

Food and Drug Administration Establishment Inspection Report

Date Assigned: 05/16/2017

Inspection Start Date: 05/22/2017

Inspection End Date: 06/02/2017

Firm Name & Address: Celltrion Inc. , Yeonsu-gu , Plant 1: 23 Academy-Ro Incheon City

Firm Mailing Address: Yeonsu-Gu, Plant 1: 23 Academy-Ro, Incheon City ,406-840, Korea (the Republic of)

FEI: 3005241015

JD/TA:

County:

Est Size: Unknown

Phone:

District: IOG

Profiled: Yes

Conveyance Type:

% Interstate:

Inspectional Responsibility:

Endorsement

A post-approval and GMP inspection of this foreign drug substance and drug product manufacturer was conducted per FY17 work plans. The firm manufactures one product for the US market, Inflectra (infliximab-dyyb) under BLA 125544. Coverage was given to compliance program 7346.843, Post-Approval Inspections, compliance program 7356.002A, Sterile Drug Process Inspections, and compliance program 7356.002M, Inspections of Licensed Biological Therapeutic Drug Products. The Quality, Facilities & Equipment, Production, and Laboratory systems received coverage.

The previous FDA inspection dated 4/6/15 - 4/9/15 was a BIMO sponsor inspection. The most recent inspection to cover GMP production activities was a Pre-License inspection for BLA 125544 dated 2/23/15 - 3/6/15. The inspection was classified VAI and there was a 15-item FDA 483, Inspectional Observations.

The current inspection found the firm continues to manufacture a drug substance and lyophilized injectable drug product for the US market. At the conclusion of the inspection a 12-item FDA 483 was issued including observations for: investigations of discrepancies were not thorough or timely; procedures for aseptic processing were not established and followed; validation of the aseptic process was deficient; appropriate procedures for environmental monitoring of the aseptic processing areas were not established; cleaning procedures for the aseptic processing areas were not adequate; equipment in the aseptic processing areas was not of an appropriate design; process validation studies did not evaluate intra-batch variability; complete testing records are not maintained and reviewed; controls over electronic records are not established; document issuance and use is not controlled; data is not documented contemporaneously; and batch records do not contain complete information related to the production of a batch.

Firm management promised corrections to 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

Distribution: EIR in eNSpect & OSAR

Endorsement Location:

Inspector Name

Date & Time of Signature

Supervisor Name

Date & Time of Signature

ET

ET

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Firm Name & Address: Celltrion Inc. , Yeonsu-gu , Plant 1: 23 Academy-Ro Incheon City

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

Registration Type

DRG Drug

Registration Dates

01/01/2018 12/01/2016 12/31/2015

Establishment Type

4 Commercial Sponsor-Monitor
M Manufacturer
M Manufacturer
M Manufacturer
M Manufacturer

Industry Code

66 Human and Animal Drugs
57 Bio & Licensed In-Vivo & In-Vitro Diag
60 Human and Animal Drugs
61 Human and Animal Drugs
62 Human and Animal Drugs

District Use Code:

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Firm Name & Address: Celltrion Inc. , Yeonsu-gu , Plant 1: 23 Academy-Ro Incheon City

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56002A	Manufacturer	61 Y C P				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/12/2017	Official Action Indicated (OAI)	Boyd, Justin A	IOG

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/19/2017	Official Action Indicated (OAI)	Minden, Claire M	IOG

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	01/26/2018	Official Action Indicated (OAI)	Xu, Lixin	CDER-OMQ

Remarks: WL 320-18-28 issued 1/26/2108

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56002M	Manufacturer	61 Y C P				Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/12/2017	Official Action Indicated (OAI)	Boyd, Justin A	IOG

Remarks:

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
Y	01/26/2018	Official Action Indicated (OAI)	Xu, Lixin	CDER-OMQ

Remarks: WL 320-18-28 issued 1/26/2108

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56843	Manufacturer	61 Y C P				Correction Indicated (CI)

Food and Drug Administration Establishment Inspection Report

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/12/2017	Official Action Indicated (OAI)	Boyd, Justin A	IOG

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	06/19/2017	Official Action Indicated (OAI)	Minden, Claire M	IOG

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	01/26/2018	Official Action Indicated (OAI)	Xu, Lixin	CDER-OMQ

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Firm Name & Address: Celltrion Inc. , Yeonsu-gu , Plant 1: 23 Academy-Ro Incheon City

Products Covered

Product Code	Est Type	Description	Additional Product Description
61 Y C P 01	Manufacturer	Infliximab Human - Rx/Single Ingredient Small Volume Parenteral <100ml	

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Boyd, Justin A	DDC	IOG-MPT	56002A	Manufacturer	61 Y C P	50
Boyd, Justin A	DDC	IOG-MPT	56002M	Manufacturer	61 Y C P	50
Boyd, Justin A	DDC	IOG-MPT	56843	Manufacturer	61 Y C P	50
Total Hours:						150

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Firm Name & Address: Celltrion Inc. , Yeonsu-gu , Plant 1: 23 Academy-Ro Incheon City

Inspection Result

EIR Location

Trips Num
2017-217D

Inspection Summary

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The current inspection found the firm continues to manufacture a drug substance and lyophilized injectable drug product for the US market. At the conclusion of the inspection a 12-item FDA 483 was issued including observations for: investigations of discrepancies were not thorough or timely; procedures for aseptic processing were not established and followed; validation of the aseptic process was deficient; appropriate procedures for environmental monitoring of the aseptic processing areas were not established; cleaning procedures for the aseptic processing areas were not adequate; equipment in the aseptic processing areas was not of an appropriate design; process validation studies did not evaluate intra-batch variability; complete testing records are not maintained and reviewed; controls over electronic records are not established; document issuance and use is not controlled; data is not documented contemporaneously; and batch records do not contain complete information related to the production of a batch.

IB Suggested Actions

Action	Remarks
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Referrals

Org Name	Mail Code	Remarks
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Refusals

Date: 02/16/2018

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Firm Name & Address: Celltrion Inc. , Yeonsu-gu , Plant 1: 23 Academy-Ro Incheon City

Inspection Refusals: No refusal

Samples Collected

Recall Numbers

Related Complaints

Sample Number

Recall Number

Consumer Complaint Number

FDA 483 Responses

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

Response Type	Response Mode	Response Date	Response Summary
Inadequate 483 Response	Letter	06/22/2017	

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Firm management promised corrections to 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:	Celltrion, Inc.
Location:	23 Academy-ro, Yeonsu-gu, Incheon, 406-840, Republic of Korea
Phone:	+82-32-850-6551
Mailing address:	23 Academy-ro, Yeonsu-gu, Incheon, 406-840, Republic of Korea
Dates of inspection:	05/22/2017, 05/23/2017, 05/24/2017, 05/25/2017, 05/26/2017, 05/29/2017, 05/30/2017, 05/31/2017, 06/01/2017, 06/02/2017

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Days in the facility:	10
Participants:	Justin A. Boyd, Investigator

HISTORY

Celltrion was founded in February 2002 as a mammalian cell culture based recombinant protein drug substance and drug product manufacturer. Commercial manufacturing in Plant I (Drug Substance) started in 2007. Commercial manufacturing in Plant II (Drug Product) started in 2012. There are no other locations for this company.

Previous FDA inspections were conducted October 2007 (pre-approval GMP, NAI) and April 2015 (BIMO, NAI). The most recent FDA inspection to cover GMP manufacturing was March 2015 and classified VAI. There was a 15-item FDA 483, Inspectional Observations, issued that included observations for: Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed; a procedure has not been established for performing identity testing on the contents of a final CT-P13 drug product vial of each lot after all labeling operations have been completed as required by 21CFR610.14; alert limits for bioburden and endotoxin are not established for CT-P13 drug substance in-process (b)(4) qualification studies for the (b)(4) lyophilizer, (b)(4) are not adequate; the visual inspection program (FF24010) for CT-P13 drug product vials is inadequate; the media fill program (CP2205) is deficient in that acceptance criterion for yield has not been established for media fills; the investigation for Deviation DE-(b)(4)-12-246 is inadequate; bioburden excursions for CT-P13 drug substance are not adequately investigated; qualification of assays conducted in the Research and Development Laboratory to evaluate infliximab biosimilarity for regulatory purposes was documented retrospectively; the (b)(4) dye penetration test used to evaluate CT-P13 drug product container closure integrity is inadequate; the in-process endotoxin test for drug substance is not adequately conducted; numerous leaks from the media vessel during media transfer to the bioreactor have occurred since 2013 and appear to be ongoing; the disinfectant efficacy study (Report GR-QC-15-003.AD1) conducted to validate disinfectants used for CT-P13 drug substance and drug product manufacturing facility cleaning is inadequate; establishment of the reliability of the stopper supplier's Certificate of Analysis is deficient in that the test results are not appropriately validated at appropriate intervals; and the raw material specifications for CT-P13 are inadequate.

Official FDA correspondence and FMD-145 correspondence to the most responsible individual onsite should be addressed to:

Woo Sung Kee, President
 23 Academy-ro, Yeonsu-gu,
 Incheon, 22014, Republic of Korea
 Phone: +82 32 850 5115
 E-mail: WooSung.Kee@celltrion.com

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 Celltrion, Inc.
 Yeonsu-gu, Incheon, Republic of Korea

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The firm's US Agent is:
 PAREXEL International
 Contact: Sugato De
 4600 East-west Highway, Suite 350,
 Bethesda, MD 20814
 Phone: +1 301 634 8010
 E-mail: sugato.de@parexel.com

The manufacturing areas operate (b) (4) and (b) (4) on (b) (4). The other departments work 9:00 (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 for distribution in the US market is included as **Exhibit #1**.

JURISDICTION

This facility manufactures one product for the US market Inflectra (infliximab-dyyb) under BLA 125544. They manufacture both the drug substance and the finished drug product. The following products are manufactured at this site:

Product	API	CT-P#	Dosage Form	Strength	Market	Status
Inflectra®	Infliximab	CT-P13	Lyophilized small volume parenteral	100mg	For Global market including US	FDA Approval April of 2016
(b) (4)	(b) (4)	(b) (4)	(b) (4) small volume parenteral	(b) (4) mg, (b) (4) mg	For Global market including US	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4) parenteral	(b) (4) mg, (b) (4) mg	For Global market including US	(b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

At the initiation of this inspection, I presented my FDA credentials and exchanged business cards with the most responsible person for this facility, Mr. Woo Sung Kee, President. A list of all personnel present for the initiation of this inspection is included as **Exhibit #2**.

Top management personnel and their duties include:

Name	Job Title	Duties	Reports to
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Name	Job Title	Duties	Reports to
Mr. Woo Sung Kee	President	Overall the most responsible person for Celltrion. All employees ultimately report to Mr. Woo Sung Ki. Responsible for hiring or firing managers. Approves capital expenditures.	Not Applicable
Mr. Myung Keun Oh	Head of Quality Division (Senior Vice President)	Most responsible for the inspected facility on a day to day basis. Responsible for the quality decisions at Celltrion facilities.	President
Mr. Sung Wook Yang	Director of Supply Chain QA	Responsible for product release, complaint, recall, deviation, and change control.	Head of Quality Division
Mr. Ji Young Joo	Senior Manager of Technical QA	Responsible for training and document control.	Head of Quality Division
Ms. Seon Mi Shin	Senior Manager of Microbiology QC	Responsible for microbiology laboratories.	Head of Quality Division
Ms. Gye Mee Jang	Senior Manager of Chemistry & Immunology QC	Responsible for chemistry & immunology laboratories.	Head of Quality Division
Mr. (b) (6)	Team Leader of Corporate QA	Responsible for coordination of regulatory inspections.	Head of Quality Division
Mr. Jeong Won Yun	Head of Manufacturing Division (Senior Vice President)	Responsible for manufacturing operations at Celltrion facilities.	President
Mr. Javier Camposano	Managing Director of MFG Fill & Finish	Responsible for fill & finish manufacturing activities.	Head of Manufacturing Division
Mr. Yun Mo Koo	Managing Director of MFG Engineering	Responsible for engineering.	Head of Manufacturing Division
Mr. Jong Hyun Kim	Director of Purchasing	Responsible for warehouse (Raw Materials, Drug Substances, and Finished Products).	President

The organizational charts are included as **Exhibit #3**.

FIRM'S TRAINING PROGRAM

I reviewed the training program. Training of personnel is tracked through an electronic database. New employees are required to receive GMP training and pass a GMP certification exam. To maintain the GMP certification, each employee must pass the GMP exam (b) (4). After the basic GMP training, regular employees must attend at least (b) (4) advanced GMP training sessions (b) (4). In addition, all procedures applicable to the tasks of an individual must be reviewed and signed for all procedure revisions.

I observed the firm uses contract employees and I reviewed training files for selected contract employees. These employees perform cleaning and monitoring of the utility systems. They must pass the GMP certification exam (b) (4) like regular employees. However, they do not

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receive any of the ongoing advanced GMP training. I verbally discussed with firm management the contract employees would also benefit from the ongoing advanced GMP training. I reviewed training files for contract employees that had worked for multiple years, yet they could only attend the basic GMP training.

MANUFACTURING/DESIGN OPERATIONS

Quality

The quality unit is composed of quality assurance and quality control departments. There is crossover between Plant (b) (4) and Plant (b) (4) for employees of both QA and QC. I observed there was a lack of quality oversight in the production areas. For example, the aseptic filling areas perform filling operations primarily on the (b) (4). The QA staff only works the (b) (4). Therefore, the QA does not routinely observe the aseptic filling activities. Additionally, programs such as environmental monitoring are the responsibility of the production personnel. There is no oversight by the QA or the QC microbiology groups. These are discussed further in **Observation #2 and #4**.

I reviewed the complaint logbooks and I chose examples of complaint investigations to review. One of the most common complaints received was related to “no (b) (4)” in the vial. This made (b) (4) of the lyophilized (b) (4) difficult. Since the last inspection they had received 140 complaints related to this issue for product manufactured at this site. The investigation confirmed these complaints and identified a root cause of stoppers sticking to the lyophilizer shelves. This slightly raised the stopper, allowing the (b) (4) to be lost. The issue of sticking stoppers has been ongoing for multiple years, yet effective corrective actions have not been timely and effective. Further, the investigation of product on the market that lacked (b) (4) was not thorough. This is discussed in **Observation #1**.

I reviewed the written procedures and the logbook of deviations. I found the investigations were not timely and thorough, see **Observation #1**. I reviewed the written procedure and examples of laboratory OOS. These included OOS results for foreign particles on stability samples and batches that had been released for (b) (4) packaging and labeling. I found the investigations were not timely, see **Observation #1**.

I reviewed examples of change controls. These included changes made to the lyophilizer in an attempt to reduce sticking of the stoppers. The change controls did not include a thorough evaluation of what was necessary. Further, they did not include an evaluation after the change was made to determine the effectiveness of the change that was made. This is discussed further in **Observation #1**.

Facilities and Equipment

There are (b) (4) production facilities on this campus. Plant (b) (4) is used for manufacturing drug substances only. The drug substance for Inflectra is manufactured in Plant # (b) (4). Plant # (b) (4) is used for

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drug product and drug substance manufacturing. For Inflectra, the compounding, aseptic filling, lyophilization, and visual inspection is performed in Plant #^(b)₍₄₎. No drug substance manufacturing related to the US market product Inflectra is performed in Plant #^(b)₍₄₎.

I conducted a walkthrough inspection of the Plant #^(b)₍₄₎ and Plant #^(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, beta-lactams, steroids, hormones, or cytotoxic products.

I observed that the equipment was labeled with its status, identification number, and calibration/qualification dates where applicable. There were associated use logs. The equipment appeared to be maintained appropriately.

I reviewed cleaning and disinfection procedures. The disinfectants used in the filling room are not supported by data from the disinfectant efficacy studies, see **Observation #5**. I observed the Plant #^(b)₍₄₎ and filling area for the drug substance area had dirty vents in the ISO 7 area, see **Observation #5**.

I reviewed equipment qualifications after new lyophilizer shelves were installed in the ^(b)₍₄₎ lyophilizer in Plant #^(b)₍₄₎. I did not note any significant discrepancies in the records that I reviewed.

Materials

I reviewed specifications, sampling plans, and test methods for raw materials and components. I reviewed the excipients sucrose and polysorbate 80 as well as the primary packaging components, stoppers and vials. I did not note any significant discrepancies in the records that I reviewed.

Production

A flow chart of the manufacturing process is included as **Exhibit #4**. I covered the manufacturing process of both the drug substance and the drug product for Inflectra. There have been no significant changes to this manufacturing process since the previous inspection. A brief description of the manufacturing process is as follows:

^(b)₍₄₎



(b) (4)



During the inspection I observed the production activities as they were occurring. While I watched production I verified the steps and documentation in the batch records. I found that data was not always documented contemporaneously, see **Observation #11**. I also found that the production personnel maintained unofficial records of the production activities. These records contained information not reflected in the official batch records, see **Observation #12**.

I observed set-up and filling operations in the drug product production area. I observed deficiencies in aseptic behavior, see **Observation #2**. I reviewed the media fills performed to validate the aseptic process. I found deficiencies with the media fill that are described in **Observation #3**.

I reviewed the 100% visual inspection program for lyophilized product. Inspection for the US market batches is performed manually. Operators inspect vials and categorize any rejects. At the (b) (4) the process an AQL inspection is performed by QA of the vials that passed visual inspection. I observed the following deficiencies related to the visual inspection process:

- Commonly seen particles that result in rejected vials have not been investigated to determine root causes, see **Observation #1**.
- Deviation investigations are only initiated when the overall yield for visual inspection of (b) (4) % is not met. There are limits for specific defect types and reasons for exceeding them are documented, but there is no full deviation investigation for individual rejects.
- The specific type of defect is not captured in the visual inspection record. For example, it may state “glass particle”. This could be an extrinsic piece of glass or a defect in the vial that is attached to the vial.
- The training and qualification kit lacks documentation of what types of particles are included. The kit does not incorporate rejects from actual manufacturing.

I reviewed the environmental monitoring program. This included the use of active air monitoring, settle plates, surface contact plates, personnel monitoring, and non-viable particle counts. I observed deficiencies related to the environmental monitoring program, which are described in **Observation**

#4. Investigations into adverse trends detected during the environmental monitoring were not investigated, see **Observation #1.**

Packaging and Labeling

Packaging and labeling operations do not occur at this site. Once visual inspection is complete and QA reviews the batch, it can be released as unlabeled vials to a packaging and labeling site. Product can be packaged and labeled at the following sites:

(b) (4)



After labeling a sample is shipped back to the Celltrion site for a (b) (4) identification test of the labeled product.

Laboratory

I performed inspection of the QC laboratory in both Plant #^(b)₍₄₎ and Plant #^(b)₍₄₎. The labs are divided into sections for Microbiology and Chemistry & Immunology. I found that the labs appeared to have the necessary equipment to perform specified analyses. 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.

I reviewed raw data from the analytical records for selected batches. The raw data appeared to be complete and supported the reported values. System suitability was performed for chromatographic systems.

Electronic laboratory systems had access controls, protection of raw data, and audit trails. There are procedures for reviewing audit trails. Until just prior to the inspection these reviews were performed by the person performing the data acquisition or review. This is now assigned to a different QC person, but it could be someone still responsible for the data review. We discussed reviews should be independent of the person reviewing and approving the data. Additionally, the audit trail review procedure was written broadly to cover all different types of software. It did not include specific detail necessary to review different types of software, see **Observation #9.**

The same controls of the electronic systems did not exist for in-process laboratory tests. For example, the (b) (4) used in the (b) (4) area or the filter integrity testing device did not have established access controls and the audit trails were not being reviewed, see **Observation #9**.

I inspected the microbiology laboratory in Plant #^(b)₍₄₎ and Plant #^(b)₍₄₎. I reconciled samples present with sampling plans and did not note any discrepancies. I observed the (b) (4) of settle plates was (b) (4) see **Observation #4**.

MANUFACTURING CODES

Drug Substance, (b) (4) where:

(b) (4)



Drug Product, (b) (4) where:

(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 present, Myung Keun Oh, Senior Vice President of Global Quality, Operation Division. Firm management committed to correcting the observations and responding in writing to the observations within 15 business days. In addition to Mr. Oh, a list of the personnel that were present for the closeout discussions is included as **Exhibit #5**.

Observations listed on form FDA 483

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OBSERVATION 1

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

1. Since the fourth quarter of 2015, 140 complaints have been received for difficult (b) (4) because of no (b) (4) in the vials of CT-P13 000B Inflectra. Vials are stoppered at the (b) (4) lyophilization under a (b) (4) w (b) (4) Document G (b) (4) -FF-16-059 states: "The purpose of (b) (4) step is (b) (4) (b) (4) into vials to prevent the (b) (4) Another purpose is co (b) (4) users during (b) (4) "

Investigations confirmed the complaints and identified a root cause of stoppers sticking to the lyophilizer shelves. The sticking raises the stopper allowing for ingress of ambient air instead of a (b) (4) Adequate corrective and preventive actions have not yet been implemented to address already released product, eliminate the root causes for on-going manufacturing, and ensure that vials without (b) (4) can be detected and removed prior to the release of batches.

The investigations have not been thorough and timely:

a. Yield investigation DE (b) (4) -15-051 dated 14 April 2015 identified sticking stoppers during lyophilizer unloading as a root cause. It identified sticking of stoppers as an ongoing occurrence. Enhanced lyophilizer cleaning corrective actions were not evaluated for effectiveness in eliminating the sticking stoppers. Production personnel reported to QA an even larger frequency in the observation of stopper sticking during lyophilizer unloading in quarter four of 2015. QA confirmed they were informed of this issue, but there is no QA documentation of this communication. Deviations DE (b) (4) -16-073 from 25 May 2016 and DE (b) (4) -16-116 from 09 August 2016 documented yield deviations and described ongoing problems related to sticking of stoppers during lyophilizer unloading.

b. No study has been conducted to determine the interaction of the stoppers and the shelves that impact the sticking.

c. No study has been performed to evaluate the frequency of no (b) (4) vials or to evaluate how they are distributed within the (b) (4) different lyophilizers.

d. Full release and stability tests have not been performed on vials without (b) (4) For example, (b) (4) content, (b) (4) time, color and clarity (b) (4) (b) (4), or particles (b) (4) (b) (4) have not been evaluated for vials without (b) (4)

e. Only three vials without (b) (4) from one batch, 12B1C012, have been tested for (b) (4) using peptide mapping.

f. A sensor is installed to reject vials with raised stoppers. This sensitivity of the sensor to reject vials with partially raised stoppers has not been thoroughly evaluated.

g. An inadequate blowback feature of vials has been identified as a potential cause for raised stoppers. However, the blowback feature on vials without (b) (4) has not been evaluated.

h. Corrective actions taken have not been thoroughly evaluated for effectiveness before or after implementation:

The production department initiated change control CC2-15-164 to increase the (b) (4) of the shelves for the (b) (4) lyophilizer. There was no documented evaluation of how much (b) (4) was (b) (4) prior to approving the change.

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The action was ineffective and an addendum was initiated to again increase the (b) (4). This was still unsuccessful in preventing sticking. (b) (4) shelves were installed per change control CC (b) (4). There was no evaluation to determine whether the (b) (4) shelves were effective in reducing vials without (b) (4).

Change control CC-15-194 was initiated to implement the use of (b) (4) stoppers. No evaluation was performed to evaluate the effectiveness of this change to reduce sticking and eliminate vials with no (b) (4) during the subsequent process validation studies conducted with the new stoppers. A study of (b) (4) volume was later performed for batch (b) (4) but was limited to 15 vials. Further, there is no requirement that the (b) (4) stoppers be used instead of (b) (4) stoppers for ongoing production.

2. Investigations into foreign matter detected in drug product and drug substance are not investigated in a timely manner.

a. On 03 February 2017 and 08 February 2017 Celltrion was informed by a contract laboratory of an OOS for particles in CTP-13 000B batch 15B4C22 and 16B1C32A respectively. These batches had been released for packaging and labeling. The samples were returned to Celltrion on 14 February 2017. Identification was not completed until 28 February 2017 when it was confirmed that the particles consisted of (b) (4) fibers. Deviation DE (b) (4) 17-042 was not opened until 28 February 2017.

No further action was taken until additional samples were requested from the secondary packaging site on 29 March 2017. Samples were received at Celltrion for further evaluation on 13 April 2017. As of 31 May 2017 none of these samples has been evaluated for foreign particles, no investigation has been performed into the root cause of the (b) (4) fibers, and the investigation remains open.

b. On 16 March 2017 a stability sample at the one month time point from lot 17200B001 of CTP-13 000B drug substance was found to have “Too Numerous To Count” particles against a limit of less than or equal to (b) (4) for proteinaceous particles. On 20 March 2017 some of the particles were identified to be (b) (4) a foreign particle that failed the specification of (b) (4). No OOS investigation was opened until 21 March 2017. As of 31 May 2017 no investigation has been performed into the root cause of the failure and the investigation remains open.

c. On 13 April 2017 a stability sample at the two month time point from lot 17100B003 of CTP-13 000B drug substance was confirmed to have a foreign particle. These particles were later identified to be (b) (4). An OOS investigation was not opened until 12 May 2017 and a deviation investigation was not opened until 16 May 2017. As of 31 May 2017 no investigation has been performed into the root cause of the foreign particle and the investigation remains open.

d. Particles detected during visual inspection have not been evaluated to determine their source. For example, the source of particles identified as “diaphragm”, seen in multiple 2017 batches, has not been identified. Further, the reject vials from actual production have not been incorporated into the visual inspection training and qualification kit.

3. Investigations of unexpected trends in the environmental monitoring data are not investigated thoroughly and in a timely manner.

a. The (b) (4) trending report for the environmental monitoring of Plant # (b) (4) for (b) (4) had not been completed as of 31 May 2017. Trending procedure QC1031 “Trend Analysis of Environmental/Clean Utility Monitoring” states that completion of the (b) (4) trend report is “recommended” by the (b) (4). The data from (b) (4) showed a higher level of exc (b) (4) s compared to (b) (4) and it was reported by QC personnel that a CAPA was necessary for the

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abnormal trend. However, no CAPA has been initiated as of 31 May 2017 to address the (b)(4) trend. The (b)(4) data has shown the excursions are occurring at an even higher rate than in (b)(4)

b. Review of trending of the environmental monitoring data does not ensure changes in the microbial flora are detected and evaluated. The (b)(4) trending for Plant # (b)(4) showed no mold organisms were recovered. From 22 February 2016 to 21 May 2016 mold organisms were recovered in the ISO 7 areas six times, five of which were Aspergillus species. No investigation was performed to identify the source of the mold organisms.

Supporting Evidence and Relevance:

1. (b)(4)

(b)(4) This is described in the “Background” section of Document G (b)(4) -FF-16-059, see **Exhibit #6**.

Celltrion has received 140 complaints on distributed product for “no (b)(4)”. This was apparent to the user because for these vials, the (b)(4) is not drawn into the vial by the (b)(4) as would occur with other vials. The list of complaints is included as **Exhibit #7**. It identifies CLT and (b)(4). The “CLT” complaints are complaints for batches that were manufactured at this facility. The same product is contract manufactured at a (b)(4) facility, identified in this record as (b)(4). That site has received similar complaints of vials without (b)(4). The QA at this site covers complaints for either site. My review focused on the Celltrion complaints because the US market product is manufactured at Celltrion.

The complaints for Celltrion “CLT” are further divided based on the lyophilizer used to manufacture the product (b)(4). At the end of 2015 (b)(4) new (b)(4) lyophilizers were installed. Prior to that time only the (b)(4) lyophilizer was used at this site. The complaints show that the “no (b)(4)” problem affects batches made in all (b)(4) of the lyophilizers.

The first complaint received for vials without (b)(4) at the Celltrion site was received 22 July 2014, see **Exhibit #8**. This complaint states thorough investigation will not be performed and it states if additional complaints are received then in-depth investigation would occur.

In the fourth quarter of 2015 the number of complaints for no (b)(4) increased for the same product manufactured at this site, see **Exhibit #7**. Deviation DE (b)(4) -16-003 was opened on 06 January 2015, see **Exhibit #9**. At that time the deviation was opened, 20 complaints had already been received for batch 12B1C012. An additional 35 complaints were received by 01 April 2016, when the deviation was closed. Additional complaints were received for two other batches, 12B1C014 and 12B1C015. This deviation covered a total of 95 complaints by

the time it was closed. The deviation states that distribution of these three batches was stopped.

All of the complaints that were part of this investigation are documented in **Exhibit #10**. These complaints all come from the (b) (4) market. At the time the product was not commercially distributed in the US market. Upon approval in April 2016, batches were distributed to the US market which would have been manufactured under conditions that may have led to the same no (b) (4) problem.

The investigations of these complaints confirmed that the vials did not have a (b) (4). The root cause was identified to be stoppers sticking to the lyophilizer shelves during stoppering. When the shelves lifted, the stoppers could be raised slightly, significantly, or be pulled completely off. Those vials with clearly displaced stoppers were removed by the production operators during the unloading process. However, the slightly raised stoppers were not readily apparent. These vials continued on to the capping process. Until the capping step, the stoppers were not completely seated. This allowed for ingress of ambient air that eliminated the (b) (4) and displaced the (b) (4) environment.

There was no further deviation investigation. A memo summarizing the activities and an impact assessment was written 03 March 2017, see **Exhibit #11**. I reviewed the associated CAPAs and change controls described in this document. I found the investigation of the root causes, evaluation of product that has already been distributed, and implementation of preventive actions has not been thorough and timely:

- a. When these complaints were received, the identified root cause was determined in part because production had seen sticking of the stoppers during unloading of the lyophilizer. This had reportedly been occurring for years. The first mention in a quality document was yield investigation DE-(b) (4) -15-051 dated 14 April 2015, see **Exhibit #12**. The investigation identified sticking stoppers during lyophilizer unloading as a root cause and as an ongoing occurrence. The conclusion states “*it is a noticeable fact that there have been issues with the stoppers sticking to the shelves constantly observed from the (b) (4) lyophilizer*”. At the time, only the (b) (4) yophilizer was used for commercial production.

The investigation identifies two CAPAs. The first is to improve cleaning of the shelves and the other was to evaluate the lyophilizer to determine corrective actions, such as (b) (4) shelves. Enhanced lyophilizer cleaning corrective actions were not evaluated for effectiveness in eliminating the sticking stoppers.

Mr (b) (6) Manufacturing Supervisor, told me that in the fall of 2015 the observation of sticking became a much more common occurrence. This unexpected occurrence was not formally documented. However, Mr. (b) (6) told me he informed QA. Mr. (b) (6) Team Leader QA and Mr. Hyunbun Kim, Assistant Manager QA,

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confirmed QA had been informed by production of this unexpected occurrence. They confirmed that this had not been documented anywhere within the quality system and no further investigation had been opened.

I asked Mr. (b) (6) Team Leader QA, whether the lyophilizer used had an impact on the amount the stoppers stick to the shelves. He reported he did not know and confirmed no study had been performed. When I asked Mr. (b) (6) Manufacturing Supervisor, the same question, he stated that the sticking appeared at a higher frequency on the (b) (4) Lyophilizer than the (b) (4) newer (b) (4) Lyophilizers.

Although these observations by production personnel were not captured in the quality system, change controls were initiated to attempt to modify the shelves of the (b) (4) Lyophilizer. See point (h) below. These included increasing the (b) (4) of the lyophilizer shelves. There was no evaluation before or after these changes to ensure that it adequately prevented sticking of the stoppers.

Deviations DE-(b) (4) -16-073 from 25 May 2016, see **Exhibit #13**, and DE-(b) (4) -16-116 from 09 August 2016, see **Exhibit #14**, documented yield deviations and described ongoing problems related to sticking of stoppers during lyophilizer unloading. This was after the previous corrective actions of manually cleaning the shelves and increasing the (b) (4) of the (b) (4) Lyophilizer shelves. These investigations concluded there is no product impact. However, they do not address the previous investigations of the complaints for no (b) (4) hat were also related to stoppers sticking to the shelves.

- b. There has been no definitive investigation to identify the mechanism that causes the stoppers to stick. I was provided different explanations during the inspection, but none of the explanations was fully documented in any of the investigations. One explanation was that a material interaction between the stopper and shelf caused the tackiness of the stopper to adhere to the shelf. Another explanation was that a (b) (4) was created between the stopper and the vial due to the shape of the stopper and stoppering under a (b) (4). No study has been conducted to determine which of these explanations is the primary interaction that causes sticking stoppers. Without determining the primary mechanism that causes sticking, appropriate corrective actions cannot be developed.

If the primary cause is the formation of a (b) (4) between the stopper and the shelf, then these vials may not be represented during media fills. Media fill vials are stoppered after (b) (4) with (b) (4) and (b) (4) pressure conditions to ensure an aerobic environment to support grow (b) (4) croorganisms.

I requested trending data from the commercial batch rejects, which consist of fully removed or obviously raised stoppers, and the same rejects in media fill. This type of data had not been collected or analyzed as part of their investigations. During media fills

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the same vials and stoppers are used, but the vials are stoppered at (b) (4) versus a (b) (4) (b) (4) for commercial batches. The data is included as **Exhibit #15**.

On (b) (4) page, (b) (4))
The first bar (blue) represents fallen vials removed during unloading. These may or may not be related to sticking. The second bar (red) represents rejects by the stopper sensor at the capping machine. None of these rejects would be the same as the no (b) (4) vials because the no (b) (4) vials are not detected. However, if there is widespread sticking, than undetected slightly raised stoppers may also be present.

During the media fill for the (b) (4) lyophilizers there is a lower number of “fallen” rejects for the (b) (4) Lyophilizers. (b) (4)
these batches are about (b) (4) the size of a commercial batch. The commercial batches show much higher number of these types of rejects. If sticking doesn’t occur during media fill, then sterility assurance of these vials may not be fully understood.

- c. There has been no study throughout these investigations to identify the frequency of the vials with no (b) (4) within the batch. There has been no study to evaluate whether these vials are distributed randomly within the batch or whether they are related to certain shelves or certain areas within a shelf on the lyophilizer. For example, any warping of a shelf that would prevent the shelf from applying force equally to all stoppers. At this site there are (b) (4) lyophilizers. The complaints in **Exhibit #7** identify that complaints of vials with no (b) (4) are observed from all (b) (4) of the lyophilizers.

Reliable, non-destructive methods are not available to perform this type of study. There is currently no (b) (4) analysis equipment on site to non-destructively determine if th (b) (4) It was reported that a bench top (b) (4) analyzer was recently ordered, but it would not be available for another month after the conclusion of the inspection.

The method currently used to evaluate the presence of a (b) (4) is a destructive method in which a vial is (b) (4) The amount of (b) (4) that is drawn into the vial by the (b) (4) is measured. This should be approximately (b) (4) If it (b) (4) in significantly less, than it is assumed there is not an adequate (b) (4) is is not a routine test.

Without adequately identifying the frequency and distribution of the no (b) (4) vials, the firm has not been able to assess the impact and implement corrective actions because they haven’t determined why some stoppers stick and others do not.

- d. Full release and stability tests have not been performed on vials with no (b) (4). For example, (b) (4) content, (b) (4) time, color and clarity (b) (4) (b) (4) or particles (b) (4) (b) (4) have not been evaluated for vials without (b) (4) to determine (b) (4) ambient air impacts the quality of the product.

As part of DE-(b) (4) -16-003, see **Exhibit #9**, limited analytical testing was performed on vials with no (b) (4) from batch 12B1C012. (b) (4) vials were evaluated in January of 2016, see **Exhibit #16**. Container closure integrity was performed on all (b) (4) vials and all passed. Then the vials were (b) (4). This revealed 4 of the (b) (4) vials did not appear to have a (b) (4). Of these four vials, two were used for peptide mapping by LC-MS to evaluate (b) (4) of (b) (4) one was used for a sterility test, and one was used for an in-vitro assay test. All (b) (4) conformed to specifications. Peptide mapping by LC-MS to evaluate (b) (4) of (b) (4) is not a routine test. There is no specification. The amount of (b) (4) (b) (4) compared to a vial with a (b) (4) and the RSD must be less than (b) (4) %. The method for peptide mapping is included as **Exhibit #17**.

The same testing was completed again in January 2017 with batch 12B1C012, using (b) (4) more vials, see **Exhibit #18**. Container closure integrity was performed on all (b) (4) vials and all passed. Then the vials were (b) (4). This revealed 3 of the (b) (4) vials did not appear to have a (b) (4). Of these three vials, two were used for peptide mapping by LC-MS to evaluate (b) (4) of (b) (4) and one was used for an in-vitro assay test. All testing conformed.

This means that for the total of 7 vials that have been analytically analyzed, the following tests have occurred:

- 7 of 7 tested for container closure integrity
- 4 of 7 tested for (b) (4) of (b) (4) using LC-MS
- 2 of 7 tested for in-vitro assay
- 1 of 7 tested for sterility
- 0 vials were tested for (b) (4) content, (b) (4) time, color and clarity (b) (4) (b) (4) particles (b) (4) (b) (4) or any other stability specification.

- e. The FDA 483 states that only “three” vials without (b) (4) have been evaluated for (b) (4) using peptide mapping. This should state “four” vials from batch 12B1C012 as described in point (d) of this observation.

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The analytical testing for (b) (4) described in point (d) has been limited to a single batch, batch 12B1C012, and limited to only four vials from the batch. No other batches have been evaluated, even though there have been complaints for other batches. Other batches have been manufactured in other lyophilizers or may be impacted differently. For example, if the unloading process takes longer the vials will be subject to ambient air for a longer period of time or differences in ambient conditions between different production days. Further, batch 12B1C012 has not yet reached its expiration of October 2017.

- f. As I reviewed investigations for non-viable particle failures during lyophilizer unloading, I found that the investigations determined there was no impact because any vials exposed would be rejected. This is due to a sensor (b) (4) capping that detects the presence of a stopper. It rejects vials that are not completely stoppered. I reviewed the qualification documentation and found that the system was challenged with a single vial no stopper and a single vial that had a raised stopper. There was no analytical measurement to describe how much the stopper was raised in the challenge vial. The qualification documentation is included as **Exhibit #19**.

This sensitivity of this sensor has not been evaluated as part of these on-going investigations. The sensor as currently configured does not have the ability to detect and reject vials with raised stoppers like the ones that caused the no (b) (4) complaints because it was in place and functioning at the time those batches were manufactured.

- g. Change control CC2-15-133 implemented an incoming check of vials for adequacy of the blowback feature of the stoppers, see **Exhibit #20**. The blowback is designed to prevent the stopper from coming back out after it has been placed. The change control states that defects of the blowback feature can cause a loss of (b) (4)

The facility has received numerous complaint samples for no (b) (4) vials. Many of these samples have been returned. QA personnel confirmed that the adequacy of the blowback feature of the returned complaint vials has not been evaluated. The blowback is evaluated with AQL testing on incoming lots of vials.

- h. Change control CC2-15-164 was issued and approved to increase the (b) (4) of the shelves for the (b) (4) lyophilizer, see **Exhibit #21**. Prior to approving (b) (4), no study was done to determine the amount of (b) (4) that was necessary to achieve the stated reason for the change, which was preventing sticking of the stoppers to the shelves. The change was made by maintenance (b) (4) the shelves to match the (b) (4) of the newly installed (b) (4) lyophilizers. It targeted the change of (b) (4) from (b) (4) to (b) (4)

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This was not effective and the sticking problem continued. An addendum to this change controlled was issued to again increase the (b) (4) this time from (b) (4) to (b) (4). Again there was no study to determine the appropriate level of (b) (4) prior to approving the change. Again, the change was found to be ineffective in preventing sticking of the stoppers.

Change control CC-16-132 was issued to change the shelves on the (b) (4) lyophilizer to a (b) (4) shelf, see **Exhibit #23**. This only applied to the (b) (4) lyophilizer because the (b) (4) lyophilizer shelves could not be changed. Again no study was made before making the change of whether this would be effective to stop sticking and prevent no- (b) (4) vials. The change was implemented, but no study to evaluate the effectiveness has been performed. Production personnel verbally confirmed that while the (b) (4) (b) (4) appeared to reduce the amount of sticking observed, sticking still occurs. No study has been performed to determine the frequency of slightly raised stoppers, which are not visually detectable and result in the no (b) (4) vials.

Prior to the change for the (b) (4) shelves, change control CC-15-194 was initiated to implement the use of (b) (4) stoppers, see **Exhibit #24**. There were two stated reasons for the change: to ensure the flexibility of the stopper supply and resolve the stopper sticking. After approval of the change, process validation was performed using the new stoppers for three batches. The process validation sampling and analysis did not include any evaluation of (b) (4) in vials. While the number of rejected vials during unloading was reduced, it is unknown whether visually undetectable raised stoppers continued to be present after the change.

After the process validation was approved, there was no requirement to use the (b) (4) (b) (4) stoppers instead of the (b) (4) stoppers. Production personnel confirmed they have the option to use (b) (4) or (b) (4) stoppers. Therefore, this is not a corrective action that has been in effect for the ongoing production for the US market pending release. A list of the batches shipped to the US market that used (b) (4) stoppers is included as **Exhibit #25**. It is limited to the three process validation batches manufactured in December 2015. Since that time (b) (4) stoppers have not been used for US market batches manufactured in 2016 or 2017. **Exhibit #25** indicated they would be using the (b) (4) stoppers for a US batch intended to be manufactured the week following the close of the inspection.

QA explained that the only study to evaluate the presence of (b) (4) on vials manufactured using (b) (4) stoppers was performed for EU batch (b) (4). For this batch 15 vials were sampled for testing the amount of (b) (4) (b) (4) into the vial, see **Exhibit #26**. These results indicated the 15 vials had a (b) (4). The documentation does not explain how these 15 vials were representative of the approximate (b) (4) vial batch size.

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In addition to the potential for ingress of ambient air impacting the chemical properties of the product, the incomplete stoppering could also impact the microbiology quality and physical properties of the product. **Exhibit #11** contains an impact assessment of the no (b) (4) vials that concludes sterility is not compromised for no (b) (4) vials. I made the following evaluation of mitigating factors described in the impact assessment:

Container closure integrity – no (b) (4) vials are not stoppered properly at the (b) (4) lyophilization, potentially resulting in non-integral container closure integrity.

- There have not been failures for container closure integrity checks during the production of routine batches. This may not be representative because the vials sampled for container closure integrity test may not have been no (b) (4) vials. The only known vials with no (b) (4) tested for container closure integrity came from batch 12B1C012. A total of seven vials with no (b) (4) passed the container closure integrity test, see point (d) of this observation.

Microbiology – no (b) (4) vials are not stoppered properly at the (b) (4) lyophilization and have an increased risk of microbial contamination until capped.

- Sterility test – there have been no sterility failures since the last inspection. The samples taken for sterility testing may not be representative of vials with no (b) (4). For batch 12B1C012 there was one vial confirmed to have no (b) (4) that was used for a sterility test that passed.
- Media fill – there have been no media fill failures since the last inspection. The interaction that causes sticking is not known. If sticking is affected by the amount of (b) (4) at the time of stoppering, then this would not be replicated by stoppering under ambient conditions that occurs during media fills. Therefore the improperly stoppered vials during unloading may not be represented during the media fill. Further, **Observation #3** discusses deficiencies with the media fill.
- Vials remain in an ISO 5 area from the unloading of the lyophilizer to the capping station. **Observation #3** discusses deficiencies with the smoke studies. These areas have not been adequately evaluated to determine that proper laminar flow exists.

Physical – no (b) (4) vials are not stoppered properly at the (b) (4) lyophilization and have an increased risk for ingress of particles.

- I reviewed excursions of non-viable particle counts during unloading of the lyophilizer and capping. The investigations all conclude there is no risk because the vials are stoppered. They do not consider the vials with improper stoppering that are not rejected and result in the no (b) (4) vials. Deviation DE-(b) (4)-17-008 documents a non-viable particle failure during lyophilizer unloading, see **Exhibit #27**. It also describes 6 previous non-viable particle count excursions in this area. Deviation DE-(b) (4)-17-064 documents a non-viable particle failure during capping, see **Exhibit #28**.

It also describes 2 previous non-viable particle count excursions in this area. A summary of excursions from the (b) (4) Plant (b) (b) (4) report of excursions is included as **Exhibit #50**.

2. Procedure QC0020 “Out of Specification (OOS)” describes in section 5.1.4 that an OOS investigation must be initiated within (b) (4) of being observed and in section 5.15 that the investigation be completed within (b) (4) of being initiated, see **Exhibit #29**. Procedure QA2002 “Deviation and Corrective Action Preventive Action” also requires deviations to be initiated within (b) (4) of being observed. Section 6.2.13.1 states that deviation investigations are to be completed within (b) (4) and all approvals need to be completed within (b) (4) see **Exhibit #30**.

I reviewed investigations into foreign matter detected in drug product and drug substance. The specifications for each are (b) (4). They are permitted to have ≤ (b) (4) proteinaceous particles. If there are visible particles in the (b) (4) solution they are examined using a microscope to determine whether or not they are proteinaceous.

- a. The following is a timeline for the finding of particulate matter and the investigational steps taken for batches 15B4C22 and 16B1C32A of Inflectra drug product.

- 02 February 2017, Inflectra batch 15B4C22 is tested at (b) (4) and found to be OOS for a particle. (b) (4) is a contract lab in (b) (4) (b) (4) that performs release testing of all batches that are packaged and labeled in a (b) (4) facility, which is required by (b) (4) regulations. The batch is released unlabeled by Celltrion for packaging and labeling.

(b) (4) performed an initial laboratory OOS investigation and did not note any discrepancies. The OOS result is reported to Celltrion on 03 February 2017. The notification e-mail and the (b) (4) OOS investigation are included as **Exhibit #31**. (b) (4) does not confirm whether or not the particle is proteinaceous, so Celltrion must request the sample be returned for examination.

- 06 February 2017, Celltrion requests the vials with a particle from batch 15B4C22 be returned for identification of the particle.
- 07 February 2017, Inflectra batch 16B1C32A is tested at (b) (4) and found to be OOS for a particle. (b) (4) performed an initial laboratory OOS investigation and did not note any discrepancies. The OOS result is reported to Celltrion on 08 February 2017. The notification e-mail and the (b) (4) OOS investigation are included as **Exhibit #32**.

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- 08 February 2017, Celltrion requests the vials with a particle from batch 16B1C32A be returned for identification of the particle.
- 14 February 2017, the samples from batch 15B4C22 arrive at Celltrion, see **Exhibit #33**. No action is taken to immediately confirm whether or not the result is a true OOS.
- 16 February 2017, the samples from batch 16B1C32A arrive at Celltrion, see **Exhibit #33**. No action is taken to immediately confirm whether or not the result is a true OOS.
- 28 February 2017, identification of the returned vials is completed. It confirms both of the vials contained a (b)(4) fiber, see **Exhibit #34**. The OOS result has been confirmed.
- 06 March 2017, the initiation of deviation DE-(b)(4)-17-042 is signed, see **Exhibit #35**. The FDA 483 incorrectly identified the initiation date as 28 February 2017. The initiation part of the deviation was not completed within (b)(4) of the confirmed OOS. The deviation states “*Discussion for further investigation has been performed by relevant department in Celltrion, so deviation initiation has been delayed.*” The initiation form establishes a target completion of 20 March 2017 for the investigation and 30 March 2017 for final approvals.
- 29 March 2017, an extension for deviation DE-(b)(4)-17-042 was initiated and approved, see **Exhibit #36**. It approves the extension of the investigation to 30 June 2017.

The justification for extension describes that expanded sampling still needed to be done according to procedure QC1059 “Investigation for Failure in QC Visible Particle Test”, see **Exhibit #37**. This procedure requires additional samples be analyzed, but until 29 March 2017, the additional samples had not even been requested from the packaging and labeling site in (b)(4). The justification does not explain why this had not previously been done.

Further, the justification for extension explains that a risk assessment per the procedure GR2-FF-17-069 “Determination of intrinsic particle and extrinsic particle” was necessary. This procedure had not been written. On 31 May 2017, the procedure was still in draft, see **Exhibit #38**.

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- 13 April 2017, samples from both batches arrive at Celltrion from the packaging and labeling site. They are transferred to the QC lab.
 - 31 May 2017, I reviewed the OOS and associated deviation during the inspection. QC personnel confirmed that nothing has been done with the additional samples that have been received. QA confirmed that no actions have been taken to further identify the root cause, assess the impact to these batches and other batches, or implement corrective and preventive actions.
- b. The following is a timeline for the finding of particulate matter and the investigational steps taken for batch 17200B001 of Inflectra drug product at the one month stability time point.
- 16 March 2017, testing at the one month stability time point for batch 17200B001 of Inflectra drug substance identifies the presence of “Too Numerous To Count” particles against a limit of less than or equal to (b)(4) for proteinaceous particles, an OOS result, see page #1 of **Exhibit #39**.
 - 20 March 2017, microscopic identification of the particles is started, see page #2-8 of **Exhibit #39**. The particles were identified to be foreign. This is an additional OOS result because the specification of “(b)(4)” is not met. The particles are identified to be (b)(4) reviewed and signed off until 30 March 2017.
 - 21 March 2017, a Lab Investigation 17079 is opened, see **Exhibit #40**. No problems are found related to the testing. An expanded OOS investigation or deviation investigation is not promptly started.
 - 31 March 2017, an OOS investigation is opened, see **Exhibit #41**. This is more than (b)(4) after the initial observation of an OOS result for TNTC particles on 16 March 2017 or identification of foreign particles on 20 March 2017. The OOS form inaccurately describes the observed date as 31 March 2017. A target closure date of 31 April 2017 was assigned.
 - 06 April 2017, deviation DE-(b)(4)-17-071 is initiated, see **Exhibit #42**.
 - 31 May 2017, I reviewed the deviation and OOS investigation during the inspection. They were not completed, even though the date for assigned completion was one month earlier, 31 April 2017. I was provided a DRAFT request for an extension of the OOS investigation, see **Exhibit #43** and a DRAFT

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request for an extension of the deviation investigation, see **Exhibit #44**. The extension requested a new completion date of 31 July 2017. This date did not ensure that the finding of foreign particle during stability testing was investigated in a timely manner so corrective and preventive actions could be taken for this batch and other potentially impacted batches.

- c. The following is a timeline for the finding of particulate matter and the investigational steps taken for batch 17100B003 of Inflectra drug product at the two month stability time point. This is a different batch than described in point (b). However, it has the same type of OOS for foreign matter identified to be (b)(4)
- 13 April 2017, testing at the two month stability time point for batch 17200B003 of Inflectra drug substance identifies the presence of 2 foreign particles, see page #1 of **Exhibit #45**. Page #2 of the exhibit shows further identification of the particles by microscope, also on 13 April 2017. This confirmed the particles were not proteinaceous. An OOS should have been initiated within (b)(4) but was not.
 - 12 May 2017, the final identification of the particles as (b)(4) is signed as reviewed, see page #7 of **Exhibit #45**. An OOS investigation OOS-000B-17-004 is opened, see **Exhibit #46**. The investigation finds no laboratory error with the initial testing performed 13 April 2017.
 - 16 May 2017, deviation DE-(b)(4)-17-055 is initiated, see **Exhibit #47**. It inaccurately identifies the occurrence and observed date as 16 May 2017, instead of when the OOS was recognized on 13 April 2017.
 - 31 May 2017, I reviewed the deviation investigation during the inspection. It was not completed. The investigation did not describe the already open investigation for the same type of foreign particle (b)(4) that is described in point (b). The timeliness of this investigation did not ensure that the finding of foreign particles during stability testing was investigated so corrective and preventive actions could be taken for this batch, the batch described in point (b), and other potentially impacted batches.
- d. I reviewed the 100% visual inspection program. Visual inspection is a manual process. Since the drug product is a lyophilized (b)(4) it is more difficult to detect particles compared to after the product has been (b)(4). Therefore, the release criteria require (b)(4) and inspection of vials, which is how the OOS on two batches described in point (a) of this observation were identified.

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During the 100% visual inspection of the lyophilized (b) (4) foreign particles have been identified. I found that these particles, even though below the limit for particles, have not been evaluated to determine their source. For example, I reviewed 2017 inspected batches for the US market. There were rejects for particles identified as “diaphragm”. This is a different category than foreign particles related to “stoppers”. I was told that “diaphragm” would be similar to equipment gasket material that may break down and get into the product. I evaluated the filling process and did not note any gaskets that appeared similar to this type of particle located after the (b) (4) which should not let these particles through. The manufacturing personnel noted there could potentially be another source, but they didn’t know what that would be. Because the counts were below the acceptance criteria for particles of $\leq (b) (4) \%$, they have never attempted to identify the source of these particles.

Examples of vials rejected for particles in 2017 US market batches include:

Batch	Date	Vials rejected for foreign particles
17B4C04B	02 May 2017	1 Diaphragm
17B4C03C	05 May 2017	2 Diaphragm
17B4C02C	05 May 2017	1 Diaphragm
17B4C02B	26 April 2017	1 Diaphragm
17B4C01C	13 April 2017	1 Glass
17B4C01B	11 April 2017	1 Diaphragm

These are documented in **Exhibit #48**. A list with trending of all vials rejected during visual inspection is included as **Exhibit #58**. The trending only identified “particles”, not specifically what type of particle was identified.

The “diaphragm” particles found during actual inspection had not been incorporated into the training and qualification kit. All of the vials with foreign particles in the kit had particles that were manually added to create the kit. These may not be representative of the types of rejects observed in the routine production as the added particles are not embedded into the (b) (4). It was reported that the “diaphragm” particles are often at the bottom of the vial embedded in the (b) (4).

3. I reviewed trending of the environmental monitoring results. Trending is reviewed (b) (4). An (b) (4) report is written and any corrective actions are to be taken for any adverse trends. I found the review of the trending had not been timely and actions were not taken when adverse trends were observed.
 - a. Procedure QC1031 “Trend Analysis of Environmental/Clean Utility Monitoring” states in section 6.4 “It is recommended that the (b) (4) Report be completed by (b) (4)”.

(b) (4) for establishment of alert limit”, see **Exhibit #49**. QC personnel explained that this means that the (b) (4) trend should be completed by (b) (4) however since it is “recommended” it does not have to be done by this date. If the date is missed no action is taken. I discussed with management that “recommended” does not provide clear instruction needed for GMP procedures. The “recommended” wording for time frames appeared in other documents as well. For example, see section 9.7.4 of QC0032 “Stability Testing in Quality Control” which recommends that stability sample testing be completed within (b) (4) but does not require it, see **Exhibit #56**.

The environmental monitoring (b) (4) report for (b) (4) of Plant # (b) (4) was not completed by the “recommended” time frame of (b) (4). As of 31 May 2017 when I requested the document, it was still not completed and approved. I was provided a DRAFT version of the (b) (4) report, see **Exhibit #51**. Logbooks of (b) (4) excursions through 31 May 2017 are included as **Exhibit #52**. The following alert/action limits have occurred during environmental monitoring:

	(b) (4)	(b) (4)	(b) (4) through 31 May 2017
Action Level Excursions	4	17	9
Alert Level Excursions	7	23	24

On page #38 the conclusion of the DRAFT (b) (4) trend report states “*considering increased excursion number, CAPA and further monitoring is required*”. The QC personnel responsible for this report confirmed that a CAPA would be initiated to investigate why the excursions had increased during (b) (4) and implement corrective actions. This CAPA and investigation had not been started as of 31 May 2017, even though they applied to (b) (4) data. As a result, no actions had been taken to address the adverse trend. The (b) (4) data through 31 May 2017 shows the increased excursions had continued at an even higher rate than (b) (4).

- b. I reviewed the trending for Plant # (b) (4) for (b) (4). The (b) (4) trending data for organism identification is included as **Exhibit #53**. There were no mold organisms identified. The (b) (4) trending for organism identification is included as **Exhibit #54**. It identifies a total of 8 instances when mold organisms were identified. More specifically, from 22 February 2016 to 21 May 2016 mold organisms were recovered in the ISO 7 areas six times, five of which were Aspergillus species.

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Despite this apparent shift, no investigation was performed to identify the source of the mold organisms. The QC personnel reported that since the counts were below the alert and action levels, no investigation was required.

Discussion with Management:

Firm management understood this observation. As it related to point #1, Mr. Camposano explained that a benchtop (b) (4) analysis equipment should be arriving within one month. This device will allow them to perform non-destructive offline testing for presence of (b) (4) in vials. This will allow a more thorough investigation to occur. Additionally, a (b) (4) % (b) (4) (b) (4) analyzer will be purchased. It will take approximately a year to receive, install, and qualify.

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

During set-up and filling of batch 17B4C11 of CTP-13 on 23 May 2017:

1. An operator was observed to perform an intervention during filling to remove a jammed stopper by reaching over the exposed stoppers in the stopper bowl with the Restrictive Access Barrier system (RABS) (b) (4)
2. During set-up, the operators were observed to reach over exposed sterile surfaces including the stopper (b) (4) and the chutes of the stopper (b) (4) with their hands and arms.
3. The (b) (4) to the RABS was left open unnecessarily while operators obtained new wipes for sanitization at the (b) (4) the equipment set-up.
4. The quality unit does not provide oversight of aseptic production operations that occur during (b) (4)

Supporting Evidence and Relevance:

Observation #1 from the March 2015 FDA inspection cited deficiencies in good aseptic behavior. On 23 May 2017, I observed the aseptic filling of batch 17B4C11 of CTP-13 (Inflectra).

1. I observed an intervention during the filling operation. The line was stopped because stoppers were no longer making it to the stoppering machine. This was due to a jammed stopper that was blocking the path of stoppers as they moved toward the stoppering machine. The operators started and stopped the machine multiple times in an attempt to get the jam to clear without an intervention. However, this was unsuccessful.

(b) (4) operators worked together using the RABS (b) (4) to clear the jammed stopper. One retrieved a sterile forceps and handed it to (b) (4). The forceps was used to clear the jammed stopper. The operator stood on the opposite side of the (b) (4) from where the

jammed stopper was located. This caused the operator to reach over the (b) (4) with the RABS (b) (4) while he worked to remove the jammed stopper. Once the stopper was removed, the line was restarted without clearing any of the sterile stoppers the operator was working over.

The RABS (b) (4) are not sterilized. They are left in place from batch to batch and sanitized (b) (4) batches. Procedure FF23003 "Operation of Filling Machine" describes the interventions. In point 6.27.2 it states "If the (b) (4) stopper gets stuck in the (b) (4) stop the machine and remove the vials using RABS (b) (4). Reset the alarm and proceed with the process", see **Exhibit #55**.

There is no requirement to remove the stoppers that the non-sterile (b) (4). The description described in FF23003 is the same for fallen vials in that it does not describe any vial clearance. In practice I observed that vials are removed around the fallen vial. I was told this was because the RABS (b) (4) the vial. This is described in procedure FF23010 "Operation of Filling Machine RABS" which states: "If the vial that need to be removed from the line to clear broken or fallen or jammed or affected product during production, remove the number of vials described on Table 1. The surrounding vials are removed (b) (4) at the (b) (4) RABS (b) (4)", see **Exhibit #57**. Mr. Camposano agreed that there were inconsistencies in the procedures between how to handle vials and stoppers.

2. I watched the set-up of the aseptic filling line on 23 May 2017 for batch 17B4C11 of CTP-13. This is done by opening the RABS (b) (4) and the operators manually install the parts of the machine that had been removed for (b) (4) sterilization. This is done without the use of the RABS (b) (4). The stopper (b) (4) chutes, and (b) (4) are all sterile surfaces that contact the sterile stoppers and are removed for sterilization (b) (4) batches. They are (b) (4) consisting of an (b) (4) that protects the sterile surfaces. The (b) (4) is removed as they are (b) (4) the RABS. The pieces are assembled and after assembling, the (b) (4) is

After mounting the stopper (b) (4) the operator attempted to remove the (b) (4). However, once the (b) (4) is mounted, the (b) (4) could not be removed because it was (b) (4) the stopper (b) (4) that it attaches to. It appears what I observed could not have been the normal procedure since it would not allow the operator to remove the (b) (4). It is not fully described in a procedure and set-up operations have not been included in smoke studies, see **Observation #3**.

Since the (b) (4) the operator needed to partially dislodge the stopper (b) (4) in order to be able to free the (b) (4). Once the (b) (4) was free, the operator reached their hands and arm over the sterile surfaces of the stopper (b) (4) to fully remove the (b) (4). The need for the operator to reach over the sterile surfaces with their hands and arms similarly occurred during removal of the (b) (4) for the chutes and (b) (4).

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3. During the previous inspection in March of 2015, the FDA 483 included an observation that cited unnecessarily leaving the RABS (b)(4) open.

At the (b)(4) the operators are required to sanitize the inner surface of the RABS (b)(4) that have been opened. I observed the operator open the (b)(4) and wipe surfaces while folding the wipe after each stroke. Once all of the surfaces of the wipe were used, the operator obtained a new wipe. This process of obtaining a new wipe required the operator to leave the (b)(4) walk to the edge of the laminar flow area and hand the old wipe to another operator for disposal. Then a new wipe was taken from a cart, disinfectant was applied. In between these steps the operator would stop for several seconds to ensure movements were slow as described in the procedure. In total, this process took about a minute.

During this time, the (b)(4) to the RABS which was being wiped was left open unnecessarily. One operator always left the (b)(4) open while getting a new wipe. A second operator sometimes closed the (b)(4) while getting a wipe and sometimes left it partially open.

4. On 23 May 2017, I remained at the firm into the (b)(4) to watch filling activities. Aseptic filling operations normally occur during the (b)(4). The normal (b)(4) is 9:00am-(b)(4). A list of the May 2017 filling start time and end times is included as **Exhibit #66** and it shows most batches were started after (b)(4). There are no QA personnel that work on the (b)(4) when these aseptic activities occur, such as those cited in points #1-3 of this observation. There is no requirement in any procedure to ensure that QA provides oversight of the aseptic operations.

Discussion with Management:

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

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

1. During media fills performed to validate the aseptic filling process, integral media filled vials are rejected. They are not incubated as described in media fill procedure CP2205 “Media Fill Plan for Sterile Injectable Products”

a. Media fill (b) (4) 19 vials were rejected for “fallen at the conveyor” during unloading of the lyophilizer. These vials were stoppered and integral and are not required to be rejected during routine operations as described in procedure FF23010 “Operation of Filling Machine RABS”.

b. In both media fill (b) (4) and (b) (4) (b) (4) media filled and stoppered vials were rejected during simulation of a power failure at the capping station.

c. Media fill (b) (4), 5 media filled vials were rejected due to gross weights out of range.

d. Media fill (b) (4), 2 vials were removed during the unloading of the lyophilizer with no assignable root cause.

2. Personnel are permitted to enter the filling and lyophilization room during aseptic operations based on gowning qualification. They are not required to participate in a media fill. Further, there is no effective system to identify which personnel have entered the filling room.

3. The media fill procedures do not require (b) (4) f the media fill vials (b) (4) of incubation.

4. There is no documentation of the personnel that participate in the reading of the media fill units, no qualification for the personnel that read the media fill units, and no procedure describing the techniques for reading the media fill units.

5. No dynamic airflow studies (e.g., smoke studies) have been performed to demonstrate unidirectional airflow and to determine risk to product sterility throughout the RABS area. Only points along the path where (b) (4) vials travel were included in the study instead of covering the entire RABS area. The studies did not include routine aseptic interventions such as set-up activities or removal of jammed stoppers. The smoke generated was not sufficient to demonstrate airflow of the evaluated areas.

Supporting Evidence and Relevance:

1. I reviewed two media fill batch records, (b) (4) and (b) (4). During my review of the machine reports and reconciliation of rejects, I found that integral media filled units were rejected without adequate justification. Media fill procedure CP2205 “Media Fill Plan for Sterile Injectable Products” states in section 6.6.2: “*Rejected vials information should be recorded in detail to verify... That the reason for the rejected vials is reasonable.*” Further, the procedure states in section 6.6.3: “*All applicable vials except the vials affected by container integrity shall undergo (b) (4) and shall be clearly marked as rejected*”, see **Exhibit #59**. However, the rejects were not always reasonable and integral rejects are not being maintained.

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- a. During media fill ^{(b) (4)} there were 19 vials rejected for “fallen at the conveyor”, see **Exhibit #60**. I asked the production personnel if these were integral and they confirmed that the vials would have been stoppered and integral. Vials without stoppers or vials that are broken are listed in a different category (“broken vial” or “missing stopper”). Removal of these types of vials is not required during routine production. Procedure FF23010 “Operation of Filling Machine RABS” states: *“Removing fallen vials during unloading is not necessary if the condition of fallen vial is visually fine as all the vials are ^{(b) (4)} stoppered ^{(b) (4)} unloading process”*, see **Exhibit #57**.
 - b. One of the interventions performed is a simulation of a power failure at the capping station. At the capping station the vials are already ^{(b) (4)} stoppered, but a cap has not yet been applied. During the power failure simulation the laminar flow is turned off. The line is cleared, the area is cleaned, and the line is restarted. This results in ^{(b) (4)} vials in this area being rejected by the machine, see **Exhibit #61 and 62**. We discussed how these vials represented activities that occurred and should not be rejected. This failure is a simulation, therefore all vials could be capped and the area cleared prior to simulating the power loss. At a minimum they should have been capped and incubated as “rejects” as described in CP2205 “Media Fill Plan for Sterile Injectable Products”.
 - c. During the media fill the same specification for filled vial weight is used as during production. This is a tight range that will reject the vial if it is just above or below. This results in integral vials that have been filled with media being rejected if they are outside of this range. During media fill ^{(b) (4)} there were 5 weight check rejects. The machine report identified two gross weight rejects from station # ^{(b) (4)}, one gross weight reject from station # ^{(b) (4)} and two gross weight rejects from station # ^{(b) (4)} see **Exhibit #63**. Production personnel confirmed these vials likely had been filled with media.
 - d. During media fill ^{(b) (4)} the unloading of the lyophilizer identifies one rejected vials from each of the lyophilizers with the description “Remove of Vial”, see **Exhibit #64**. I asked the production personnel what this meant and they stated they could not tell based on this description.
2. Access to the filling room was reported to be restricted based on a card or biometric fingerprint reader located at the entrance of the filling room. I requested a list of all personnel that had access to the room and the last time they participated in a media fill. The list is included as **Exhibit #65**. Numerous personnel on the access list have never participated during a media fill. I asked Mr. ^{(b) (6)} Team Leader for the Fill and Finish area, if any of these personnel are present during filling of routine commercial batches. He explained that they are present in the aseptic filling room; however they are not supposed to be performing the aseptic interventions on the filling line. We discussed that all personnel that will be present during routine aseptic filling should be participating during media fills.

I compared card access logs to the times of aseptic operations. I confirmed that personnel that had not participated in media fills are present in the filling room during filling or lyophilizer loading operations. A list of the times of aseptic operations for the month of May is included as **Exhibit #66**.

Mr. (b) (6) is a (b) (4) fill and finish employee with a gowning qualification, but no participation in media fill. He entered the filling room at (b) (4) on 20 May 2017, see **Exhibit #67**. Filling started at (b) (4) on that day, see **Exhibit #66**. It was reported he would likely have been unloading the (b) (4). To do this activity he would have needed to enter the filling room.

Mr. (b) (6) is a (b) (4) fill and finish employee with a gowning qualification, but no participation in a media fill. He entered the filling room at 16:23 on 26 May 2017, see **Exhibit #68**. Unloading of the lyophilizer occurred from 13:25 to (b) (4) that day, see **Exhibit #66**.

In addition to not participating in media fill, no routine personnel monitoring is conducted on these operators if they are not directly involved in filling, see **Observation #4**.

I reconciled entrance logs created by the access reader to the personnel listed as performing interventions in the batch records. I found discrepancies in which personnel documented to perform interventions did not appear on the entrance log. Production personnel reported that routinely a single operator will swipe their card to open the (b) (4) but a second person will enter with them. The second person does not swipe their card. Therefore the access control is not effective. Further, there is no other record to document who enters the filling room and the time of entrance or exit.

3. Microbiology personnel confirmed there is no requirement to (b) (4) the media filled vials (b) (4) of incubation. We discussed how (b) (4) the vials will ensure the media contacts all surfaces of the vial and the stopper. After (b) (4) of incubation, the vials are (b) (4).
4. It was reported that many people are involved in the reading of the media fill units. However, these people are not documented in any record. The reading record contains the signature of a single operator and verifier, see **Exhibit #69**. It was reported that this is the person that makes the record, but many other personnel actually perform the activity.

There is no procedure describing the technique for reading the media fill unit such as lighting conditions, background, how long to examine, or (b) (4) of the media. Additionally, there

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is no qualification to ensure the person responsible for reading the sample will reliably detect growth if it is present.

5. I reviewed the smoke studies for the RABS of the filling and lyophilizer loading area. The videos are included as **Exhibit #70**. The documentation describing the smoke studies for the filling area is included as **Exhibit #71**.

The test procedures on page #1 of **Exhibit #71** state: “(b) (4) the smoke source from (b) (4) HEPA filter (b) (4) at approximately (b) (4) from the HEPA filter. Repeat it to cover the entire RABS (b) (4)”. The entire area (b) (4) the RABS was not covered. Instead the smoke was placed in selected areas rather than evaluating the entire area. For example, the diagram on page #3 of **Exhibit #71** describes the RABS in “Areas”. Area # (b) (4) covers the area where partially stoppered vials travel from the filling area to the lyophilizers for loading and the area where vials travel to the capping room after lyophilization. Rather than conduct studies over this whole length, the smoke was evaluated in a single point. There is no evaluation in the corners of this area.

The studies did not include evaluation of the common aseptic activities. For example, set-up activities were not considered during the studies. During set-up, (b) (4) operators are installing sterile contact surfaces, such as the stopper (b) (4) with the RABS (b) (4) open. I observed deficiencies in aseptic behavior when the set-up was performed, see **Observation #2**.

The other interventions were grouped together as representative interventions, as described on page #11-13 of **Exhibit #71**. I did not find the chosen interventions to be representative. For example, for the area # (b) (4) interventions, removal of vial was chosen as a representative intervention. This is not representative of the removal of jammed stoppers. I observed the removal of a jammed stopper during a routine batch and noted deficiencies in aseptic behavior, see **Observation #2**. During this intervention (b) (4) operators worked together, with (b) (4) operator awkwardly bending their arm to try to reach a sterile forceps. This was passed to (b) (4) operator that removed the stopper by reaching over the exposed stoppers and likely disrupting the air flow. The representative intervention performed in the studies used a single operator, at a different location, using different (b) (4) and performed a more simple operation. Other representative interventions performed are also different in action and different in location as the interventions they are supposed to represent.

At many points in the videos of the representative interventions the smoke appears very light. This prevents an evaluation of the airflow from top to bottom to ensure laminar flow is maintained. Engineering personnel reported their current equipment did not allow for more robust smoke generation.

Discussion with Management:

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

OBSERVATION 4

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

1. At the (b) (4) incubation on 23 May 2017 settle plate samples (b) (4) collected from filling room (b) (4) during the aseptic filling of batch (b) (4) were observed to have (b) (4) b) (4)
2. Active volumetric air sampling is not included in the environmental monitoring program for the aseptic filling areas during dynamic filling operations.
3. The surface monitoring of the ISO 5 areas of the (b) (4) area is performed (b) (4) operations occur, but not after. The active air and non-viable particle monitoring occur (b) (4) operations, not during dynamic operations.
4. No personnel monitoring frequency has been established for personnel that are not directly involved in filling operations, but enter the filling and lyophilization room during production operations.
5. The locations for surface monitoring are not described in written procedures with enough detail to ensure reproducible sampling.
6. Production personnel perform the environmental monitoring and personnel monitoring. There is no required oversight of these activities by the quality unit.

Supporting Evidence and Relevance:

1. On 22 May 2017 I inspected the microbiology laboratory. At the time of my inspection there was ongoing reading of environmental monitoring plates for batch (b) (4). I observed that one analyst read the plate by looking at the (b) (4) without removing the lid. The plate was then handed to a second operator for verification of the count.

I inspected plates that had already been read by these two individuals. From the (b) (4) settle plates collected in the ISO 7 area during this batch, I identified three (b) (4) (b) (4) and (b) (4) with (b) (4) of the media, see **Exhibit #72**.

I reviewed the data that had been recorded for these plates and found that no documentation had been made that this (b) (4) had been observed. The plates had already been discarded. The copy of the record provided to me for the samples contains a footnote that (b) (4) was observed for these samples, see **Exhibit #73**. This note was made after I showed them the plates and was not on the original record made by the two analysts.

One of the analysts reading the plates reported he had seen similar (b) (4) before, but it not been documented and no further actions had been taken.

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2. No active air volumetric sampling is conducted during dynamic filling operations. Active air volumetric sampling is conducted (b) (4) (b) (4). The samples are not collected again until after all filling is complete. During set-up and filling, only passive settle plates are used for viable monitoring. Section 6.3.1.2 of procedure FF21017 “Environmental Monitoring in Operation for Fill and Finish Process” states: (b) (4) (b) (4) see **Exhibit #74**.
3. I reviewed environmental monitoring of the ISO 5 and ISO 7 areas of the drug substance manufacturing area. A summary of the sampling points and frequencies is described in QC4008 and included as **Exhibit #75**. For the (b) (4) Area, the viable and non-viable samples and the surface sample points have a foot note that state “*In case of BSC or LFH, sampling of airborne non-viable/viable particle and surface viable are performed whenever it turns on (b) (4) of BSC or LFH.*” The LFH is the laminar flow hood and the BSC is biosafety cabinet. Both are ISO 5 areas where the production steps occur.

The production personnel are responsible for sample collection and the associated sampling sites and schedules (see point #6 of this observation). They could not provide a rationale for why the surface monitoring is not done at the (b) (4) the operations. They could also not provide rationale for why the active air and non-viable counts taken (b) (4) operations is representative of the activities occurring during operations.

4. I reviewed the biometric/card access records for entry into the filling room. I observed examples of personnel entering the fill room during aseptic operations with no corresponding personnel monitoring. It was explained that only the filling operators that directly participate in the filling activities are monitored (b) (4) (b) (4). Other personnel enter the filling room throughout the aseptic operations, but not required to be monitored. These operators are only monitored during (b) (4) gowning qualification, not associated with production.

For example, Mr. (b) (6) is a (b) (4) fill and finish employee with a gowning qualification. He entered the filling room at (b) (4) on 20 May 2017, see **Exhibit #67**. Filling started at (b) (4) on that day, see **Exhibit #66**. It was reported he would likely have been unloading the (b) (4). Even though he was present in the room and performing activities indirectly related, since he was not directly involved in filling he was not required to be monitored (b) (4) (b) (4).

Me. (b) (6) is a (b) (4) fill and finish employee with a gowning qualification. He entered the filling room at 16:23 on 26 May 2017, see **Exhibit #68**. Unloading of the lyophilizer occurred from 13:25 to (b) (4) that day, see **Exhibit #66**. Although he was performing other activities in the room at that time and not directly participating in unloading, he was not required to be monitored.

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5. There are no written descriptions, pictures, or adequate diagrams to describe the environmental monitoring sampling points. The procedure FF21017-A1 describes the sampling points, see **Exhibit #76**. The procedure contains no written description. It has a diagram, but the specific points are unclear in the diagram. When I asked Mr. (b) (6) (b) (6) Team Leader for the Fill and Finish Area, to explain the points, he struggled to explain exactly where the samples are taken from. Instead he provided general descriptions.

Mr. Camposano, Managing Director of MFG Fill & Finish, stated that if the locations were specific then the personnel would clean those areas more carefully. Since the locations are only general, the personnel doing cleaning do not know exactly where the sample will be taken. I explained that all areas should be cleaned equally following established procedures. Further, I explained why his explanation was a further example of why quality oversight or operations in these areas was needed, see point #6 of this observation and point #4 of **Observation #2**.

I also reviewed the document that described the establishment of the monitoring points to determine if specific locations had been identified during the initial qualification. However, this document did not have any additional description, see **Exhibit #77**. It also lacked documented rationale describing how the points were chosen.

6. Mr. (b) (6) Team Leader for the Fill and Finish Area informed me he was responsible for the environmental monitoring and personnel monitoring programs. Mr. (b) (6) is a production employee that does not have any formal microbiology education. He explained he had received training from the QC department. When I asked him about sampling techniques for use of (b) (4) plates or when (b) (4) samples should be used versus swab, he could not provide answers.

The quality unit, including the microbiologists, provides no oversight for the collection of the samples. Production personnel perform environmental monitoring and collect personnel monitoring from each other. The microbiology department is not required to review or approve the procedures describing sampling sites and sampling techniques, see **Exhibit #74 and 76**.

The production personnel collect all of the environmental monitoring samples (active air, settle plates, and surfaces) as well as personnel monitoring. Operators reportedly monitor each other, so there is no self-monitoring. However, no record clearly document who is performing the monitoring. These monitoring activities associated with a batch will normally occur on an (b) (4). No QA or QA personnel work on the (b) (4).

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

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

1. Results of disinfectant efficacy studies were not used in the establishment of disinfectant use schedules in Plant (b) (4). For example:

a. Disinfectant (b) (4) is used as the only equipment disinfectant for the ISO 7, 8, and 9 areas for (b) (4). The disinfectant failed the acceptance criteria for all surfaces against the organisms *Staphylococcus aureus*, *Candida albicans*, *Aspergillus brasiliensis*, and *Micrococcus luteus*.

b. Disinfectant (b) (4) is used as the only disinfectant for walls and ceilings on (b) (4) (b) (4) (b) (4). The disinfectant failed the acceptance criteria for *Aspergillus brasiliensis* on 8 of (b) (4) surfaces, including (b) (4) Wall". Disinfectant (b) (4) is used as the only disinfectant for walls and ceilings on (b) (4) (b) (4). The disinfectant failed the acceptance criteria for (b) (4) Wall" for *Staphylococcus aureus*, *Candida albicans*, *Aspergillus brasiliensis*, and *Micrococcus luteus*.

No action was taken to ensure there was an effective disinfectant used on the walls for mold. The (b) (4) EM trending identified mold was recovered in the ISO 7 areas eight times, including five that were *Aspergillus* species.

2. The disinfectant efficacy studies did not include surfaces that are disinfected and left in place (b) (4) batches in the critical areas. For example (b) (4) used for the filling machine (b) (4) and (b) (4) used for the exterior of the (b) (4).

3. The air intake vents located in the ISO 7 area for the laminar flow hood used for (b) (4) and fill of the drug substance had visible dust build-up on their surfaces.

Supporting Evidence and Relevance:

1. I reviewed the disinfectant efficacy studies designed to evaluate the effectiveness of the chosen disinfectants on surfaces and verify their expiration dates. The study is included as **Exhibit #78**. The study showed multiple failures of the established acceptance criteria for disinfectants and the surface coupons used. However, these results did not appear to be used when establishing the disinfectant use schedule for the clean room areas. Higher concentrations of disinfectants or the use of multiple disinfectants was not implemented. Procedure FF26003 establishes the schedule for using disinfectants in the clean room, see **Exhibit #79**.

a. The disinfectant (b) (4) is used as the only equipment disinfectant for the ISO 7, 8, and 9 areas for (b) (4) see page #21 of **Exhibit #79**. The disinfectant failed the acceptance criteria for all surfaces with the organisms *Staphylococcus aureus*, *Candida albicans*, *Aspergillus brasiliensis*, and *Micrococcus luteus*, see page #20 of **Exhibit #78**.

- b. Procedure FF26003 establishes the use of (b) (4) during (b) (4) and (b) (4) during (b) (4) for the purpose of disinfectant the walls and ceilings of the ISO 7 area, see page #8 of **Exhibit #79**.

The (b) (4) failed the acceptance criteria for *Aspergillus brasiliensis* on 8 of (b) (4) surfaces, including (b) (4) Wall”, see page #15 of **Exhibit #78**. Disinfectant (b) (4) failed the acceptance criteria for (b) (4) Wall” for *Staphylococcus aureus*, *Candida albicans*, *Aspergillus brasiliensis*, and *Micrococcus luteus*, see page #16 of **Exhibit #78**.

This schedule does not ensure effective disinfectants are used to control the microorganisms in this area. Further, both of these disinfectants failed for the mold organism *Aspergillus brasiliensis*. During (b) (4) mold was recovered in the ISO 7 areas eight times, including five that were *Aspergillus* species, see **Exhibit #54**.

2. The types of coupons used for the disinfectant efficacy is included on page #4 of **Exhibit #78**. Surfaces tested did not include (b) (4) of the surfaces that are disinfected in place on the filling line. The test did not include (b) (4) used for the (b) (4). The test did not include (b) (4) used for the (b) (4). A picture of where these types of materials are used in the filling machine is included as **Exhibit #80**.
3. On 30 May 2017, I inspected the (b) (4) and filling room for the drug substance manufacturing. The (b) (4) and filling is performed under laminar air flow in an area classified as ISO 5. The surrounding room is classified ISO 7. The air intake for the ISO laminar flow hood is located (b) (4) into the ISO 5 area. It appeared very dirty. There was build-up of dust on the vents and hanging strands of foreign material. The operators walk under this area to enter the laminar flow hood. A picture of the area is included as **Exhibit #81**.

Discussion with Management:

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

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OBSERVATION 6

Equipment used in the manufacturing areas of a drug product is not of appropriate design.

1. Calibration tags on the non-viable particle counters (b) (4) of the filling RABS are attached with beaded chains.
2. Identification numbers for (b) (4) are taped onto equipment surfaces (b) (4) the filling RABS.

Supporting Evidence and Relevance:

1. In the filling area calibration tags are hung on the non-viable particle counters with beaded chains. These are in close proximity to the open vials. A picture is included as **Exhibit #80**. The beads on these chains did not appear to be easily cleanable.
2. I observed that the (b) (4) on the conveyor line had numbers on them. These were reportedly added for maintenance tracking. The number identification was created by printing paper with the number and then placing clear tape over the number on to the surface of the (b) (4). A picture is included as **Exhibit #80**. The use of tape in the aseptic filling areas may create areas that are not easily cleanable.

Discussion with Management:

Firm management understood this observation. I was shown a picture that the beaded chains and the taped on identification had been removed.

OBSERVATION 7

Failure to demonstrate that your manufacturing process can reproducibly manufacture drug substance meeting its predetermined quality attributes.

Process validation studies for the drug substance 000B did not establish scientifically sound sampling plans to evaluate intra batch variability.

This is a Repeat Observation from the March 2015 FDA 483.

Supporting Evidence and Relevance:

The March 2015 FDA 483 cited the firm for sampling plans that were not scientifically justified for the process validation of the drug product manufacturing. I reviewed an updated process validation for the drug product and found that the sampling plan had been expanded. This allowed for evaluation of the intra-batch and inter-batch variability.

I also reviewed the process validation for the drug substance. This process validation had not been updated. It did not use expanded, scientifically sound sampling plans. The same sampling as routine batch production was used. This included single samples of the (b) (4) drug substance and at

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the critical intermediate steps. It did not allow for evaluation of intra-batch variability. The process validation report for the drug substance is included as **Exhibit #82**.

Discussion with Management:

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

OBSERVATION 8

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Failing filter integrity test results are not reported as required by procedure MO1040 "Operation and Maintenance of Filter Integrity Tester". After failures, the tests are repeated without documenting the failing results, the actions taken, or the reasons for invalidating the original results. For example:

1. The (b) (4) Filter lot # (b) (4) ailed the (b) (4) test at 15:30, 16:13, 16:52, (b) (4) and (b) (4) on 24 March 2017. The test passed at (u) (9) on 25 March 2017. Only the passing result was reported.
2. The (b) (4) filter lot # (b) (4) ailed the (b) (4) integrity test at 9:52, 10:20, 15:35, and 16:02 on 17 May 2017. The filter was instead tested according to (u) (9) on 17 May 2017 at (b) (4) with a passing result. Only the passing result was reported.

Supporting Evidence and Relevance:

I reviewed the audit trail associated with the Sartocheck4 Filter Integrity Tester. The audit trail and electronic data is not reviewed, see **Observation #9**. Only the printout the operator attaches to the batch record is reviewed. Therefore the reviewer is unaware of any failures that occur, but are not reported.

When I reviewed the audit trail I observed numerous failures. Procedure MO1040 "Operation and Maintenance of Filter Integrity Tester" is included as **Exhibit #83**. In section 7.4.5.10 it states: "*All test result must be attached to the batch record, including all failed integrity test.*" Section 7.4.6.1 states: "*If th (b) (4) "Gross Leak" is displayed or test has failed, notify supervisor*". Section 7.4.6.4 states: "*If the filter fails after (b) (4) test without any problem of system connection of wetting status, it will be deemed as testing discontinued. Notify supervisor...*".

The operation personnel confirmed that these steps are not followed. When there is a failure, the test is repeated. Checks on the system will be performed according to procedure MO1040. If allowed by procedure, they will change from a (b) (4) integrity test to a (b) (4) test. However, the actions taken are not documented and the supervisor is not notified. The failing results were not attached to the batch record for any of the failures I reviewed. The filters were used for general media preparation operations in the (b) (4) area of Plant # (b) (4).

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1. A picture of the result screen for (b) (4) is included as **Exhibit #84**. It shows a failure for a filter identified as (b) (4) at (b) (4) 16:13, 16:52, (b) (4) and (b) (4) all on 24 March 2017. There is a passing result for (b) (4) on 25 March 2017 at (b) (4). This corresponds to filter lot # (b) (4). Only the final result was reported, see **Exhibit #85**. This was the only (b) (4) filter tested during this time period. The request for testing of the filter was made 24 March 2017, see **Exhibit #86**. There was no documentation of the steps taken between the failing tests. Additionally, if there were (b) (4) failures, testing should have been discontinued and a deviation started according to section 7.4.5.10 of Procedure MO1040.
2. A picture of the result screen for (b) (4) Filter is included as **Exhibit #87**. It shows a failure of the (b) (4) integrity test for a filter identified as (b) (4) at 9:52, 10:20, 15:35, and 16:02 on 17 May 2017. The filter was instead tested according to (b) (4) on 17 May 2017 at (b) (4) with a passing result. These entries corresponded to filter lot # (b) (4). The reported data is included as **Exhibit #88** and only the passing result was reported.

Discussion with Management:

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

OBSERVATION 9

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

1. Operation personnel share a common username and password to access the Sartocheck4 Filter Integrity Tester unit 0034202581. The electronic data can be deleted and the audit trails are not reviewed.
2. Operation personnel share a common username and password to access the (b) (4). The electronic data can be deleted and the audit trails are not reviewed.
3. Specific procedures to describe review of audit trails of the different software used have not been established.

Supporting Evidence and Relevance:

1. I reviewed the performance of the filter integrity tests using the Sartocheck4 Filter Integrity Tester. I observed an operator log on using the generic username "operator". It was reported that all users enter the same username and there is a common password. The other username is "supervisor". The supervisor can modify set methods and create users. The system has the capability of assigning unique username and passwords to operators. These have not been assigned to ensure that entries are attributable to an individual.

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The system maintains the raw data collected electronically. It also maintains metadata, including audit trails. The raw data can be deleted by the users, see **Exhibit #89**, which shows a delete button on individual data files. This data is not backed-up or reviewed. The audit trails have not been reviewed.

I reviewed the audit trails and observed instances of failing results. These failing results were not reported as required by the established procedures and no investigations were opened after multiple failures of the same filter. This is discussed in **Observation #8**.

2. I reviewed the use of the (b) (4) This instrument is located in the production area. It is used for in-process tests during the (b) (4) and (b) (4) steps for the drug substance. I observed that the operators logged on using the generic username "operator". They all used this username and a shared password, though the system allowed for unique username and passwords to be established.

The data for the system is saved on the "C" drive of the attached standalone computer. The file path can be seen in a printout of data from the system included as **Exhibit #90**. Although it states the file is "protected data", I found that there are not actually any protections and any result can be deleted. I was told this is data they want protected and the protected data folder tells the operators that data should be kept, without a control to enforce the protection.

I asked if the system had audit trails. The operators did not know. They searched as a result of my request and found that the system did have audit trails. They confirmed that previously no one had ever reviewed the audit trail.

3. There are no specific procedures to describe audit trail review. I was provided with a newly implemented procedure QC0046 that was effective 19 May 2017, see **Exhibit #100**. The procedure broadly described audit trail review. I interviewed personnel responsible for reviewing audit trails on specific equipment. They struggled to explain how the elements of the procedure are applied to individual types of software. We discussed that procedures needed to provide specific detail to ensure the intended reviews were being completed.

Discussion with Management:

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

OBSERVATION 10

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

There was no system to track the issuance and use of all laboratory raw data forms, such as microorganism identification forms described in QC-4004. Laboratory personnel had access to blank electronic forms for printing without control. Controls for these forms were scheduled to be implemented 26 May 2017. However, these new controls did not apply to all forms that capture original GMP data, for example form QC0046-F1 “Audit Trail Inspection and Abnormal Finding Reporting”. Additionally, the QC laboratory had a document shredder that was filled with shredded documents on 22 May 2017. There is no control over the use of the shredder.

Supporting Evidence and Relevance:

On 22 May 2017, I reviewed documents in the laboratory used to record raw data that lacked controls for issuance and reconciliation. Specifically, I looked at the raw data sheets for recording Gram Stain and Colony Morphology forms, see **Exhibit JAB #91 and 92**. I asked how they could detect if forms were missing or had been replaced. The laboratory management confirmed there was no system in place at that time.

As an example I observed a stack of identification forms to be filed for tests conducted in 2017. Within this stack I found **Exhibit JAB #91** which is from 2014. All of the 2014 data was reported to have been archived. Only 2017 and 2016 was available. There is no system when collecting the documents to ensure they are all accounted for.

On 22 May 2017, if an analyst needed a form such as those in **Exhibit #91 or 92**, then the analyst accessed an electronic database that contained blank laboratory forms. This included forms for both the chemistry and microbiology laboratories. The analyst could print these blank forms as needed. There was no control on the number that were printed and no ability to perform reconciliation.

The QA management explained that they had identified this deficiency during April of 2017. They had initiated a risk assessment to determine which forms would receive a QA assigned tracking number and post use reconciliation. The forms in **Exhibit #91 and 92** were included with an implementation of a tracking number issued by QA and a reconciliation log that would be effective on 26 May 2017.

I reviewed the risk assessment and found that many GMP forms used stated they did not need this additional control. For example, form QC0046-F1 is used for audit trail reviews, see **Exhibit JAB #93**. This form records the raw data of observations of the review and documentation that it occurs. I explained that any forms like these that capture raw GMP data and fulfill a GMP requirement needed assurance that the document is original.

Discussion with Management:

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

OBSERVATION 11

Data is not documented contemporaneously.

1. On 29 May 2017, vessel V1120 was filled with (b) (4) reported to be for batch (b) (4) of (b) (4) media. The batch record entries for (b) (4) addition as well as previous batch record steps for the area clearance, equipment cleanliness verification, and the verification of (b) (4) had not been documented.

2. On 29 May 2017, batch record (b) (4) or (b) (4) had no entries for the (b) (4) in step (b) (4). It was reported that this step had been completed the previous (b) (4).

3. Collection times of environmental monitoring samples are not recorded at the time samples are taken. General times are recorded to represent multiple samples in multiple areas.

Supporting Evidence and Relevance:

During my inspection of the drug substance facility I observed that the batch record routinely appeared to be stored in production offices rather than located in the production area where they would be needed to document information contemporaneously. I also observed the use of computers in these areas where the batch information was recorded on “unofficial” records rather than batch records, see **Observation #12**. When I retrieved batch records from the offices, I observed that entries had not yet been made for steps that had already been completed.

1. On 29 May 2017 I inspected the media preparation area to support (b) (4). I inspected vessel V1120 and observed it to be partially filled with (b) (4). The status tag on the equipment stated “clean”, but I was told it was already in use and should have been identified as such. The (b) (4) had been dispensed for batch (b) (4) of (b) (4) media. I asked to review the batch record and found it to be blank. The actual batch record as I reviewed it is included as **Exhibit #94** and the English translation of the same pages is included as **Exhibit #95**.

Step (b) (4) describes the addition of the (b) (4). Although this was already done, it had not been contemporaneously entered. Additionally, steps for area clearance, equipment cleanliness verification, and the verification of (b) (4) had not been documented.

2. On 29 May 2017, I inspected batch records stored in the production office of the cell culture area. I reviewed batch record (b) (4) for (b) (4) on the (b) (4) Bioreactor. The entries for step (b) (4) were not documented, yet I observed subsequent manufacturing steps had occurred. Production personnel confirmed that this step had been completed the previous (b) (4). The results, signature of the performer, and signature of the verifier had not been made contemporaneously. The actual batch record page as I reviewed it is included as **Exhibit #96** and the English translation of the same page is included as **Exhibit #97**.

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3. I reviewed environmental monitoring records for plant #^(b)₍₄₎ see **Exhibit #98**. I observed that ^(b)₍₄₎ettle plates (“Se” samples) located in ^(b)₍₄₎ different rooms, had a start time of 10:10 on 24 May 2017. Additionally, ^(b)₍₄₎ surface monitoring plates from room ^(b)₍₄₎ have a collection time of 10:10. There is one person listed as the “Sampled By”. Production personnel confirmed that the times are general and not accurate to the actual time.

Additionally, page #1 of **Exhibit #98** documents the samples for ^(b)₍₄₎. The ^(b)₍₄₎ reading results are recorded and were reported to occur on 26 May 2017. When I reviewed the record on 30 May 2017 the document had not been signed or dated by the person that performed the reading.

Discussion with Management:

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

OBSERVATION 12

Batch production records do not contain complete information relating to the production and control of each batch.

The production personnel in Plant #^(b)₍₄₎ use computers located within the production area to create unofficial records of the production activities. These unofficial records are not described by any procedure or reviewed. The unofficial records contained information that was not captured in the official batch records. For example:

1. An unofficial spreadsheet documenting preparation of the ^(b)₍₄₎ ^(b)₍₄₎ media ^(b)₍₄₎ ^(b)₍₄₎ documented it was necessary to use a ^(b)₍₄₎. ^(b)₍₄₎ These comments were not reflected in the official batch record.
2. The unofficial spreadsheet for ^(b)₍₄₎ ^(b)₍₄₎ media ^(b)₍₄₎ documented the use of a bench top ^(b)₍₄₎ or batch ^(b)₍₄₎ after ^(b)₍₄₎ because ^(b)₍₄₎ called ^(b)₍₄₎ was not providing accurate results. This is not reflected in the official batch record.
3. The unofficial spreadsheet for ^(b)₍₄₎ contains notes for slow ^(b)₍₄₎ due to ^(b)₍₄₎ clogging. This is not reflected in the official batch record.
4. The unofficial spreadsheet for ^(b)₍₄₎ ^(b)₍₄₎ media ^(b)₍₄₎ contains measurements from bench top ^(b)₍₄₎. It was reported that the production personnel do this because the installed ^(b)₍₄₎ are not always reliable. The bench top values are not recorded in the official record and no investigation into the unreliability of the installed ^(b)₍₄₎ to implement corrective actions has been initiated.

Supporting Evidence and Relevance:

During my inspection of the drug substance manufacturing area, I observed the presence of computers in many locations. These computers were networked. The production personnel were

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working on files saved on a shared drive. I reviewed examples of these documents consisting of Excel spreadsheets.

These spreadsheets contained all of the information related to the production of the batches. Kyung Jin Lee, Assistant Senior Manager for Cell Culture, explained these are “uncontrolled documents”. They are not described or required by any procedure. They are not reviewed by the quality unit. She explained they are used to track and trend so the production personnel can know what to expect or react to trends. In the examples I reviewed I found comments about problems encountered during the batches. These were not reflected in the official records.

1. The unofficial spreadsheet that included documentation for preparation of the (b) (4) media (b) (4) (b) (4) is include as **Exhibit #99**. It documents that it was necessary to use (b) (4). The batch record established a (b) (4) was acceptable. These comments were not reflected in the official batch record.
2. The unofficial spreadsheet for (b) (4) media (b) (4) documented the use of a bench top (b) (4) for batch (b) (4) after (b) (4) see **Exhibit #101**. Pro (b) (4) personnel re (b) (4) is would have been done because the installed (b) (4) in the bioreactor was not providing accurate results. This unexpected occurrence and use of a different (b) (4) is not reflected in the official batch record.
3. The unofficial spreadsheet for (b) (4) contains notes for slow (b) (4) due to (b) (4) clogging, see **Exhibit #102**. This is not reflected in the official batch record.
4. The unofficial spreadsheet for (b) (4) media (b) (4) contains measurements from bench top (b) (4) see **Exhibit #103**. It was reported (b) (4) e production personnel do this bec (b) (4) stalled (b) (4) are not always reliable. The bench top values are not recorded in the official record and no investigation into the unreliability of the installed (b) (4) to implement corrective actions has been initiated.

Discussion with Management:

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

REFUSALS

There were no refusals.

ADDITIONAL INFORMATION

During the inspection I stayed at The Holiday Inn Incheon Songdo. The hotel was adequate for business purposes and would be recommended for future travelers. It is within walking distance of many restaurants and a grocery store. It is located approximately 10 minutes by car from the facility.

SAMPLES COLLECTED

No samples were collected.

VOLUNTARY CORRECTIONS

I reviewed corrective actions taken by the firm as a result of items cited on the FDA 483 during the previous inspection. I found the following corrections had been made:

Observation #1 - Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

*I observed aseptic operations during the current inspection. I observed deficiencies in good aseptic practices, see **Observation #2**.*

Observation #2 - A procedure has not been established for performing identity testing on the contents of a final CT-P13 drug product vial of each lot after all labeling operations have been completed as required by 21CFR610.14.

The vials are labeled at an outside secondary packaging site. Samples of the labeled vials from each batch are returned to this site and an identity test using an Isoelectric Focusing method.

Observation #3 - Alert limits for bioburden and endotoxin are not established for CT-P13 drug substance in-process (b) (4)

I reviewed limits which have been established for the in-process (b) (4) I reviewed trending data and did not note any significant discrepancies in the records that I review

Observation #4 - Qualification studies for the (b) (4) lyophilizer, (b) (4) are not adequate.

I reviewed qualification studies for lyophilizers. They included temperature mapping studies. I did not note any significant discrepancies in the records that I reviewed.

Observation #5 - The visual inspection program (FF24010) for CT-P13 drug product vials is inadequate because there is no AQL testing.

AQL testing is now performed by QA for (b) (4) batch.

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Observation #6 - The media fill program (CP2205) is deficient in that acceptance criterion for yield has not been established for media fills.

*Yield limits have been established. I reviewed the documentation of yield and accountability. I observed that integral vials were being rejected, which was inconsistent with the established procedures. This is discussed in **Observation #3**.*

Observation #7 - The investigation for Deviation DE-(b)(4)-12-246 related to loading of the lyophilizer is inadequate.

*I reviewed deviation investigations and found that they were not thorough or timely, see **Observation #1**. I did not observe a similar deviation during the current inspection.*

Observation #8 - Bioburden excursions for CT-P13 drug substance are not adequately investigated.

I reviewed investigations for bioburden excursions. I did not note any significant discrepancies in the records that I reviewed.

Observation #9 - Qualification of assays conducted in the Research and Development Laboratory to evaluate infliximab biosimilarity for regulatory purposes was documented retrospectively.

I reviewed peptide mapping studies performed by the Research and Development Laboratory to evaluate (b)(4) of CT-P13 as part of an investigation into “no (b)(4)” in the vials. A qualification study was performed for the method (b)(4) performing the testing. However, the data collected did not follow GMP and the quality unit did not provide oversight or review of the raw data.

Observation #10 - The (b)(4) dye penetration test used to evaluate CT-P13 drug product container closure integrity is inadequate.

I reviewed the (b)(4) dye penetration test method. The test now requires the product to be (b)(4)

Observation #11 - The in-process endotoxin test for drug substance is not adequately conducted.

I reviewed studies performed to support the sample hold times for endotoxin samples. The established testing time frame is (b)(4) for endotoxin and (b)(4) for bioburden. I did not note any significant discrepancies in the records that I reviewed.

Observation #12 - Numerous leaks from the media vessel during media transfer to the bioreactor have occurred since 2013 and appear to be ongoing.

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I reviewed one bioreactor contamination failure that occurred since the last inspection. The root cause differed from the previous repeat occurrences. I did not note any significant discrepancies in the records that I reviewed.

Observation #13 - The disinfectant efficacy study (Report GR-QC-15-003.AD1) conducted to validate disinfectants used for CT-P13 drug substance and drug product manufacturing facility cleaning is inadequate.

*I reviewed the updated disinfectant efficacy studies and found that many of the disinfectants had failed the acceptance criteria at the established concentration and hold times. The results of the study are not reflected in the established disinfectant use schedules, see **Observation #5**.*

Observation #14 - Establishment of the reliability of the stopper supplier's Certificate of Analysis is deficient in that the test results are not appropriately validated. Bioburden and endotoxin testing is taken from a COA without periodically verifying the COA results.

Bioburden and endotoxin testing have since been removed from the reduced testing program. batch of stoppers that is received is sampled and tested for bioburden and endotoxin.

(b) (4)

Observation #15 - The raw material specifications for CT-P13 are inadequate because appropriate endotoxin limits have not been established for excipients.

I reviewed the raw material specifications for the excipients Polysorbate 80 and Sucrose. Endotoxin limits have been established and are evaluated for batch received.

EXHIBITS COLLECTED

1. Batches shipped for US distribution. (2 Pages)
2. Personnel for the initiation of the inspection. (1 Page)
3. Organizational Chart. (1 Page)
4. Flow chart of manufacturing process. (15 Pages)
5. Personnel for the close of the inspection. (2 Pages)
6. Document G^(b)₍₄₎-FF-16-059. (17 Pages)
7. Complaint list for no ^(b)₍₄₎ (1 Page)
8. Complaint 14-0011. (5 Pages)
9. Deviation DE^(b)₍₄₎-16-003. (17 Pages)
10. Listing of complaints for DE^(b)₍₄₎-16-003. (2 Pages)
11. Impact assessment no ^(b)₍₄₎ memo. (6 Pages)
12. Deviation DE^(b)₍₄₎ 15-051. (13 Pages)
13. Deviation DE^(b)₍₄₎ 16-073. (8 Pages)
14. Deviation DE^(b)₍₄₎ 16-116. (15 Pages)
15. Trending of rejects. (2 Pages)
16. January 2016 evaluation of 12B1C012. (8 Pages)
17. Method qualification for peptide mapping. (25 Pages)
18. January 2017 evaluation of 12B1C012. (8 Pages)

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19. Qualification of stopper sensor. (2 Pages)
 20. Change control CC2-15-133. (14 Pages)
 21. Change control CC2-15-164. (18 Pages)
 22. Change control CC2-15-164 addendum. (18 Pages)
 23. Change control CC-16-132. (18 Pages)
 24. Change control CC-15-194. (24 Pages)
 25. Batches released to US with (b)(4) stoppers. (1 Page)
 26. Batch (b)(4) (1 Page)
 27. Deviation DE (b)(4) -17-008. (11 Pages)
 28. Deviation DE (b)(4) -17-064. (9 Pages)
 29. Procedure QC0020. (3 Pages)
 30. Procedure QC2002. (4 Pages)
 31. Notification of OOS 15B4C22. (7 Pages)
 32. Notification of OOS 16B1C32A. (6 Pages)
 33. Arrival of OOS samples. (2 Pages)
 34. Identification of particles. (6 Pages)
 35. Initiation of deviation DE (b)(4) -17-042. (5 Pages)
 36. Extension request for DE (b)(4) -17-042. (2 Pages)
 37. Procedure QC1059. (15 Pages)
 38. Procedure GR2-FF-17-069. (7 Pages)
 39. Visible particle observation 17200B001. (8 Pages)
 40. Lab Investigation 17079. (2 Pages)
 41. OOS-000B-17-002. (3 Pages)
 42. Deviation DE (b)(4) -17-071. (6 Pages)
 43. DRAFT OOS investigation extension form. (1 Page)
 44. DRAFT deviation investigation extension form. (3 Pages)
 45. Visible particle observation 17200B003. (7 Pages)
 46. OOS-000B-17-004. (3 Pages)
 47. Deviation DE-17-055. (7 Pages)
 48. Visual inspection summary of 2017 batches. (21 Pages)
 49. Procedure QC1031. (1 Page)
 50. Non-viable particle excursions. (6 Pages)
 51. 2016 EM trending Plant (b)(4) DRAFT. (39 Pages)
 52. 2017 EM excursions Plant # (b)(4). (7 Pages)
 53. 2015 microbial identification. (1 Page)
 54. 2016 microbial identification. (3 Pages)
 55. Procedure FF23003. (4 Pages)
 56. Procedure QC0032. (2 Pages)
 57. Procedure FF23010. (2 Pages)
 58. Trending of visual inspection rejects. (7 Pages)
 59. Procedure CP2205. (22 Pages)
 60. Media fill (b)(4) rejects. (1 Page)
 61. Capping rejects (b)(4) (1 Page)
 62. Capping rejects (b)(4) (3 Pages)

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63. Weight check rejects (b) (4) (2 Pages)
 64. Unloading rejects (b) (4) (2 Pages)
 65. Filling room access and media fill dates. (3 Pages)
 66. Filling and unloading times for May 2017. (1 Page)
 67. (b) (6) entrance log. (1 Page)
 68. (b) (6) entrance log. (1 Page)
 69. Media fill reading record. (2 Pages)
 70. Smoke studies. (CD)
 71. Smoke study report. (18 Pages)
 72. Pictures of (b) (4) plates. (3 Pages)
 73. ISO 7 EM data for (b) (4) (6 Pages)
 74. Procedure FF21017. (28 Pages)
 75. Procedure QC4008. (2 Pages)
 76. Procedure FF21017-A1. (3 Pages)
 77. EM Sampling Site Selection. (14 Pages)
 78. Disinfectant efficacy study. (32 Pages)
 79. Procedure FF26003. (29 Pages)
 80. Picture of filling area. (1 Page)
 81. Picture of filter and fill area. (1 Page)
 82. Drug substance process validation. (27 Pages)
 83. Procedure MO1040. (78 Pages)
 84. Picture (b) (4) filter integrity test. (1 Page)
 85. Reported (b) (4) filter integrity test. (1 Page)
 86. Filter integrity request log. (1 Page)
 87. Picture (b) (4) filter integrity test. (2 Pages)
 88. Reported (b) (4) filter integrity test. (1 Page)
 89. Pictures of (b) (4) filter integrity tester screens. (2 Pages)
 90. (b) (4) printout. (2 Pages)
 91. Colony Morphology raw data form. (1 Page)
 92. Gram Stain raw data form. (2 Pages)
 93. Form QC0046-F1. (5 Pages)
 94. Batch record pages (b) (4) (4 Pages)
 95. English translation of batch record pages (b) (4) (4 Pages)
 96. Batch record page (b) (4) . (1 Page)
 97. English translation batch record page (b) (4) (1 Page)
 98. Environmental monitoring records. (5 Pages)
 99. Picture of unofficial spreadsheet (b) (4) . (1 Page)
 100. Procedure QC0046. (11 Page)
 101. Picture of unofficial spreadsheet (b) (4) . (1 Page)
 102. Picture of unofficial spreadsheet (b) (4) (1 Page)
 103. Picture of unofficial spreadsheet (b) (4) (1 Page)

ATTACHMENTS

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FDA 483 Inspectional Observations

Signature Line

6/14/2017

X Justin A. Boyd

Justin A. Boyd

Investigator

Signed by: Justin A. Boyd -S