to "tailgate" or "piggyback" and enter with someone else. A picture is included as **Exhibit JAB #42.**

   When we compared the production records to the biometric access records, we found that personnel signing for steps were not actually present at the time indicated in the records.

   a. (JAB) I reviewed media fill batch record (b)(4) that was conducted October 24-25, 2016. The batch record is included as **Exhibit JAB #43.** I observed that "(b)(6)" signed for the "checked by" portions of the batch record throughout the filling, a time period that covered entries made at (b)(4) on 24 October 2016 through 17:00 on 25 October 2016.

      I reviewed the attendance records for (b)(6) ". These are controlled by a personal card scanned at the front gate and documents the hours the employee is present to determine their pay. The records for (b)(6) " entering at the gate is included as **Exhibit JAB #44.** They show he was paid for (b)(4) hours on 24 October 2016 and (b)(4) hours on 25 October 2016. The times were manually entered for 24 October 2016, which reportedly occur if he didn't have his card with him to scan. The manually entered time was an arrival at 9:00am. On 25 October 2016 he scanned at the front gate at 1:47pm to enter and to exit at (b)(4) pm. This is inconsistent with operations documented in the batch record which show he was present (b)(4) hours over these two days and at different times.

I reviewed his biometric access records, which are included as **Exhibit JAB #45.** They show him enter into "Employee change area Block[(b) (4)] This is the entrance area to Block[(b) (4)] where employees enter from the outside. It also shows him enter the "Filling area[(b) (4)] Block". This is to enter the gowning area of the filling room where the media fill was occurring. When I compared these entries to documentation in the batch record, I found that he appeared to be in other areas of the facility at the same time as steps were documented to occur in the batch record, which he signed. Examples include, but are not limited to:

i. Page #36 of the batch record (page #37 in **Exhibit JAB #43**), documentation of differential pressures, temperatures, and speeds of the[(b) (4)] [(b) (4)] were recorded at[(b) (4)] and[(b) (4)] of 24 October 2016. Page #34 of the batch record (page #33 in **Exhibit JAB #43**), in-process checks for the[(b) (4)] are documented to be performed at[(b) (4)] However, the biometric entry data showed the employee[(b) (6)] " that signed these steps entering the[(b) (4)] block from outside at[(b) (4)] see **Exhibit JAB #45**.

   After entering from outside, there is an initial gowning room in which the employee will change into the plant clothes. The employee must then walk through the building to the entrance of the filling room. Here the employee will need to fully gown with sterile area gowns that provide complete coverage of the skin, put on goggles, and put on sterile[(b) (4)] before entering the filling room where these steps documented in the batch record would occur.

   My observation found that the fastest these two gowning steps to enter from the outside and make it into the filling room would be at least 10 minutes. Further, **Exhibit JAB #45** shows this employee enter the first change room at[(b) (4)] but the employee does not enter the filling room on the record until 8:34:43 the following morning. Therefore, if the employee did enter the filling room during this time, then the employee did not follow established procedures that require him to individually access the area using the biometric access reader.

ii. Page #66 of the batch record (page #67 in **Exhibit JAB #43**), documents an intervention for fallen/rejected vial removal from 16:39 to 16:40. [(b) (6)] " signed as checking this step. Biometric entry shows the operator entering the changing room to enter the filling room at 16:41:56, see **Exhibit JAB #45**. He would have needed to gown before he could enter the room and would not have been present to "check" and observe the intervention at the time it is documented to occur.

iii. Page #65 of the batch record (page #67 in **Exhibit JAB #43**), documents sterilized seals addition at 16:49 to 16:50 and (b) (6) " signs for witnessing this step. The biometric access shows he was entering the Block (b) (4) building from the outside at 16:54:35, see **Exhibit JAB #45**. If (b) (6) " was present to watch the steps at 16:49-16:50, he would not have enough time to remove gowning from the sterile area, travel to the second change room, change from plant clothes into clothes for outside, exit the building, and then enter back into the building at 16:54:35.

iv. The biometric entry data does not show the employee entering the change room to enter the "Filling Area (b) (4) Block" until 08:34:43 on 25 October 2016, see **Exhibit JAB #45**. However, the employee performs many activities from approximately (b) (4) on 24 October 2016 until (b) (4) (b) (4) Examples include, but are not limited to Page #36 of the batch record (page #37 in **Exhibit JAB #43**), documentation of differential pressures, temperatures, and speeds of the (b) (4) were recorded at (b) (4) and (b) (4) of 24 October 2016. Page #34 of the batch record (page #33 in **Exhibit JAB #43**), in-process checks for the (b) (4) are documented to be performed at (b) (4)

On 03 March 2017, I spoke with (b) (6) " about these findings. He told me that he is always present for the steps he signs for. I gave examples and he told me he would be standing with the operator to observe steps such as those described in points ii and iii. I asked for an explanation of the time discrepancies between his statements, the batch record, and the biometric entry records. He could not explain, but insisted he would be present to document contemporaneously.

As I found more examples of time discrepancies, I asked to speak with him again. He initially again repeated that he was always present, but ultimately confirmed he may verify some steps at a later time. A pattern of employee providing false and misleading information to us is described further in the **Refusals** section of this report.

b. (TBO) On March 3, 2017, I reviewed (b) (4) Injection, batch (b) (4) batch record **(Exhibit TBO23)**. I noted that the operator who verified and signed the "Checked by" column for completion of process step (b) (4) of the batch record (process instructions) was not present at the time of performance. Step (b) (4) was performed between 14:00 to 14:10. However, according to the Biometric Access System **(Exhibit TBO24)**, the operator was at the exterior entrance to the (b) (4) block at 14:04, and entered the change room for the critical area at 14:21. I interviewed the

operator (b) (6) who verified the process step. He confirmed that he did not witness the operation. He signed the batch record after the process step was completed.

2. (JAB) I reviewed media fill batch record (b) (4) Page #14 of the batch record (page #15 in **Exhibit JAB #43**), includes the step (b) (4) for cleaning of LAF and step (b) (4) for switching the LAF on and recording the reading on the (b) (4) gauge. These steps were documented to be done by (b) (6) " and then checked by (b) (6) " on 23 October 2016 around 9:00am.

   I reviewed the attendance records and biometric access records. These showed that neither of these operators were present in the facility at that time. The records for (b) (6) show he was present (b) (4) on 23 October 2016 until (b) (4) see **Exhibit JAB #46.** This is after the steps documented in the batch record occurred. The previous day was his weekly day off. The records for (b) (6) " show 23 October 2016 was his weekly day off. He was not present until (b) (4) on 23 October 2016, after the steps he signed for had occurred, see **Exhibit JAB #47.**

   Further investigation by the production personnel found that these entries had been copied out of the LAF logbook, see **Exhibit JAB #48**. The entry was then signed and backdated by these individuals that had not performed the steps or even been present at the time they were performed. There was no documentation made to indicate these entries were copied out of a logbook instead of contemporaneous documentation by the personnel that performed the step.

3. (TBO) During the walkthrough of the firm's premises on 27 February 2017, we observed several discarded bags and drums that contained drug products, container closures, and garments (overall gown) stored in the waste disposal building. All the discarded materials are listed on the Request for Solid/Liquid Waste Disposal form **(Exhibit TBO30)**. I noted that the discarded drug products were not listed on the disposal form. Due to time constraints, we could not review why the drug products were discarded.

   The discarded garments were observed in a waste area identified to be for FTO7 in a bag identified as waste from FTO7. We reviewed the garment inspection record for FTO7 **(Exhibit TBO25)** and noted that the discarded garment (Code No.10012017-07) was documented to still be in use. I interviewed the gown inspector (b) (6), and she confirmed that the gown was inspected and found acceptable on 28 February 2017, which was documented on the inspection record. I expressed my concerns to the firm management about the discrepancy between the records showing the gown was inspected gown and found acceptable on 28 February 2017, yet we observed the gown was discarded and located in the waste area on 27 February 2017. Photograph of the garment and other materials observed in the waste area is attached as **Exhibit TBO26, photo #24**.

4. (JAB) Visual inspection records for (b) (4) show that there were only two vials rejected for "Black Particles", see **Exhibit JAB #48**. However, the defect library identifies one vial from batch (b) (4) with black particles is part of the library, see page #9 of **Exhibit JAB #33.** I inspected the defect library and confirmed this vial was present.

   I also reviewed analytical request records which show two additional vials from batch (b) (4) were submitted for identification of black particles to an outside lab, see **Exhibit JAB #49**. These results were not yet available.

   This is a total of three vials. Yet, the visual inspection records which are signed by the inspectors and verified by a supervisor only document there being two vials found with black particles.

Discussion with Management:

Firm management understood this observation. They explained their preliminary investigation had found a gown with the same number as the gown described in point #3 was used in FT09. They were investigating how it may have ended up in the FTO7 waste bags and the FTO7 waste area.

OBSERVATION 5

Written procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed, including validation of all aseptic process.

1. Requirements of what activities need to be performed during a media fill to qualify a person to perform aseptic activities have not been established. For example, document FT 7PR155/A07 "Media Fill Participation List of Personnel for Performing Aseptic Activities" identifies that operator (b) (6) and (b) (6) are "qualified for performing aseptic activities" based on the media fill conducted 12 January 2017. The corresponding media fill batch record does not document these personnel performing aseptic operations.

2. There are no entrance or exit logs to show which operators were present and when they were present in the filling room. The intervention of maximum (b) (4) people in the room during media fill batch (b) (4) does not document which (b) (4) operators were in the room. The biometric access data for this time period does not show the entrance of (b) (4) people into the filling area.

3. On 07 March 2017, upon entering the line (b) (4) illing area, (b) (4) operators were already in the room, exceeding the limit of (b) (4) which was qualified during media fills.

4. On 27 February 2017, during the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) sample bags, plastic wrappers from environmental monitoring media, and packaged materials that included clamps, forceps, twist ties, and filters were observed to be partially blocking the air returns inside of the (b) (4)

5. Procedure OPR518-00 "Operation of Online Continuous Particle Monitoring System (Line (b) (4) " does not describe actions to take when non-viable particle counts are exceeded during set-up. On 07 March 2017 an alarm for action level of the non-viable particle counts occurred just prior to performing aseptic connections. The personnel performing activities did not stop working when the alarm occurred.

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Supporting Evidence and Relevance:

1. (JAB) There are no established requirements of what activities need to be performed during a media fill to qualify a person to perform aseptic activities. Document FT 7PR155/A07 "Media Fill Participation List of Personnel for Performing Aseptic Activities" identifies that operator (b) (6) and (b) (6) are "qualified for performing aseptic activities" based on the media fill conducted 12 January 2017, see **Exhibit JAB #51**.

   I reviewed the batch record with interventions for the media fill conducted 12 January 2017, see **Exhibit JAB #52.** It does not document these three operators performing any of the aseptic activities or interventions.

2. (JAB) I reviewed media fill batch (b) (4) One of the interventions included the maximum (b) (4) people in the room. The batch record did not identify which (b) (4) people were in the room, see page #70 of **Exhibit JAB #43**. The batch record shows that the (b) (4) people were present from 9:00 to 9:20. It also shows that a break was documented to occur 8:00 to 9:00. It was explained that every person must exit during the break simulation, de-gown, and re-enter to at least simulate a break, even if they don't take an actual break. There is no log to track that all personnel did exit. After de-gowning, in order to enter the gowning area, they must use their finger to gain access from the biometric reader. I requested the biometric access data from 7:50-9:30. It only shows (b) (4) people enter into the filling area during this time period, see **Exhibit JAB #53.**

3. (JAB) The maximum number of people permitted in the filling area by procedure is (b) (4) people. This is the challenge used during media fills. On 07 March 2017, upon entering the line (b) (4) filling area with Mr. Tiwari, Director of Operations, (b) (4) operators were already in the room. When Mr. Tiwari and I entered, there were a total of (b) (4) Mr. Tiwari confirmed there is no way to track the number of people in the room to ensure that the (b) (4) person limit is being followed.

4. (TBO) During the walkthrough of the facility 27 February 2017, I observed the filling operation of (b) (4) Injection (b) (4) mg/mL, batch (b) (4) using (b) (4) line (b) (4) I observed sample bags, plastic wrappers from environmental monitoring media, and packaged materials that included clamps, forceps, twist ties, and filters were partially blocking the air returns inside of the (b) (4) I pointed it out to Mr. Laxmikant D Tiwari, Director, Operations, who acknowledged my observation. Photographs of the materials were taken and attached as **Exhibit TBO26, photos 3 - 6.**

5. (JAB) On 07 March 2017 I observed the set-up of the (b) (4) of line (b) (4) Just prior to making the aseptic connection to the (b) (4) filter, m sounded for non-viable particles that exceeded the action limit. The personnel performing the set-up did not stop and continued set-up, including the aseptic connections. A supervisor went over to a controlling computer and acknowledged the alarm to silence it. In order to acknowledge the alarm he had to enter a justification, which stated "aseptic assembling", see **Exhibit JAB #54**.

Procedure OPR518-00 "Operation of Online Continuous Particle Monitoring System (Line (b) (4)', see **Exhibit JAB #55**, does not describe actions to take when non-viable particle counts are exceeded during set-up. During operations if there is an excursion, all operations must be stopped until the area returns to normal.

Discussion with Management:

Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 6

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

1. Surface monitoring inside of the (b) (4) performed using (b) (4) plates was observed on 27 February 2017. After sampling (b) (4) was sprayed onto wipes held with the (b) (4) in order to wipe the sampled (b) (4) surfaces. In spraying the wipe, the operators were observed to get (b) (4) on the (b) (4) This is prior to performing subsequent monitoring of the (b) (4)

2. The microbiology media used for settle plates, active air samples, and touch plate monitoring of the (b) (4) do not contain (b) (4) agents. (b) (4) is sprayed in the areas where the monitoring occurs.

3. (b) (4) contact plates are used for surfaces that are not flat, such as (b) (4) rounded pumps, or forceps.

4. On 27 February 2017 the person performing monitoring of the inside of the stopper bowl did not first move the stoppers. This prevented the plate from contacting the flat surface of the stopper bowl and the stoppers caused damage to the (b) (4) surface of the plate.

Supporting Evidence and Relevance:

(JAB) On 27 February 2017 I observed post filling environmental monitoring of the surfaces inside of the (b) (4) I observed sampling conducted by two operators, (b) (6) These individuals reportedly performed sampling of this area on a routine basis. However, they appeared to be unable to answer basic questions about how and where the samples were collected. They retrieved their SOP and discussed the locations extensively before collecting many of the samples. Further the (b) (4) had not been set up with (b) (4) plates, and wipes present in the locations they needed it. The amount of time it took to collect samples, 13:05 to 15:20 as shown in **Exhibit JAB #56,** was significantly longer than other times when sampling occurred and didn't include their time to place the plates where they needed to be. For example, the same sampling was done from (b) (4) to (b) (4) on 14 February 2017, see **Exhibit JAB #57.** During my observation of the sampling I noted the following deficiencies:

1. (JAB) I watched surface monitoring inside of the (b) (4) on 27 February 2017. Sampling is done using (b) (4) plates for surfaces and (b) (4) nm touch plates for sampling of the (b) (4) (b) (4) In the area at the filling station I watched the operator use (b) (4) plates to sample

locations on the filling machine. After collecting each sample, they would use the (b) (4) to hold a wipe and then spray the (b) (4) onto the wipe. Using the (b) (4) they would wipe the sampled surface. In the process they would get (b) (4) on the surfaces of the (b) (4) After using the (b) (4) plates, they would then use the (b) (4) mm touch plates and touch the fingers of the (b) (4) for sampling. The reliability of the sampling of the (b) (4) could be compromised by spraying (b) (4) on the (b) (4) prior to sampling the

2. (JAB) The microbiology media used for settle plates, active air samples, and touch plate monitoring of the (b) (4) is (b) (4) The supplier description of this media is included as **Exhibit JAB #58.** It contains no (b) (4) During the active air and settle plate monitoring the use of sprayed (b) (4) was observed in the (b) (4) As described in point #1 of this observation, I also observed the use of sprayed (b) (4) on the (b) (4) prior to sampling the (b) (4)

3. (JAB) Swabs are used for monitoring of surfaces such as conveyor areas. For all other surfaces, (b) (4) contact plates are used. This included surface that appeared as though they could be more effectively monitored with swabs. For example, non-flat surfaces such as (b) (4) rounded pumps, or forceps. The person collecting the samples was observed to try and roll the (b) (4) plate or drag it across the surfaces. This caused visible damage to the (b) (4) surface for some of the samples.

4. (JAB) The bottom of the stopper bowl is identified as one of the sampling locations and it is monitored with a (b) (4) contact plate. I observed that the operator did not first remove the stoppers from the surface to be sampled. Therefore the (b) (4) surface was contacting the stoppers and not the bowl. As the operator pushed down a stopper was temporarily lodged in the (b) (4) When he took the plate out a piece of (b) (4) fell back into the bowl.

Discussion with Management:
Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 7

Procedures for the preparation of master production and control records are not followed.

1. Master copies of raw data forms are available on a shared computer drive in the microbiology laboratory. These can be modified with batch information and printed. For example, raw data sheets for sterility testing or performing microbial limits tests.

2. Blank GMP forms can be copied by laboratory of production personnel. For example, batch record pages or analytical testing raw data forms. There is no process to uniquely identify the original document.

3. There is no effective process to ensure reconciliation of documents. QA does not reconcile the forms issued and the forms returned if no additional pages are re-issued. Reconciliation when additional pages were issued was found to be ineffective in detecting discrepancies. For example, 5 pages issued for Analytical Record 890000853527 could not be found in the archived data on 01 March 2017. The reconciliation of this batch had noted no discrepancies at the time it was archived. The 5 extra pages were later found filed with Analytical Record 890000853752. This record had also been reconciled, but the five extra pages were not detected.

Supporting Evidence and Relevance:

1. (JAB) We inspected general use computers in the microbiology laboratory. All analysts had access to a shared drive. This shared drive had the master copies of raw data forms. These forms were saved in a Microsoft Word format and could be modified with batch information and printed.

   Routinely an analyst would generate the form through SAP. The SAP would assign the associated sample number and include a date printed. An example would look like the form included in **Exhibit JAB #59**. However, an analyst could enter the same information into one of the blank master forms and create a form that is indistinguishable from a form generated through SAP.

   Examples of raw data sheets included, but are not limited to sterility testing forms and microbial limits test forms. I had an analyst enter "FDA Test" instead of a specification number and the same sample number as the listed in the SAP form included as **Exhibit JAB #59.** This was done on a blank sterility test form to demonstrate the information could be changed, see **Exhibit JAB #60.**

2. (JAB) Blank GMP forms are printed from the SAP system by the laboratory or production personnel. These forms are printed on yellow paper (laboratory forms) or blue paper (batch record pages). The analysts and production personnel were observed to have access to this colored paper and to photocopying machines. Copies would be indistinguishable from a form generated through SAP.

3. (JAB) QA does not have a system to effectively reconcile the forms that are issued and the forms that are returned. There is no requirement to perform a reconciliation to verify all issued forms are returned if the original form is not re-issued. This can be seen in the document issuance log included as **Exhibit JAB #61.** There are blanks for the checked/verified returned documents.

   If there are extra pages issued then the QA is supposed to reconcile the forms. I reviewed the analytical record 890000853527 documented in the issuance log included as **Exhibit JAB #61.** The log noted no discrepancies at the time it was archived. It identifies 17 pages were issued and 11 were later reissued. A total of 122 were archived, which includes issued pages and attached chromatograms. The 122 matched the total number I counted in the archived documents and includes the issued pages with raw data and printouts such as chromatograms.

However, when I counted just the issued pages, of which there should have been 28 (11+17), I found that there were five pages missing.

After searching through many documents, the QA personnel eventually found the five missing pages archived with Analytical Record 890000853752. This document had also been reconciled and no discrepancies had been noted, despite the five extra pages.

Discussion with Management:

Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 8

Appropriate controls are not exercised over computer or related systems to assure that changes to master production records and control records or other records are instituted only by authorized personnel.

1. General computers are used in the laboratories and production areas. The personnel can create and delete files on these systems without oversight or specific procedures to describe how the computers are to be used. During the inspection recent files were observed to have been deleted off these computers, the computer "Recycle Bins" were emptied, and in some cases the personnel had deleted the "Recent" document list in programs such as Microsoft Word and Excel.

Further, when asked about these activities during the inspection, an employee from the chemistry laboratory, two employees from the microbiology laboratory, and two employees from the production department provided repeated false and misleading statements before later admitting they had recently deleted files from the computers.

2. Filter integrity test results can be deleted from the Sartorius tester. A demonstration of the deletion process was performed by a production employee on 02 March 2017.

3. (b) (4) integrity test results can be deleted. A demonstration of the deletion process was demonstrated by a production em e.

4. The production supervisor has access to change date/time on the (b) (4) PLC (Programmable Logic Controller).

Supporting Evidence and Relevance:

1. (JAB) We observed that the laboratories and production areas had general use computers in which personnel were using Microsoft Word and Microsoft Excel. There were no procedures to describe the use or quality oversight of how these computers were used. These computers had blank master records like those discussed in point #1 of **Observation #7**. The personnel can create and delete files on these systems.

   During the inspection I attempted to review these computers to evaluate how they were being used in the GMP production areas and GMP laboratories. I found that recent files were listed in Microsoft Word and Microsoft Excel. However, these files would not open since they had

been recently deleted and the "Recycle Bins" had been emptied. When I asked analysts about how or why the documents were deleted, or what the documents had been used for, I was repeatedly provided false and misleading statements by employees in the chemistry laboratory, the microbiology laboratory, and the production area.

After we had first discovered documents had been deleted by looking at the "Recent" documents in Microsoft Word and Excel software, on subsequent days we found that employees had also started deleting the "Recent" documents. When asked about whether they had done this and why they had done, the personnel again provided false and misleading information.

Some examples of documents that appeared to be GMP related included "Gram Negative Isolates Identified", "Risk Assessment (b) (4), and "Filling Room Excursions". A full description of what occurred and what we were told is described in the **Refusals** section of this report.

2. (TBO) On March 2, 2017, while inspecting the filling area line (b) (4) I asked the production operator (b) (6) to demonstrate the use of the filter integrity tester. When he accessed the results stored on the device, I asked him if results can be deleted, he replied that files can be deleted when the memory is full. He demonstrated how test results are deleted. **Photographs of the deletion process are attached as Exhibit TBO26, photos 7 - 10.**

3. (JAB) On 02 March 2017 we inspected the filling area for line # (b) (4) A production supervisor demonstrated the use of the (b) (4) integrity testing device. When he accessed the data there was an opportunity for him to delete test results. There are three profiles in the system: operators, production supervisors, and administrators (which are IT employees). Individual operators were unable to delete results. We discussed how the production supervisors responsible for reviewing and approving data should not have the ability to delete data.

4. (TBO) On March 2, 2017, a production supervisor demonstrated the use of the controls on the (b) (4) via the PLC. When he accessed the settings of the system, I noted he can change the date/time on the (b) (4) Photographs are attached as **Exhibit TBO26, photos 15 &16.**

Discussion with Management:

Firm management understood this observation. They explained that they do review audit trails and any deletion of files would be detected during the audit trail review.

OBSERVATION 9

Data is not documented contemporaneously.

1. (b) (4) sampling records and environmental monitoring records are not made at the time of sampling. The records are made at a later time when the samples are delivered to the laboratory. Additionally, the person collecting the samples does not sign or date the record, which is a REPEAT OBSERVATION from the 06 March 2015 FDA 483.

2 (b) (4) plates, (b) (4) ouch plates, and swabs used for surface monitoring are not labeled at the time the samples are collected. The media is left in place unlabeled until all samples are collected.

3. A missing entry in the batch record for batch (b) (4) was made at a later time without any indication that it had not been made contemporaneously.

Supporting Evidence and Relevance:
(JAB)

1. I reviewed (b) (4) sampling records, see **Exhibit JAB #62,** and environmental monitoring records, see **Exhibit JAB #57**. I found that these records are not made at the time of sampling. The records are made at a later time when the samples are delivered to the laboratory. The logbooks or forms do not leave the laboratory, where the sampling is actually performed. The laboratory personnel confirmed that records can be made by different personnel than actually collect the samples. The person making the record will enter the name of the "sampled by" person rather than that person signing for the sampling that they had performed.

   The 06 March 2015 FDA 483 had cited instances in which a supervisor wrote in the names of personnel performing tasks rather than those people signing for themselves.

2. On 27 March 2017 I watched surface monitoring inside of the (b) (4) The analyst used unlabeled plates to perform monitoring and then placed them in various locations. After the sampling was completed and the (b) (4) was opened, the plates were then labeled. The operator had to remember which sample was which based on where it had been placed. During the sampling I observed these plates get moved around to sample different areas. I also observed that sterile markers were used in the (b) (4) to label air monitoring plates at the time of sampling. However, the analyst performing the surface monitoring did not label his plates at the time.

3. Point #2 of **Observation #1** describes repeated instances of documentation errors. I reviewed the batch record for (b) (4) Injection batch (b) (4) that was found with errors. A list of all errors is included as **Exhibit JAB #63.**

   One of the errors was a missed signature on a label verification page. When I reviewed this page I found no missing signatures, see **Exhibit JAB #64**. I was informed the responsible individual would have been informed of the missing signature and made the signature at a later time. In correcting the error, there was no note as required by the established Good Documentation Practices, procedure, that indicated that the entry was made at a later date.

Discussion with Management:

Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 10

Thorough review of documents is not performed.

Documentation of settle plates in logbook FT7QC228/F13-00 was done two different ways. Some analysts recorded the start time and end time of the exposure. More commonly the analyst recorded only the amount of time it took to open the plate and did not record the end time of exposure in the record. The person reviewing the documentation signed both ways as being approved.

Supporting Evidence and Relevance:

I reviewed logbook FT7QC228/F13-00 for settle plates exposed during our inspection of Line (b) (4) on 27 February 2017 of batch (b) (4) I observed that the "From" and "To" times were only a few minutes apart, see **Exhibit JAB #65**. I asked the microbiologists responsible and he explained that they were recording the amount of time it took them to open and expose the plates, not the total exposure time. He reported that he didn't actually document the end of the exposure time unless it was less than (b) (4) In that case the actual time was written on the control plate and then the information was used to make the record upon return to the microbiology laboratory. Records are not made contemporaneously, as described in point #1 of **Observation #9.**

During my review of the logbook I found examples of analysts documenting the same way, writing only to time to open plates, such as batch (b) (4) see **Exhibit JAB #66.** These had been signed and approved by the document reviewer. I also found in the same logbook that other analysts had documented the "From" and "To" as the total exposure time, such as batch (b) (4) see **Exhibit JAB #67.** These had also been signed and approved by the same reviewer. My discussion with analysts could not confirm exactly which way they were supposed to do the documentation and it wasn't clearly defined in any procedure. However, I explained that it appeared the reviewer did not detect that one of the ways was incorrect.

Discussion with Management:

Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 11

Procedures for maintenance of equipment had not been established and followed.

1. The (b) (4) sealant used to seal the lower bottom area of the (b) (4) used for filling line # (b) (4) appears to be cracking.

2. The (b) (4) covering the HEPA filters inside of the (b) (4) of filling line (b) (4) had tears with exposed fibers above the incoming vial (b) (4)

3. Approved procedures for preventative maintenance did not include maintenance recommended by the equipment manufacturer. For example, the supplier manual for the (b) (4) Equipment recommends (b) (4) inspection of the air ducts for dust. This is not performed as part of the routine cleaning or maintenance. When the (b) (4) air duct of the "Clean" (b) (4) equipment in block (b) (4) was inspected on 01 March 2017, dust and an unidentified black residue was observed. This piece of equipment is not product dedicated.

Supporting Evidence and Relevance:

1. (TBO) On February 27, 2017, while observing the filling operation of the (b) (4) Injection (b) (4) mg/mL, batch (b) (4) I noted the (b) (4) sealant used to seal the lower bottom of the (b) (4) appeared to be cracking. This was pointed out to Mr. D Tiwari, and he acknowledged my observation. Photographs are attached as **Exhibit TBO26, photos 17 - 19.**

2. (JAB) On 02 March 2017 during inspection of the Line # (b) (4) filling (b) (4) I observed that (b) (4) over the HEPA filter was tearing. Above the open vials at the incoming vial (b) (4) here were holes and the (b) (4) had pulled away from the edges. There were exposed fibers from these tears. A picture is included as **Exhibit TBO26, photos 20 & 21.**

3. (JAB) On 01 March 2017 we inspected the "clean" (b) (4) equipment in Block (b) (4) This piece of equipment is not product dedicated. I requested that the firm open the valve on the air (b) (4) duct. They reported that this was not done as part of routine cleaning or maintenance. When the valve was opened we observed dust and an unidentified black residue. We used a wipe to wipe the surface and a picture of the wipe is included as **Exhibit TBO26, photos 22 & 23.**

   I reviewed the manufacturer's manual. In the recommended maintenance it describes (b) (4) cleaning and checks of the air duct for dust, see **Exhibit JAB #68**. This is not included as part of the maintenance check list that has been approved, see **Exhibit JAB #69.**

Discussion with Management:

Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 12

Review of process performance qualification (PPQ) for (b) (4) Injection (b) (4) mg/vial, batch (b) (4) revealed that the samples collected for finished product release testing is not statistically representative of the manufactured batch. According to the Assistant Manager, Manufacturing Science & Technology, the samples collected in the PPQ are limited to the number of samples required to conduct the testing. There is no evidence and/or documentation to support when and how the samples were collected throughout the batch manufacturing. This is a REPEAT OBSERVATION from the 06 March 2015 FDA 483.

Supporting Evidence and Relevance:

(TBO) On March 7, 2017, I reviewed the process performance qualification for (b) (4) Injection (b) (4) mg/vial, batch (b) (4) **(Exhibit TBO28)** with Mr. Sitaram Potnuro, Assistant Manager, Manufacturing Science and Technology. The PPQ report did not establish or evaluate statistical criteria for the samples collected. The number of samples tested for the study was limited to the number of vials required for conducting the tests for each routine batch. There was no increase in the number of samplings to support the process validation activities. According to the batch record **(Exhibit TBO29)**, (b) (4) vials were collected for finished product release testing. There is no sampling plan to support how the samples were collected during batch production. Mr. Potnuro stated that samples needed for testing were collected and he did not know how the samples were collected.

Discussion with Management:

Firm management understood this observation and had no specific comments during the closeout discussions.

OBSERVATION 13

Samples collected to evaluate conformance of a batch are not representative.

Samples taken for bioburden and endotoxin monitoring of unfiltered bulk product are taken at the conclusion of compounding activities. During the subsequent testing for release of the bulk and preparation for filling (which was observed to take up to (b) (4) as well as the filling process (which can take up to (b) (4) the bulk product remains unfiltered.

Supporting Evidence and Relevance:

(JAB)

Pre-filtration samples are taken to evaluate bioburden and endotoxin. These samples are taken at the end of compounding. The product is not (b) (4) filtered until the time of filling. It remains unfiltered in the compounding tank.

On 02 March 2017 I observed that the time from when the sample was taken and the start of the filling process was approximately (b) (4) The filling is permitted to take up to (b) (4) We discussed how sampling at the end of compounding may not be representative if the bioburden increases during the filling process while it remains in an unfiltered state.

Discussion with Management:

Firm management understood this observation. They stated they have (b) (4) bulk hold time studies for their products. They also indicated that as a corrective action, they planned to start sampling at the end of the filling process.

REFUSALS

Over multiple days in multiple departments we were provided false and misleading answers to the questions that we asked employees. We repeatedly expressed our concerns directly to the most

responsible personnel present, Mr. Shukla, Vice President of Operations, and Mr. Choube, Vice President of Quality, at the time of these incidents. We also expressed our concerns at the start of the day on numerous days. However, the pattern of providing false and misleading statements persisted throughout the inspection.

On 27 March 2017 during inspection of the QC laboratory we observed an employee,(b) (6) working on a general computer in one of the HPLC rooms. The computer was not connected to the Empower network, but had access to the SAP system and programs such as Microsoft Excel, Microsoft Word, and Adobe. The employee explained that the computer was used for printing labels, reviewing and revising SOPs, or trending of data.

I asked him to show me Microsoft Word and Microsoft Excel. Upon opening the software I observed a list of "Recent" documents that had been opened with Word. Pictures are included as page #1 of **Exhibit JAB #70.** These included documents such as "Calibration Report for Agilent HPLC" or "Label for Calibration". The file path indicated these were saved in places such as the Desktop, "My Documents" or the D: drive of the computer, which was a local drive specific to this analyst. When we attempted to open the documents an error was received indicating the file could not be found, see **Exhibit JAB #71.** When I checked the desktop and D: drive, I found that none of these documents were present. The "Recycling Bin" that would contain deleted files prior to final deletion was also empty.

I asked the analyst if these files had been deleted and he told me "No". I asked why I did not see them and he told me he did not know. I opened the Excel files and similarly observed multiple documents in the "Recent" folder, see page #2 of **Exhibit JAB #70.** These included documents such as "Balance Accuracy", "Flow Calculation" and "HPLC Linearity". These files could not be opened and were not present on the computer Desktop or local D: drive. I asked again if the files had been deleted and he told me "No". I showed him that the files had existed and recently saved on his computer, but were now gone. I asked again if the files were deleted and he told me "Yes".

I asked him why they were deleted and he told me he could not remember. I pointed out that some of the files had titles suggesting they were very recent, such as "SOP Index 25-02-2017", a date two days earlier. He then stated that his computer was slow, so he had contacted IT and IT had deleted everything. I asked him when this occurred and he told me he could not remember. He never provided an answer, though it appeared based on the name of the files it would have been after 25 February 2017 and before our inspection of the area on 26 February 2017.

I asked IT people to explain what had occurred. The IT personnel, including Mr. Laxmixharan Acharya, Manager IT, arrived and stated they had not done anything to this computer. I asked if the files were remotely deleted and they said "No". I asked the analyst(b) (6) who from IT had done this and he told me he could not remember the person's name. The IT personnel indicated the files would have had to been deleted at the work station. The IT personnel confirmed that the

analyst (b) (6) would have had to have logged on for them and been knowledgeable of what occurred if he had not deleted the files himself.

Mr. Choube, Head of Quality of Injectables was present. I explained that this employee had provided me what appeared to be false, misleading, and incomplete answers about the deletion of these files. I explained that this was unacceptable and asked him to ensure all of the employees answer my questions directly and honestly.

On 28 March 2107, I repeated my concerns prior to starting the inspection to all of the gathered upper management that the employee appeared to have provided me false and misleading information. Mr. Shukla and Mr. Choube, ensured me that they had communicated to all employees the need to answer our questions honestly.

Later in the morning we inspected the QC microbiology laboratory. I observed a general computer in the room where the incubators are located and plates are read. I asked the employee, Mr. (b) (6) (b) (6) a microbiologist that was working in the room upon arrival to logon to the computer for us. We again observed that "Recent" documents listed in both Word and Excel listed numerous documents, see **Exhibit JAB #72.** These included documents such as "Risk Assessment (b) (4) EM" and "Rationales". The documents were identified to be on the desktop and Z: drive. When we attempted to open these documents we received an error indicating the files were unavailable, see **Exhibit JAB #73**. I confirmed that there were no files on the Desktop or the Z: drive and that the Recycle Bin was empty. Further, the Z: drive was not mapped to this user.

I asked Mr. (b) (6) if he had deleted files and he told me "No". I asked why I didn't see the files if they had not been deleted. He stated the computer was shared use and maybe somebody else had deleted them. I asked whether the login to the computer was shared and he told me each analyst that shares the computer uses their own. I asked how someone else could have deleted his files and he did not answer.

I then asked a second analyst to logon to the computer, Mr. (b) (6) microbiologist. This local computer for this analyst similarly had no files on the Desktop and the computer was not mapped to the Z: drive. The "Recycle Bin", which must be manually emptied, had no files in it. However, the recent document tabs in Word and Excel identified documents with save locations on the Desktop and Z: drive, see **Exhibit JAB #74.** The same error was received when attempting to open these files, see **Exhibit JAB #75.** I asked Mr. (b) (6) whether he deleted these documents and he said "No".

I also confirmed that the files when logged in under Mr. (b) (6) were different from Mr. (b) (6) to confirm that only when logged in under their own name will the documents be visible and available for deletion. I then asked Mr. (b) (6) again whether he had deleted the files seen when he had been logged in. He changed his answer to "Yes" he had deleted them. I asked him why he had deleted

them and he told me he could not remember. I asked him when he had deleted them and he told me he could not remember.

I reminded him that the titles of the documents, such as EM Trends for February 2017, indicated these were recent documents and that he reported he uses this computer on a daily basis. Since there were no documents in any of the folders, it appeared deletion was done recently. He then told me he deletes the documents he no longer needs.

I asked Mr. (b) (6) again if he had deleted the files and he also changed his answer to "yes". He then provided the same answer as Mr. (b) (6) that he deleted the files since they were no longer needed. I asked whether they were instructed to delete these files by someone else and both told me they had done so on their own.

Mr. Choube was again present during this discussion. Immediately at the conclusion of the discussion I spoke to Mr. Choube and explained that the false and misleading information that these employees had provided us was unacceptable and that it had caused delays in our ability to conduct our inspection. The following morning, 01 March 2017, I repeated this statement to the upper management team prior to starting the inspection for the day. Mr. Shukla stated they would be transparent and did not intend to mislead us. He explained all employees had been instructed to answer our questions truthfully and directly.

Later in the morning we inspected the production Block (b) (4) During the inspection we observed additional computers in a general office area. Mr. Pradeep Mohrana, Resource Production Manager, reported he was a user of one of the computers. He explained that he used the computers to work on investigations, change controls, procedure updates, and other documents as necessary, all in Microsoft Word. He also reported he gathered data and performed trending using Microsoft Excel. When we inspected his computer we found no files on the Desktop or any of the networked drives. The "Recycle Bin", which must be manually emptied, had no files in it. When I opened Microsoft Excel I observed that it had no documents listed in the "Recent" document list. When I opened Microsoft Word, the only "Recent" document list were related to an investigation Mr. Mohrana had been working on that morning, see **Exhibit JAB #76.** There were no documents from previous days.

I asked Mr. Mohrana if he had deleted documents that had been saved on his computer. He told me "No". This is inconsistent with his description that he uses the computer, with Microsoft Word and Excel, on a daily basis. I asked whether he cleared the documents of the "Recent" list. He told me "No". I asked whether he knew how to clear the recent documents and he told me "No". Since he reported that he used the computer with Word and Excel on a daily basis, I asked how it was possible there were no documents on his "Recent" list. He did not answer me.

At the same time I interviewed Mr. Mohrana, Investigator Oladimeji interviewed a second production operator that worked in the same area, Mr. (b) (6)

(TBO) On February 28, 2017 during inspection of the production area, I asked Mr.(b) (6) to open Microsoft Word on his computer. Upon opening the software I observed that "Recent" documents that had been opened with Word were deleted. I asked him to open the D: drive, it was also empty. When he opened the network drive, I noted four Word files that were recently modified on 02/22/2017 and 02/24/2017 on the network. I asked him why these files are not in the "Recent" documents. He initially stated he did not know. After further questions he stated that he cleared the "Recent" documents, deleted documents from the D: drive, emptied the recycle bin, and disabled the "Recent" document feature from displaying documents that have been created. I asked Mr (b) (6) when and why he disabled the feature. He responded that he disabled the feature on February 25th or 26th, 2017. He did not provide explanation why he deleted documents and disabled the feature. Photographs of the computer screen and attached as **Exhibit TBO26, photos 27 - 29.**

(JAB) After Investigator Oladimeji confirmed that Mr (b) (6) had deleted files on the computer and cleared the "Recent" list, I spoke to Mr. Shukla and Mr. Choube. I explained that it again appeared an employee, Mr. Mohrana, was providing false and misleading information to me, despite the repeated discussions that had already been had regarding employees providing truthful answers and assurances from Mr. Shukla that all employees would answer our questions honestly. Mr. Shukla told Mr. Mohrana to answer my questions honestly.

Mr. Mohrana then confirmed he had deleted the files saved on his computer, emptied the "Recycle Bin", and cleared his "Recent" list, all different than his initial answers. He had previously told me he did not know how to clear the recent list. He then proceeded to demonstrate how to clear the "Recent" list, confirming he did know how to it. I asked him why he had done this and why he had provided me different answers. He stated that he was "fearful" due to the inspection.

On the morning of 02 March 2017, for the third consecutive day, prior to the start of the inspection I spoke with the upper management team about the untruthful information provided to us by employees.

On the afternoon of 02 March 2017 I followed up further on the computers in the microbiology laboratory. I observed the "Recent" documents on the(b) (4) employees that had logged in included files saved on the Z: drive, see **Exhibit JAB #72 and #74**. However, the Z: drive was not mapped to these computers on 28 February 2017. The employees had stated the drive was mapped to a shared drive. This was the shared drive that included documents such as the master copies of analytical testing forms, see point #1 of **Observation #7.** Without the presence of these documents, it would not be readily detectable that the analysts had access to documents such as the master copies. However, it appeared this had been removed prior to the inspection.

I spoke with IT personnel that stated they had not unmapped the Z: drive from these computers. They explained it would be done individually by the person that had logged in. I asked Mr. (b) (6) to log in for me. I asked him to open a document from the Z: drive. He could not. I asked him to

save a document to the Z: drive. He could not. I asked him if he knew how to map the Z: drive or to remove and un-map the Z: drive from his computer. He did not know how to do this. However, I explained it appeared this had been done on his computer just prior to the inspection. Mr. Acharya, IT Manager, the microbiology management, and the analysts did not provide an answer for who had un-mapped the Z: drive on both Mr. (b) (6) and Mr. (b) (6) computer. Therefore I was unable to ask why this had been done just prior to the inspection.

On 03 March 2017 during review of media fill batch record (b) (4) I observed that Mr. (b) (6) (b) (6) "(b) (6)" in the records" had signed as the "Checked By" person form many steps in many different areas over an amount of time that appeared to be unreasonable. The details and supporting evidence are described in point #1 **Observation #4.**

I reviewed the attendance records and biometric access records that appeared to demonstrate that Mr. (b) (6) was not actually present in the filling area at many of the times in which he had signed for in the batch record. I asked to speak to him regarding the issue. I asked Mr. (b) (6) whether it was possible he was not always present at the times indicated in the batch record and he told me "No", that he was always present with the operator that performed the task. When I pointed out the records which showed he wasn't always present, he did not change his answer. He told me there could be discrepancies between the clocks in the production area and the biometric readers. I later reviewed an investigation from November 2016 that identified the difference between the clocks and the biometric reader to be approximately 3 minutes.

I asked to speak to Mr. Shukla, Vice President Operations and the most responsible person at this facility. I explained to him that the answers provided by Mr. (b) (6) were not consistent with the biometric reader. Mr. Shukla spoke to Mr. (b) (6) and ensured him if he had not been there to tell me and that there would be no repercussions against Mr. (b) (6) Mr. (b) (6) did not change his answer. He reaffirmed that he was present at the time indicated in the batch record each time he had signed it as the "Checked By" person.

Mr. (b) (6) left and I continued reviewing the batch records. I found further examples of Mr. (b) (6) signing for steps when the biometric access data placed him in different parts of the facility. I asked to speak to him again. I presented additional examples and again asked if it was possible if he was signing for things when he was not actually present. He changed his previous answers and confirmed that sometimes he signed at a later time than what was indicated in the batch record.

GENERAL DISCUSSION WITH MANAGEMENT
In addition to the observations cited on the FDA 483, we discussed that we had encountered multiple personnel in multiple departments that provided false and misleading answers to our questions. This had caused significant delays in covering the inspection of this facility. Examples are described in the **Refusals** section of this report.

ADDITIONAL INFORMATION

During the inspection we stayed at the Novotel Visakhapatnam Varun Beach. The hotel was adequate for business purposes and would be recommended for future travelers. It is located approximately one hour from the facility.

SAMPLES COLLECTED

No samples were collected.

VOLUNTARY CORRECTIONS

We reviewed corrective actions taken by the firm as a result of items cited on the FDA 483 during the previous inspection and the subsequent FDA Warning Letter. We found there was a failure to comprehensively address previously cited issues.

Warning Letter Observation #1 – *failure to conduct through investigations*. We found that investigations fail to identify root causes and are not supported by data. This was cited as **Observation #1.**

Warning Letter Observation #2 – *there was insufficient justification for rejection of media fill units.* During this inspection we found that all media fill units are now accounted for.

Warning Letter Observation #3 – *inadequate procedures for qualification for visual inspection operators.* We found that corrections were made for the liquid products. However, this was not extended to the (b) (4) products, see **Observation #3.**

Warning Letter Observations to other Dr. Reddy sites – *controls for data integrity of paper and electronic records were inadequate and there was the presence of unreported data*. These had not been thoroughly addressed at this site. **Observation #3** cited the presence of unreported data for analyses not included in the data integrity retrospective review. **Observation #7** cited a lack of controls over paper GMP data forms. **Observation #8** cited lack of controls over electronic data to prevent unauthorized changes.

EXHIBITS COLLECTED

JAB Exhibits

1. Dr. Reddy Locations. (3 Pages)
2. Products shipped to the US market. (15 Pages)
3. List of US products from Unit VII. (6 Pages)
4. List of US products from Unit IX. (4 Pages)
5. List of all products manufactured on site. (3 Pages)
6. Personnel present for the initiation. (1 Page)
7. Organizational Charts. (13 Pages)

8. Personnel present for the close of the inspection. (1 Page)
9. Picture of spill from filter. (2 Page)
10. Investigation into spill. (8 Pages)
11. Report of evaporation and filter leak. (13 Pages)
12. May 2016 documentation error trending. (1 Page)
13. June 2016 documentation error trending. (1 Page)
14. July 2016 documentation error trending. (1 Page)
15. August-October 2016 documentation error trending. (1 Page)
16. November 2016 documentation error trending. (4 Page)
17. Procedure FTCQC017. (32 Pages)
18. Investigation August 2014 *Burkholderia*. (6 Pages)
19. Investigation September 2014 *Acinetobacter*. (8 Pages)
20. Investigation May 2015 *Burkholderia*. (10 Pages)
21. June 2015 trending (b) (4) (1 Page)
22. Investigation 200142186. (11 Pages)
23. Investigation 200142186 addendum I. (14 Pages)
24. Investigation 200142186 addendum III. (13 Pages)
25. Investigation 200142186 addendum IV. (11 Pages)
26. Investigation 200142186 addendum V. (11 Pages)
27. Overall investigation and impact assessment 200142186. (28 Pages)
28. (b) (4) Tablets (b) (4) batch record pages. (2 Pages)
29. *Burkholderia cepacia* findings. (1 Page)
30. Incident 200166175. (18 Pages)
31. Environmental monitoring trending. (6 Pages)
32. Visual inspection trending (b) (4) (1 Page)
33. Defect library description. (11 Pages)
34. Description of qualification kits. (1 Page)
35. Description of kit #1. (7 Pages)
36. Description of kit #8. (4 Pages)
37. Description of kit #9. (10 Pages)
38. Sequence 057023_RS_002. (1 Page)
39. 057023_RS_002 chromatograms. (22 Pages)
40. Sequence 057023_RS_003 record of analysis. (30 Pages)
41. (b) (4) video checklist. (1 Page)
42. Picture of biometric access. (1 Page)
43. Media fill batch record (b) (4) (101 Pages)
44. Attendance records "(b) (6)". (1 Page)
45. Biometric entry records "(b) (6)". (1 Page)
46. Attendance record "(b) (6)". (1 Page)
47. Attendance record "(b) (6)". (1 Page)
48. LAF usage log. (1 Page)
49. Visual inspection records for (b) (4) (14 Pages)
50. Analytical request for black particles. (1 Page)
51. Personnel that can perform aseptic operations. (2 Pages)

52. Media fill interventions. (8 Pages)
53. Entrance log to filling area. (1 Page)
54. NVP alarm log. (1 Page)
55. Procedure OPR518-00. (10 Pages)
56. Surface monitoring 27 February 2017. (8 Pages)
57. Surface monitoring 14 February 2017. (4 Pages)
58. Media description. (5 Pages)
59. Blank SAP printed sterility test from. (1 Page)
60. "Test" master forms. (1 Page)
61. Document issuance log. (2 Pages)
62. (b) (4) monitoring records. (1 Page)
63. Batch (b) (4) errors. (3 Pages)
64. Batch record page with error. (1 Page)
65. Settle plate record batch (b) (4) (2 Pages)
66. Settle plate record batch (b) (4) (1 Page)
67. Settle plate record batch (b) (4) (2 Pages)
68. (b) (4) user manual maintenance. (1 Page)
69. Preventive maintenance check sheet. (3 Pages)
70. Picture of recent documents in chemistry lab. (2 Pages)
71. Picture of error when opening documents chemistry. (3 Pages)
72. Picture of recent documents in microbiology lab, (b) (6) (3 Pages)
73. Picture of error when opening documents microbiology, (b) (6) (2 Pages)
74. Picture of recent documents in microbiology lab, (b) (6) (3 Pages)
75. Picture of error when opening documents microbiology, (b) (6) (1 Pages)
76. Picture of Word with no recent documents. (1 Page)

Exhibit #	Document Description	Page(s)
TBO 1	Incident Report 200168017	7
TBO 2	Incident Report 200168685	8
TBO 3	Incident Report 200193210	16
TBO 4	Incident Report 200225061	6
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TBO 6	Incident Report 200215055	19
TBO 7	SOP OPR-00 (b) (4) Integrity Tester	16
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TBO 9	OOS 310009438	9
TBO 10	OOS 310007780	10
TBO 11	OOS 310008334	22
TBO 12	OOS 310009250	9
TBO 13	OOS 310009706	10

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TBO 14	OOS 310009622	13
TBO 15	OOS 310010270	21
TBO 16	OOS 310008552	19
TBO 17	OOS 310009929	14
TBO 18	OOS 310010238	17
TBO 19	SOP OPR012-16 Visual Inspection	33
TBO 20	(b) (4) Batch Record (b) (4)	3
TBO 21	(b) (4) Batch Record (b) (4)	5
TBO 22	(b) (4) Batch Record (b) (4)	3
TBO 23	(b) (4) Batch Record (b) (4)	4
TBO 24	Biometric Access System	2
TBO 25	Garment Inspection Record	2
TBO 26	Photographs	29
TBO 27	(b) (4) Replacement Logbook	3
TBO 28	(b) (4) PPQ Report	23
TBO 29	(b) (4) Batch Record (b) (4)	29
TBO 30	Waste Disposal Form	15

ATTACHMENTS
FDA 483 Inspectional Observations

Signature Line

4/4/2017

X Justin A. Boyd

Justin A. Boyd
Investigator
Signed by: Justin A. Boyd -S

4/3/2017

X Toyin B. Oladimeji

Toyin B. Oladimeji
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