Food and Drug Administration Establishment Inspection Report

Date Assigned: 06/28/2018 **Inspection Start Date:** 08/06/2018 **Inspection End Date:** 08/14/2018

Firm Name & Address: Immunomedics, Inc. , 300 The American Rd Morris Plains, NJ 07950-2460 US

Firm Mailing Address: 300 American Rd, Morris Plains, NJ 07950-2460 United States

FEI: 1000526871 **JD/TA:** 35 **County:** MORRIS **Est Size:** 0 - 24,999

Phone: (973)605-8200 **District:** CDER-DIA **Profiled:** Yes

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

Endorsement

This pre-license inspection of Immunomedics Inc. (b) (4) intermediate manufacturing site was conducted from August 6 ? 14, 2018 following a request by the Division of Microbiology Assessment, Branch IV (DMA/OPF/OPQ//CDER) and Division of Inspectional Assessment, Branch 1 (DIA, OPF/OPQ). The inspection was conducted in support of (b) (4) for (b) (4) .

The inspection covered (b) (4) intermediate manufacturing, testing laboratories, utilities, and warehouse. The inspection was system-based and covered Quality, Facility and Equipment, Production, Material, and Laboratory systems.

A thirteen-item Form FDA 483 was issued to the firm at the close of the inspection on August 14, 2018 with the following observation:

1. The quality control unit lacks authority to investigate critical deviations of approved procedures.

2. There is no assurance that samples and batch records from the (b) (4) intermediate process validation and commercial batches manufactured prior to February 2018 were not impacted by the data integrity breach.

3. Retesting procedure for the (b) (4) intermediate is inadequate.

4. The raw material sampling and testing program is inadequate.

5. The firm lacks procedures for inventory audit trail and for tracking and reconciliation of raw materials used to manufacture the (b) (4) (b) (4) intermediate.

6. Differential pressure between GMP areas of different area classification is not adequately maintained and monitored.

7. The design of the facility is inadequate in that no drains are present in the purification rooms. In addition, there is no SOP for liquid containment and disposal after a catastrophic spill. All process streams downstream the (b) (4) Bioreactor are held in disposable bags.

8. There is no signed Quality Agreement between (b) (4) and Immunomedics Inc.

9. No procedure is in place for (b) (4) intermediate (b) (4) trending of results.

10. Deviation investigations and CAPA implementations are inadequate.

11. Deviation initiation and closing times are inadequate.

12. Cleaning of downstream equipment, including (b) (4) and product-contact parts of the (b) (4) is not validated or verified.

13. The procedure to prevent contamination of the (b) (4) intermediate after (b) (4) is inadequate for a product stored 2 to 8?C for up to (b) (4)

Initial Recommendation: Withhold

Food and Drug Administration Establishment Inspection Report

Endorsement Location: FACTS

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
Reyes Candau-Chacon	10/02/2018 12:25 PM ET		ET

Food and Drug Administration Establishment Inspection Report

FEI: 1000526871 **Inspection Start Date:** 08/06/2018 **Inspection End Date:** 08/14/2018

Firm Name & Address: Immunomedics, Inc. , 300 The American Rd Morris Plains, NJ 07950-2460 US

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

Registration Type

DRG Drug

Registration Dates

12/01/2006 05/01/2000 04/01/1999

Establishment Type

5	Sponsor-Investigator
5	Sponsor-Investigator
M	Manufacturer
Q	Corporate Headquarters

Industry Code

57	Bio & Licensed In-Vivo & In-Vitro Diag
64	Human and Animal Drugs
57	Bio & Licensed In-Vivo & In-Vitro Diag
57	Bio & Licensed In-Vivo & In-Vitro Diag

District Use Code:

Food and Drug Administration Establishment Inspection Report

FEI: 1000526871 **Inspection Start Date:** 08/06/2018 **Inspection End Date:** 08/14/2018

Firm Name & Address: Immunomedics, Inc. , 300 The American Rd Morris Plains, NJ 07950-2460 US

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
46832M	Manufacturer	(b) (4)		08/2020	Surveillance	Correction Indicated (CI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	08/14/2018	Official Action Indicated (OAI)	Candau-Chacon, Reyes	CDER-DIA

Remarks:

==========

Food and Drug Administration Establishment Inspection Report

FEI: 1000526871 **Inspection Start Date:** 08/06/2018 **Inspection End Date:** 08/14/2018

Firm Name & Address: Immunomedics, Inc. , 300 The American Rd Morris Plains, NJ 07950-2460 US

Products Covered

Product Code	Est Type	Description	Additional Product Description
(b) (4)	Manufacturer	(b) (4) N.E.C.; For Further Manufacture	

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Candau-Chacon, Reyes	BUR	CDER-DIA	46832M	Manufacturer	(b) (4)	160
Srivastava, Rajiv R	INV	PHRM1	46832M	Manufacturer		95.5
					Total Hours:	255.5

Food and Drug Administration Establishment Inspection Report

FEI: 1000526871 **Inspection Start Date:** 08/06/2018 **Inspection End Date:** 08/14/2018

Firm Name & Address: Immunomedics, Inc. , 300 The American Rd Morris Plains, NJ 07950-2460 US

Inspection Result

EIR Location	Trips Num
DMPQ files	

Inspection Summary

This pre-license inspection of the drug substance manufacturing facility at Immunomedics Inc., Morris Plains, NJ was conducted on August 6th ? August 14th, 2018 following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER under FACTS assignment 11853796, operation ID 9856447. The inspection was conducted to support the approval of (b) (4) The inspection covered the production building (DS intermediate manufacturing) and Quality Control Laboratories in the Building (b) (4) In addition, the inspection covered the Warehouse in building 401 and the Utilities.

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals:

Samples Collected

Sample Number

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FDA 483 Responses

483 Issued?: Y **483 Location:** DMPQ files

Response Type	Response Mode	Response Date	Response Summary

I. Summary of findings

This pre-license inspection of the drug substance manufacturing facility at Immunomedics Inc., Morris Plains, NJ was conducted on August 6th – August 14th, 2018 following a request by Branch IV of Division of Microbiology Assessment, Office of Process and Facilities, Office of Pharmaceutical Quality, CDER under FACTS assignment 11853796, operation ID 9856447. The inspection was conducted to support the approval of (b) (4) (b) (4) The inspection covered the production building (DS intermediate manufacturing) and Quality Control Laboratories in the Building (b) (4) In addition, the inspection covered the Warehouse in building 401 and the Utilities.

II. Administrative data

The name and address of the site is:

Immunomedics, Inc.,
300 The American Road,
Morris Plains, NJ

The (b) (4) drug substance intermediate is manufactured in Building (b) (4)

The facility has approximately (b) (4) employees distributed as follows: (b) (4) in CMC (engineering, manufacturing, process sciences, QA, QC, micro, and supply chain), (b) (4) contractors (clinical, data management, regulatory, safety), (b) (4) in the business office, (b) (4) commercial, (b) (4) in finance and administration, (b) (4) in human resources, and (b) (4) in legal affairs. Hours of operations are (b) (4) (b) (4)

The inspection team consisted of following members:

Reyes Candau-Chacon, CDER/OPQ/OPF/DMA (RC)
Madushini Dharmasena, CDER/OPQ/OPF/DMA (MD)
Gunther Boekhoudt (GB), CDER/OPQ/OPF/DIA (GB)
Rajiv Srivastava, ORA (RS)
Dates of inspection: August 6th – August 14th, 2018 (weekend excluded)
Days in the facility: 7

Each inspector wrote his/her assigned corresponding sections of this report, as identified with initials.

At the beginning of the inspection, a 482-FDA notice of inspection (Attachment 1) and the inspection team's FDA Inspector Credentials were presented to Morris Rosenberg, PhD. Chief Technical Officer of Immunomedics and the most responsible person at the facility at the start of the inspection.

Immediately after the firm presented an overview of the company, facility, and process, the inspectors were taken on a tour through the facility. Individuals present at the opening of the inspection are listed in Exhibit 1. Individuals present at the closeout are shown in Exhibit 2.

A 13-item Form FDA 483 was issued to the firm on August 14, 2018 at the inspection's closeout meeting on August 14, 2018, to Michael Pehl, Chief Executive Officer, (Attachment 2) with the following observation summaries:

1. The quality control unit lacks authority to investigate critical deviations of approved procedures.
2. There is no assurance that samples and batch records from the (b) (4) intermediate process validation and commercial batches manufactured prior to February 2018 were not impacted by the data integrity breach.
3. Retesting procedure for the (b) (4) intermediate is inadequate.
4. The raw material sampling and testing program is inadequate.
5. The firm lacks procedures for inventory audit trail and for tracking and reconciliation of raw materials used to manufacture the (b) (4) intermediate.
6. Differential pressure between GMP areas of different area classification is not adequately maintained and monitored.
7. The design of the facility is inadequate in that no drains are present in the purification rooms. In addition, there is no SOP for liquid containment and disposal after a catastrophic spill. All process streams downstream the (b) (4) Bioreactor are held in disposable bags.
8. There is no signed Quality Agreement between (b) (4) and Immunomedics Inc. (b) (4) is the supplier of cell culture media and all (b) (4) solutions (including (b) (4)), and (b) (4) used for (b) (4) purification of the (b) (4) intermediate.
9. No procedure is in place for (b) (4) intermediate (b) (4) trending of results.
10. Deviation investigations and CAPA implementations are inadequate.
11. Deviation initiation and closing times are inadequate.
12. Cleaning of downstream equipment, including (b) (4) and product-contact parts of the (b) (4) is not validated or verified.
13. The procedure to prevent contamination of the (b) (4) intermediate after (b) (4) (b) (4) is inadequate for a product stored 2 to 8ºC for up to (b) (4)

4 verbal observations/discussion items were communicated to the firm throughout the inspection. They are provided in the General Discussion with Management Section (Section XV).

III. Refusals

The firm refused to provide documentation to assess the data integrity breach that was discovered in January 2018. The firm alleged that they could not share those documents because they were under attorney/client privilege. Review of those documents was necessary to assess the scope and impact of the data integrity breach.

IV. History

Immunomedics is a Public Biotech company, incorporated in 1982 that has historically focuses in research and early development and has no previous experience with commercialization of therapeutic products in the US.

A brief history of the company is included in the table below provided by the firm during the inspection.

Date	Key Event
July 1982	Immunomedics was founded
19 Apr 1984	IPO (NASDAQ:IMMU)
1990 - 2000	Generated antibody platform
May 2002	Acquired IBC Pharmaceuticals
2008	Developed Linker platform
(b) (4)	

The Immunomedics headquarters and manufacturing site (Building (b) (4) are located in American Enterprise Park in Morris Plains, NJ. The manufacturing and QC site (Building (b) (4) is a (b) (4) story building that was built in 1991. Immunomedics leased the building and constructed the Research and Manufacturing facilities in 1996. The laboratories and offices are architecturally segregated. The manufacturing facilities include a (b) (4) sq. ft. ((b) (4) m^2) (b) (4) facility (Rooms (b) (4) a (b) (4) sq. ft. ((b) (4) m^2) large-scale bioreactor facility (Rooms (b) (4) and a (b) (4) sq. ft. (b) (4) m^2) downstream processing facility (b) (4)

This is the first FDA inspection for biologic product manufacturing. The inspectional history of the facility, duplicated from documentation provided by the firm during the inspection, is shown below.

FDA Inspections:

- Pre-approval GCP Inspection – June 14 – August 1, 2018.
- February 13, 2006 (b) (4) – investigator came to site, but inspection not held since (b) (4) (Routine,
- January 14-17 and 23, 2003 (b) (4)
- February 27, 2001 – March 6, 2001 (Routine, (b) (4)
- July 7-11, 1997, New Manufacturing Facility Inspection (Morris Plains, NJ location (b) (4)
- March 11-14, 1996 (PAI for (b) (4) none performed for (b) (4) - not approved in US)

EMA/PEI/RP Routine Inspections for (b) (4) and/or (b) (4)

- February 22-24, 1996 (PAI)
- 3/9-11, 1998
- 3/12-14, 2001
- 9/15-20, 2004
- 3/27-28, 2007
- 1/19-21, 2010
- 9/12-14, 2012
- 4/26-28, 2016 (not held within 2-3-year period since no manufacturing was being performed)

PEI GCP Inspection for (b) (4)

- January 8-12, 2007

V. Interstate commerce

This inspection was limited to (b) (4) and at this time, Immunomedics is not approved for distribution of this product within United States (pending approval of (b) (4) (b) (4) .

VI. Jurisdiction (Products manufactured and/or distributed)

The facility has been a (b) (4) manufacturing facility since April 2017. (b) (4) A list of products manufactured at the facility in the past 5 years and their description, duplicated from documentation provided by the firm during the inspection, is shown below.

Immunomedics Product Codes (Active Past 5 years)					
IMMU Code	Internal Name	Description	Manufacturing Area	Shared Equipment	Last Production Date
(b) (4)					

Immunomedics Product Codes (Active Past 5 years)					
IMMU Code	Internal Name	Description	Manufacturing Area	Shared Equipment	Last Production Date
(b) (4)					

A list of products manufactured at the facility prior to the past 5 years, duplicated from documentation provided by the firm during the inspection, is shown below.

Immunomedics Clinical Trial Products Manufactured since 2013
(b) (4)

VII. Individual responsibilities and persons interviewed:

Michael Pehl, Chief Executive Officer, is the most responsible person at the Immunomedics site. More details on the organizational chart of the company are available in Exhibit 3.

A list of individuals who provided relevant information and accompanied us during the inspection is attached (Exhibit 4).

VIII. Firm's training program

(This section was written by MD)

The firm's training program was covered during the 8/6/2018 to 8/14/2018 pre-license inspection. According to Ms. (b) (6) Manager, Training Unit, the firm's training program is governed by following SOPS.

SOP-0660 "Qualifying Department Subject Matter Experts as Trainers" (version 2.0, Effective 6/1/2018).
SOP-0659 "Preparing training material" (version 1.0, Effective 5/31/2018).
SOP-0658 "Managing Performance Assessment" (version 1.0, Effective 5/31/2018).
SOP-0657 "Delivering Training and Conducting Assessment" (version 2.0, Effective 6/2/2018).
SOP-0158 "QA training program" (version 2.0, Effective 5/31/2018).

The firm requires all employees to attend training on current good manufacturing practices (cGMP) and (b) (4) all employees are required to take cGMP refresher course. In addition, the employees are trained on official documents such as SOPs, batch records, position responsibilities and job-specific procedures. Throughout the duration of the inspection, I (MD) requested and reviewed the following employees' training records for their GMP and job-function specific training:

- (b) (6) Director, Cell Culture Bioreactor
- (b) (6) , (b) (4) purification, Technician
- (b) (6) QC Microbiology, Technician

Their training files include job-specific trainings as well as cGMP trainings. Most training includes reading the SOPs and training on the job. In addition, some trainings are given in a classroom setting. Since there is a high turnover in the firm, most employees are new in their jobs.

No observations were made.

IX. Tours of the facility

(This section was written by GB)

On 8/6/2018, the inspection team toured the Warehouse facility (Building 410). Inside building 410, we got a tour of how materials flow in and out of the warehouse. We toured the receiving dock, material received staging area, the warehouse area where "Release" and "Quarantine" materials are kept, the new raw material sampling lab, and the warehouse staff office. We returned to Building (b) (4) and went to the raw material sampling room followed by the old warehouse, the future cell bank storage area, the current cell bank storage area, and the cell culturing area. On 8/7/2018 GB and RS toured to the QC lab and observed the execution of the (b) (4) assay. On 8/8/2018, the inspection team went back to the warehouse (Building 410) and looked inside the temporary office storage area accessible from the warehouse. Back in Building (b) (4) GB toured the QC lab and observed the training run of the HPLC assay. The inspection team also toured the (b) (4) purification suite and observed the

detergent inactivation by (b) (4) On 8/10/2018, GB toured the QC lab and observed the exsiccation of the (b) (4) assay. GB, MD and RS toured the (b) (4) purification suite and observed the set-up and the washing of the (b) (4) purification column.

X. Quality system

(This section was written by RC)

The inspection team was aware prior to the inspection that the firm had communicated to the FDA in (b) (4) that some of the employees were using procedures that were not specified in the batch records. At the beginning of the inspection I addressed the concern of a potential data integrity breach in the facility and had extensive conversations with Morris Rosenberg, CTO and Mujtaba Ali, head of Quality. They confirmed a data integrity breach that discovered during the review of bioburden data in January 2018. However, the firm did not initiate a deviation as a consequence of the data integrity breach and the firm refused to provide information to the inspection team to assess the extent and duration of the data integrity breach because the investigation had been conducted under attorney/client privilege.

> *Inspector Comment: This was a FDA-483 observation (Observation 1: The quality control unit lacks authority to investigate critical deviations of approved procedures")*

Deviation Procedures

(This section was written by RC)

I reviewed SOP-0152 "Deviation Handling" v3.0, effective June 29, 2018. The deviation procedure does not include a time limit between detection of the event and opening of the deviation.

> *Inspector Comment: This was a FDA-483 observation (Observation 11: Deviation initiation and closing times are inadequate")*

The Department manager with the help of QA decides if an event constitutes a deviation, and if it does, QA assigns a deviation number and the department manager completes the fields of the Form FRM-0074 associated with the deviation.

Deviations:
(The following was written by RC)
I reviewed the following deviations:
17-084U, 17-094U, 17-096U, 17-135P, 17-156U, 17-166U, 17-215U, 17-222U, 18-009U, 18-015U, 18-039U, 18-053U, 18-081U, 18-091U, 18-095U, 18-111U, 18-129U, 18-131U, 18-163U.

The following deviations related to filter integrity test were reviewed: 18-079U, 18-094U, 18-096U, 18-145U, 18-156U, 18-166U.

U stands for "unplanned deviation", P stands for "planned deviation". Planed changes were reported as panned deviations in 2017 and are currently reported as change controls.

> *Inspector Comment: Deviation investigations were deficient. This was a FDA-483 observation (Observation 10: Deviation investigations and CAPA implementations are inadequate.") In addition, not all fields in form FRM-0074 are completed for most deviations. The following fields are usually left blank and substituted by a summary: description of the event, initial impact assessment Investigation details, probable root cause, reoccurrence, CAPA and other actions. The summary consists of an attachment without traceability; for example, in deviation 18-009U (Exhibit RC-1), opened on March 27, 2018 and closed on March 29, 2018, most of the fields are left blank. The deviation includes an attachment that is not dated, not signed and has no information on the chronology of the deviation investigation. In addition, the summary attachment may be modified as the investigation proceeds. For example, deviation 18-081U (Exhibit RC-9) opened on May 18, 2018, indicates in the sections of the FRM-0074 form "see attachment JH 10Jul2018", but the date included in the attachment is from August 5, 2018. It is not clear if the attachment was initiated on July 10 and then modified or if the attachment was initiated on August 5. In addition, the dates cannot be verified, as it is just typed at the beginning of the attachment (no dated digital signatures). This was a verbal observation communicated to the firm during the inspection (Verbal observation RC-1: Deviations documentation is inadequate).*

(The following was written by GB)
I(GB) requested and reviewed the following events:

- NCR 17-154U: The lack to recover the (b) (4) samples from the bioreactors. No viable cells were recovered for (b) (4) culture from (b) (4) The samples taken had low starting viability (36%) on day 9 of the bioreactor. On the (b) (4) day 1 viability was < 6% and by day 2 the viability was 0%. This drop in viability was expected for bioreactor. culture between day 8 and 10. The investigation determined that the lack of (b) (4) for the (b) (4) lot was not needed since a successful culture was previously obtained from lot (b) (4) and from (b) (4) Both these (b) (4) banks were appropriately tested and satisfy the QC requirements. The Corrective and Preventative Action (CAPA) implemented based on this NCR include the construction of an (b) (4) bank from the

MCB. This (b) (4) bank was tested through (b) (4) generations to capture the maximum in-vitro age of fed-batch processing from the MCB of (b) (4) generations. This deviation has no impact to product quality and was performed appropriately.

- NCR 18-114U and 18-127U: Using expired of (b) (4) . (b) (4) purchased from (b) (4) such as, (b) (4) were randomly assigned a (b) (4) expiration date with no data supporting the it. After the plant (b) (4) most of the (b) (4) expired and (b) (4) was unable to provide new material in a timely manner. A risk assessment was conducted and determined that the use of these expired (b) (4) has a low risk to product quality. In addition, bioburden and endotoxin testing were performed providing information of the potential microbial load. The use conditional release (b) (4) are part of the umbrella deviation 18-157U. This deviation has no impact to product quality and was performed appropriately.
- NCR 18-092U and 18-098U: Clinical material request were submitted less than the required (b) (4) . Per SOP-Q242, "Shipment of Controlled and non-Controlled Materials", states that material request must be submitted to QA at least (b) (4) prior to the requested shipment date. The investigation determined that the (b) (4) timeline in the SOP is driven by business efficiency goals and is not necessary. CAPA # 18-006 was initiated to revise the SOP-Q240 to remove the required (b) (4) (b) (4) deadline. This deviation has no impact to product quality and was performed appropriately.
- NCR 18-100U: Out of range (b) (4) during the transfer of (b) (4) cultured from (b) (4) L bioreactor to the (b) (4) L bioreactor. The (b) (4) L (b) (4) bioreactor (b) (4) ranges are between (b) (4) and (b) (4) Here, for lot (b) (4) the (b) (4) reading was (b) (4) The investigation determine that the (b) (4) reading was due to a sterilization cycle on the (b) (4) bioreactor which had to go through a second sterilization cycle as part of deviation NCR 18-103U. Due to the second sterilization cycle, less time was available for the (b) (4) L bioreactor to equilibrate. Also, the culture in the (b) (4) L bioreactor had to go longer. In order avoid going out of range for (b) (4) in the (b) (4) L bioreactor, supervisor recommended to transfer the culture to the (b) (4) L bioreactor prior reaching the desired (b) (4) There was no impact to product quality since the bioreactor are allowed to run at (b) (4) as (b) (4) as (b) (4) Document change order, 18-241, was initiated to change the (b) (4) ranges. This deviation was performed appropriately.
- NCR 17-157U: Material receiving report Q500 contained multiple errors. Receiving reports dated 09-15-2017 had some data entry errors and were not properly crossed out, initialed, and dated. The correct information was provided in the package and there was no product impact. The investigation determine that the root cause was a personal error and retraining was part of the corrective action. This deviation was performed appropriately.

- NCR-18-136U: Documentation discrepancy in sample preparation for stability samples (b) (4) The SOP-0330 and SOP-0310 were not followed. The SOP specify that sample documentation must be performed on the controlled form and in a word document. In this case, samples documentations were only performed on a word document. There was no impact to product quality. The sample were later transcribed on the controlled form. The root cause was determined to be some inconsistent instructions in the SOPs. The corrective action taken was to update the SOPs. This deviation was performed appropriately.
- NCR 17-224U: Manufacturing rooms were used before completion of the environmental qualification protocol. The investigation determined that the root cause was the failure to follow SOP. The CAPA implemented includes:
    - Site-wide training
    - Reinforced awareness of change control
    - Accountability for failure to follow the change control SOP
    - Tag-out added to change control and work order SOPs to prevent use of equipment and facilities before completion of changes.

  The deviation was performed appropriately.

Annual Product Review Procedure:
(This section was written by GB)
Annual product review is described in SOP-0159 "Annual Product Review". The SOP outlines in detail the required information that need to be included in an annual product review. This will include summaries of manufacturing process control, and quality data to evaluate the commercial products licensed to Immunomedics. Responsibilities are also outline indicating who is responsible for specific section. The SOP was reviewed in its entirety and appeared to be comprehensive and appropriate.

No observations were made.

Quality Agreements & Contract Lab Qualification Procedures:
(This section was written by RC)
I reviewed the quality agreement between (b) (4) and Immunomedics and no deficiencies were found.

I reviewed a draft of the quality agreement between (b) (4) and Immunomedics Inc. However, the draft was not signed and therefore, we could not assess whether the information in the quality agreement has been implemented. all information at the time of the inspection. All raw materials used in (b) (4) purifications (b) (4) (b) (4) (b) (4) etc) and all the cell culture media is supplied by (b) (4)

Inspector Comment: This was a FDA-483 observation (Observation 8: There is no signed Quality Agreement between (b) (4) and Immunomedics Inc.)

Change Control:
(This section was written by RC)
I reviewed SOP-0163 "Change control for GxP related process, equipment, and systems" v2.0 effective June 29, 2018.

No observations were made

Complaint Procedure, AE:
(This section was written by RS)
The firm's SOP-0156 "Customer Complaint Management" v2.0 eff 7/31/2018 describes the procedure to manage and evaluate all customer complaints associated with licensed commercial products. The firm uses FRM-0134 Complaint Communication Data Sheet v1.0 eff 7/31/2018, to record the complaint and assign a tracking number. The communications with customer are recorded on FRM-0135 Complaint Communication v1.0 eff 7/31/2018. The firm has (b) (4) (b) (4) to complete the investigation and document the findings on FRM-0136 Complaint Closure Summary v1.0 eff 8/8/2018. If complaint investigation is not closed within (b) (4) (b) (4) the quality assurance can grant a second (b) (4) extension by documenting the justification on FRM-0134.

Ms. Sandra Roque, Director of Quality Assurance and Operations provided me the Product Complaint Logbook ID # 00185 issued on August 1, 2018. I observed that only one complaint was recorded, Complaint Tracking No. 18-001. The complaint was received on August 10, 2018 for two infusion vials with collapsed core. The compliant was classified as Quality Complaint and firm resoled the issue by not using the vials. I observed that FRM-0134 Complaint Communication Data Sheet was used to record the complaint.

Ms. Roque stated that since the product is not commercial, no Quality Complaint has been recorded and all the patients adverse event data from the clinical trials are compiled in the (b) (4) The firm recorded its first Quality Complaint on August 10, 2018. Ms. Roque informed me that the QA plans to complete the investigation and close it within (b) (4) I found that the firm's complain management procedure appeared to be adequate.

No observations were made

Recall
(This section was written by RS)
The firm's SOP-0161 "Product Recall" v2.0 eff 8/3/2018 describes the firm's responsibilities and procedures to initiate, evaluate, conduct, and close recall actions. I reviewed the procedure and verified that it contains all the necessary elements for an effective recall including (but not

limited to); recall classification, recall strategy, effectiveness check, and recall letter. The procedure also has provision for annual mock recall.

Mr. Mohit Gupta, Head of the Validation explained me the firm's recall policy and stated that the firm has not recalled any products so far. He also informed me that the mock recall is planned in the fall of 2018.

No observations were made

Document Control Procedures:
(This section was written by RS)
The firm's SOP-0141 "Management of Regulated Documents" v2.0 eff 6/13/2018 describes the procedure for management of regulated documents throughout their entire life cycle from creation to revision, archival, and obsoletion. The firm's Regulated Documents System is a controlled electronic and paper-based system that is managed by quality assurance department. During walkthrough of the (b) (4) system, I observed that the data for (b) (4) (Serial # 167381-1) and (b) (4) (Serial # 283447) were recorded on uncontrolled forms. In addition, >40% of the data suggested that the system was operating outside the operating range (See **Verbal Observation RS1**).

Verbal Observation RS1: The firms document control procedure is deficient

The firm's document control procedure is described in SOP-0141 "Management of Regulated Documents" v2.0 eff 6/13/2018 (**Exhibit RS-1**). Specifically,

a. Section 7.1 (**Exhibit RS-1**, page 4) indicates that "…Regulated Document System is a controlled electronic and paper-based system managed by the Quality Assurance Department." However, during walkthrough of the facility, I observed that the (b) (4) log data for the (b) (4) (Serial No. 167381-1) and the (b) (4) (b) (4) (Serial No. 283447) on the uncontrolled forms (**Exhibits RS-2**).

b. Section 7.3 (**Exhibit RS-1**, page 5) indicates that "...users of the documents are required to comply with the parameters and procedures set forth within the documents." However, the following data did not comply with the parameters set forth within the documents:

   i. The (b) (4) log data for the (b) (4) (Serial No. 167381-1) suggests that the system was operating outside the operational ranges during the period (including but not limited to) July 16, 2018 to August 3, 2018 (**Exhibit RS-2** pages 1-3) without initiating any action.
   ii. The (b) (4) log data for the (b) (4) (Serial No. 283447) suggests that the system was operating outside the operating ranges during the period

(including but not limited to) July 9, 2018 to August 8, 2018 (**Exhibit RS-2**, pages 5-6) without initiating any action.

I enquired with Mr. Mike Levitt, VP Manufacturing about the use of uncontrolled forms in the boiler room and not running the (b) (4) equipment within the defined operational ranges. Mr. Levitt acknowledged the observations and promised to correct the issues. Later in the day, Mr. Levitt informed me that the firm has opened a deviation for the use of noncontrolled forms in the boiler room and provided me a copy of the deviation # 18-1854 dated 8/9/2018 (**Exhibit RS-3**).

No observations were made

Computerized Systems:
(This section was written by RS)
The firm uses Veeva Vault v17R3 QualityDocs enterprise resource planning (ERP) system to manage all the Quality documents. This is a cloud based ERP system. I reviewed the validation summary report VV.PMO.QD.00108 v1.0 dated 4/10/2018 and found it to be adequate. The firm is migrating all the older SOPs to Veeva Vault. I found that the current quality documents that are generated through Veeva Vault has complete trackability.

No observations were made

XI. Facilities and equipment system

Facilities

The facility has been modified from the initial R&D facility by a series of upgrades that were initiated in a (b) (4) during December to March, 2018 and included the following upgrades:

Facilities Changes Post-PPQ Campaign

Seed Lab	**Cell Culture**
Replaced 2 Biosafety cabinets	Upgraded Wall systems for cleanability
Replaced (b) (4) floor	Refurbished (b) (4)
Upgraded Wall systems for cleanability	Replaced (b) (4) floor
Installed new card access points to control personnel and process flow	Installed (b) (4) to improve segregation of facility (dedicated hallway) from R&D
Rebalanced area to improved (b) (4)	Installed (b) (4) to improve pressure control
Mounted scale displays to improve cleanability	Rebalanced area to improved (b) (4)
Purification	**Utilities**
Installed new (b) (4)	Installed back up (b) (4) System (not yet qualified)
Installed new parts washer	Installed back up (b) (4) (not yet qualified)
Replaced (b) (4) with (b) (4)	Upgraded controls on existing (b) (4)
Replaced (b) (4) floor	Replaced TOC meter on (b) (4) System
Installed (b) (4) for improved protection from tankage	Installed new Environmental Control System (EMS) to monitor T, RH, Diff Pressure and Environmental Chambers
Installed viewing windows for critical process steps	**B410 Warehouse**
Installed new card access for new rooms to control personnel flow	Completed construction of a temperature controlled remote warehouse
Installed new gowning room	
Reconfigured exit equipment (b) (4)	
Rebalanced area to improved (b) (4)	
Installed (b) (4) to improve segregation of waste and permit separation of pre and post (b) (4) filtration	

In addition to these changes, the firm implemented a new (b) (4) pressure, temperature, and humidity monitoring in July and the system was being qualified during the inspection. Other changes in the planned before distribution and commercialization of the product include:

- Installation of a (b) (4) in the (b) (4) systems. This will allow for the use of the in-house generated (b) (4) to be used for manufacturing. Currently, the (b) (4) generated in-house is only used for the (b) (4) of the equipment and (b) (4) of the (b) (4) filter. The (b) (4) used for manufacturing is provided by (b) (4)
- Replacement of all HVAC air handling units,
- Commissioning of a new master cell bank storage room,
- Commissioning of raw material sampling and testing areas in the warehouse building 410,
- Implementation of Great Plains to track the raw material inventory.

Inspector Comment: The facility should be inspected after the upgrades included above are implemented and/or the systems are qualified.

During the tour to the purification areas on August 7, 2018, the inspection team noticed that the purification areas have no drains. In addition, the facility has no SOP to contain and dispose of

liquids in case of a catastrophic spill. All operations downstream the (b) (4) bioreactor are conducted using single-use bags, which may contain up to (b) (4) L liquid material.

Inspector Comment: This was a FDA-483 observation (Observation 7: The design of the facility is inadequate in that no drains are present in the purification rooms.)

HVAC and BMS

(This section was written by RC)

I reviewed the drawings of the facility. The facility was designed for research and development, with multiple small room. The manufacturing areas are Grade D (upstream processing) with Biological Safety Cabinets (BSC) monitored to Grade A for open processes, including master cell bank thaw and (b) (4) and (b) (4) and assembly of critical open operations conducted during manufacturing (for example (b) (4) . Purification areas have Grade C and D classification. All (b) (4) have the same classification that the rooms that they feed. Upstream manufacturing areas in a different part of the building that purification areas; (b) (4) purification areas and (b) (4) areas are separated by a clean corridor.

The facility is serviced by (b) (4) air handling units in the (b) (4) area and (b) (4) units in the purification areas. Air flow is segregated between cell culture, purification (b) (4) (b) (4) and (b) (4) The air handling unit that services the (b) (4) (b) (4) area (AHU7) is also used for a storage room in the (b) (4) area. However, the room has 100 % filtered air with no recirculation. The target number of air exchanges is (b) (4) room changes/hour in Grade C areas and (b) (4) room changes/hour in Grade D areas.

The differential pressure in the facility has a (b) (4) design, with pressure increasing with the criticality of the process. Pressure monitoring of the facility has been conducted manually until a (b) (4) continuous pressure monitoring system was installed in July; the system is currently being qualified.

I reviewed SOP-0239 "Monitoring differential pressure, temperature and humidity" v2.0 effective August 4, 2018. According to the SOP, temperature. Humidity and differential pressure in manufacturing areas are monitored (b) (4) during operations. However, when inspecting the pressure differential logs, it was noticed that pressure is monitored (b) (4) (b) (4) during operations. I reviewed the differential pressure data between room (b) (4) (Class C (b) (4) and (b) (4) (Class D corridor) between July 24th and August 1st, 2018. Most of the measurements were out of limits.

Inspector Comment: This was an FDA-483 observation (Observation 6.a: Air pressure in the GMP areas is not adequately maintained.")

I reviewed form FRM-0267, that is part of SOP-0239. The form lists all adjacent monitoring rooms that are alarmed in the (b) (4) continuous monitoring system. Not all adjacent rooms are monitored for pressure differential. For example, there differential pressure between room (b) (4) (b) (4) (Class C (b) (4) and (b) (4) (Class D corridor) is not alarmed.

Inspector Comment: This was an FDA-483 observation (Observation 6.b: Air pressure in the GMP areas is not adequately maintained.")

(b) (4) System and (b) (4)

(This section was written by RC)

(b) (4) used in the manufacturing process is supplied by (b) (4) The label of the (b) (4) indicates that it is (b) (4) tested to USP standards of (b) (4) therefore it was not clear the type of (b) (4) The CofA indicates that the (b) (4) is tested to (b) (4) standards. I reviewed information provided by the firm regarding the generation of the (b) (4) and the generation process includes a (b) (4) step.

(This section was written by RS)

I inspected the (b) (4) production system in Building (b) (4) I found that (b) (4)

I reviewed the SOP-Q220 "Sampling Plan for (b) (4) v13 eff 9/11/2012. The (b) (4) is sampled at (b) (4) for (b) (4) (action level > (b) (4) ppm). The TOC (action level > (b) (4) ppm) and conductivity (action level > (b) (4) µS/cm) are measured (b) (4) on (b) (4) (b) (4) TOC Analyzer in the mechanical room. Sampling for microbial testing (action level > (b) (4) cfu/mL, alert level > (b) (4) cfu/mL) is done according to SOP-Q649 "Microbial Monitoring of (b) (4) v24 eff 9/3/2013. The samples for microbial testing are collected (b) (4) (b) (4) at (b) (4) and (b) (4) at (b) (4) system). The rest of the use points are sampled on a (b) (4) basis such that each use point is sampled (b) (4)

I observed that (b) (4) was removed from the (b) (4) distribution loop through a change control CC # 17-144P. After the change, the firm requalified the (b) (4) system. I reviewed the Document No. FC-0001-PQ-03-R "Performance Qualification Final Summary Report" and found it adequate.

The (b) (4) is used as (b) (4) for the manufacturing of (b) (4) I inspected the (b) (4) system that was installed in the boiler room. The firm uses (b) (4) (Serial # 167381-1) and (b) (4) (Serial # 283447) to manufacture (b) (4) respectively. The (b) (4) is stored at (b) (4) °C in a (b) (4) -gallon (b) (4) storage tank. The storage tank

supplies (b) (4) through a distribution loop that is fitted with (b) (4) POU. The (b) (4) operates at (b) (4) °C. I observed that firm was in the process of installing (b) (4) and a storage tank to manufacture and store ambient (b) (4)

I reviewed SOP-Q626 "Monitoring of USP (b) (4) System v9 eff 4/1/2013. The (b) (4) is sampled (b) (4) from (b) (4) and (b) (4) (b) (4) for (b) (4) (action level > (b) (4) ppm), TOC (action level > (b) (4) ppm) and conductivity (action Level > (b) (4) µS/cm). The samples for microbial testing (action level > (b) (4) cfu/100 mL, alert level > (b) (4) cfu/100 mL) are collected (b) (4) at (b) (4) (b) (4) and (b) (4) from rest of the POU (except (b) (4) and (b) (4) .

In the (b) (4) manufacturing area, I observed that the data for (b) (4) (Serial # 167381-1) and (b) (4) (Serial # 283447) are recorded on uncontrolled forms. In addition, more than 40% of the recorded data suggested that the systems were operating outside the operational ranges (See **Verbal Observation RS1**). I also observed that most of the plumbing system and the recirculation loops were hidden behind the wall and the ceiling tiles.

I reviewed (b) (4) testing reports for 2017 and 2018 and the firm's procedure to report and investigate the OOS, SOP-0162 "Out of Specification Investigations" v4.0 eff8/3/2018. The SOP-Q626 "Monitoring of USP (b) (4) System v9 eff 4/1/2013 requires resampling and second consecutive OOS prior to initiating an investigation. However, the firm's resampling procedure is deficient that makes it impossible to resample a representative batch of (b) (4) (See **Verbal Observation RS2**)

Verbal Observation RS2: The resampling procedure for (b) (4) is deficient

The SOP-Q626 "Monitoring for USP (b) (4) Systems" v9.0 eff 4/1/2013 is deficient in resampling to assure the quality of the (b) (4) Specifically, the procedure requires resampling and second consecutive OOS prior to initiating an investigation. However, the resampling procedure is deficient. Section 9.3.4 (**Exhibit RS-4**, page 7) indicates that, "…routinely collected samples, subsequent to initial sample, may serve as a resample." However, the (b) (4) System continuously manufactures (b) (4) and the (b) (4) is in constant circulation. This makes it impossible to resample a representative batch of (b) (4) on a later date and/or time point. I explained to Mr. Indrajit Giri, Director, QC Raw Material and Contract Testing that the firm's current procedure is deficient in resampling of the (b) (4) Mr. Giri acknowledged my observation and promised to discuss the issue with the management.

No observations were made

Process (b) (4) (b) (4)
(This section was written by MD)
The firm's (b) (4) is governed by SOP Q697 "Routine monitoring of the (b) (4) system" (Revision 0, effective 5/31/2016) and microbial analysis is governed by SOP Q617

"Total Particulate monitoring of controlled environments using (b) (4) particulate counter". The (b) (4) distribution system is composed of (b) (4) sample ports and sampled (b) (4) (b) (4) found within the (b) (4) are in purification suites, and (b) (4) are located within (b) (4) area. The (b) (4) is (b) (4) at the point of use, except for the (b) (4) used to (b) (4) container during (b) (4) and to conduct the (b) (4) integrity test. There were no excursions or negative trends within the year 2018. Both (b) (4) verification and (b) (4) are checked (b) (4) and executed as per SOP Q697.

Inspector's comment: See (b) (4) section written by RC

The firms (b) (4) are supplied to all (b) (4) rooms and bioreactors and the (b) (4) and (b) (4) testing are governed by SOP Q823 "Identification test for (b) (4) (b) (4) (Revision 7.0, effective 5/13/2016). (b) (4) are (b) (4) (b) (4) at the point of use and the (b) (4) is tested for (b) (4) integrity. However, (b) (4) are purchased from (b) (4) are not tested for bioburden at the firm or at the supplier (supplier specifications do not include microbial testing-see Exhibit MD-1

Inspector's comment: The product contact (b) (4) used in the bioreactors are not tested for bioburden. The lack of microbial testing increases the contamination risk. This resulted in FDA-483 observation 4b.

Facility Cleaning:

(This section was written by RC)

I reviewed SOP-0076 "Sanitization of manufacturing clean areas" v5.0 effective August 4, 2018. The SOP lists the frequency of sanitization of the different areas, the sanitizing reagent, and the cleaning method using three buckets. (b) (4)

I asked (b) (6) Head of QC microbiology whether the firm had conducted studies to demonstrate the efficacy of the sanitizing agents. No study has been conducted yet. However, I was shown a study protocol that is being reviewed by Immunomedics and a contractor.

Inspector Comment: Although the firm did not conduct efficacy studies to support its room cleaning and sanitization process, the sanitizing agents are standard agents used in biotech manufacturing areas and they are not rinsed from the surfaces. In addition, the firm is in the process of conducting a study. This did not result in an FDA-483 observation.

Environmental Monitoring (EM)

(*This section was written by RC*)

I reviewed SOP-Q608 "Microbiological monitoring of the controlled manufacturing and support areas" v35.0, effective August 18, 2017. The document lists the different areas in the facility, and

the EM samples taken (air, surface and personnel), as well as a brief description on how the samples are taken, and action and alert limits (shown below, duplicated from the SOP.)

TABLE 2: Environmental Monitoring Acceptance Criteria

Grade	Viable in Air cfu/m³		Surfaces cfu (b) (4) Plate		Personnel cfu (b) (4) Plate	
	Alert*	Action*	Alert	Action	Alert	Action
(Grade A)	(b) (4)					
(Grade C)						
(Grade D)						

*** Alert and Action levels are also applicable to settling plates when used.**
N/A - Not Applicable
WE – Walls and Equipment

The SOP indicates that in case of a sample out of action limit, the area will be sanitized, and an additional sample will be taken within (b) (4) (refer to Q608 step (b) (4) and a non-conformance report will be initiated only in case that the resample is also out of action limit. This is applied to samples taken from all area classifications in and out of operations.

> *Inspector Comment: The resampling practice is inappropriate because it invalidates the first above-action-limit sample; in addition, since the resample is taken immediately after sanitization, the result would not be representative of the hygienic status of the area. This resulted in a verbal observation that was communicated to the firm throughout the inspection (Verbal observation RC-2: Environmental monitoring sampling is inadequate). However, this did not result in an FDA-483 observation because the initial results are documented in the EM result charts, the firm sanitizes the area after finding the initial excursion, lowering the risk to product contamination, and the firm has initiated a change control to initiate a deviation after the initial excursion.*

(*This section was written by MD*)
I reviewed 2018 EM monitoring results from upstream and downstream manufacturing. Only one excursion (EM18-001) occurred during this period. I reviewed the Environmental Alert form for EM18-001. According to this report, 18 CFU of *Paracoccus caeni* was found on the (b) (4) L

bioreactor on (b) (4) suite. In addition, I reviewed 2017 Environmental Monitoring Microbiological Trend Analysis Summary Report. According to this report:

- Total of 6 excursions occurred in viable air and surface sampling within the (b) (4) (b) (4) area
- 12 within Cell Culture / Upstream area
- 9 downstream manufacturing area
- 44 within for personal monitoring area

Inspector Comment: The firm initiated a non-conformance report (NCR) to investigate the root cause of the recoveries and established NCR # 17-202U and 17-203. Thus, the excursions were appropriately investigated.

No observations were made

Equipment

Equipment Maintenance (Preventative Maintenance and Calibration, Logbooks):
(This section was written by RS)
Mr. Mohit Gupta, Head of the Validation informed me that the site manufactures (b) (4) drug substance, (b) (4) and all the equipment are either single use or dedicated equipment. I reviewed a list of all the equipment used in the manufacture of (b) (4) (**Exhibit RS-5**). I found that all the equipment are qualified. I randomly selected a (b) (4) L Bioreactor Model # (b) (4) (Equipment ID # 00060) that was located in (b) (4) I reviewed the equipment use log book and observed that the equipment usages, cleaning, and maintenance was recorded in a chronological order.

I reviewed SOP-C210 "Cleaning of the (b) (4) Bioreactor" v16 eff 3/23/2018. I observed that the procedure contained all the necessary elements to effectively clean the reactor. I also reviewed the Cleaning Validation Report, Document No. CC-0135-CV-01-R dated 5/23/2017. The report provides documented evidence that the cleaning procedure, SOP-C210 v16 eff 3/23/2018 is capable of removing product residue from (b) (4) Bioreactor (Equipment ID # 00060) after its use from the manufacturing of (b) (4) drug substance. The report also establishes a (b) (4) dirty hold time.

I reviewed SOP-C399 "Preventive Maintenance Program for Cell Culture Process Equipment" v6 eff 1/31/2018 (**Exhibit RS-6**). I found that the procedure contained all the necessary elements for PM of the equipment used to manufacture (b) (4) drug substance. The procedure suggests preventive maintenance (b) (4) or after (b) (4) runs. I verified that (b) (4) Bioreactor (Equipment ID # 00060) had (b) (4) runs to its credit and the firm had conducted PM on 5/24/2018 and 7/12/2018. I reviewed the scope of PM and found that the firm failed to replace a number of consumables as suggested by the firm's SOP-C399 "Preventive

Maintenance Program for Cell Culture Process Equipment" v6 eff 1/31/2018 (See **Verbal Observation RS3**).

Verbal Observation RS3: Failing to perform preventive maintenance of the cell culture process equipment

The procedure for the PM of (b) (4) Bioreactor (Equipment ID # 00060) is included in SOP-C399 "Preventive Maintenance Program for Cell Culture Process Equipment" v6 eff 1/31/2018 (**Exhibit RS-6**, pages 9-12). I observed that the equipment received PM on 5/24/2018 and 7/12/2018. Mr. (b) (6), Interim Director of Engineering Maintenance provided me a list of consumables (**Exhibit RS-7**) that are replaced during the PM of (b) (4) Bioreactor. Mr. (b) (6) also provided me a list of the consumables (**Exhibit RS-8**) that was replaced during the PM of the (b) (4) Bioreactor. I reviewed the list and observed that a number of consumables were not replaced during the PM including (but not limited to); (b) (4) (b) (4) temperature probe port, and (b) (4) isolation to the (b) (4) filter housing. I asked Mr. (b) (6) why the consumables were not replaced. Mr. (b) (6) stated that only the highly abused items were replaced during the PM. I informed Mr. (b) (6) that the firm should adhere to it SOP-C399 "Preventive Maintenance Program for Cell Culture Process Equipment" v6 eff 1/31/2018 (**Exhibit RS-6**, pages 9-12) and any deviation for the written procedure should trigger a deviation that should be investigate. Mr. (b) (6) acknowledged the observation and promised to discuss the issue with the firm management.

No observations were made

Equipment Qualification:
(This section was written by MD)
Mr. Mohit Gupta, Head of Validation provided me (MD) with an overview of (b) (4) validation. (b) (4) in room (b) (4) was initially validated with (b) (4) loads, governed by SOPS FRM-0270, FRM-0271, FRM-0272, FRM-0273, and FRM-0274. Load 2 was found to have the (b) (4) and thus, the load 2 was run for 2 more cycles. The (b) (4) validation was carried out at (b) (4) for (b) (4) where as routine production is carried out at (b) (4) for (b) (4) The (b) (4) will be validated (b) (4) with worst case load 2. No deviations were observed.

No observations were made

(This section was written by GB)
The system to identify Immunomedics equipment is described in SOP-0235, Procedure for Equipment and Instrument Identification. The SOP entails that upon receipt of a new equipment, and equipment information record number is assigned. The instrument is identified, and a calibration assessment is performed as part of the instrument information record. If calibration is needed, the information is entered in the Instrument Master List where the schedule and measurement data template are generated. The system was tested using a decommissioned scale

(CCA476). The result showed that the equipment was tracked and showed that it was out of service.

Multiple scales, freezers, and (b) (4) are installed throughout the Immunomedics facility. I requested and reviewed the following calibration record, qualification and/or requalification reports:

- Scale QCA209, QCA240, and QCA-242
- (b) (4)
- Vi-cell XR CCA312
- UPLC E00266

The qualification of the UPLC E00266 was performed to verify the qualified wavelengths span (b) (4). These (b) (4) are important in determining the (b) (4) ratio ((b) (4)) used in the specification of DP. were qualified. The re-qualification report # 048 shows that only wavelengths between (b) (4) and (b) (4) were qualified. Further information provided by Waters (manufacturer and instrument qualification company) indicates that the qualification at these wavelengths are appropriate to support the spectral between 205 to 486nm.

No observations were made

Incubators/refrigerators

(*This section was written by MD*)

(b) (4) monitors (b) (4) refrigerators, incubators, (b) (4) The alarm management at the facility is governed by SOP-0772 (version 1.0, effective 8/4/2018). There are (b) (4) in the facility. I (MD) requested and performed cursory review of the (b) (4) used for the storage of DS intermediate. After manufacturing, the DS intermediate is stored in quarantine (b) (4) ID# E00107 until release (Labeled Quarantine). After release, the DS is transferred to (b) (4) cooler ID#E00105 (Labeled Release). In addition, (b) (4) had emergency contact information on the door. (b) (4) were calibrated at (b) (4) using (b) (4) (b) (6) the QA manager confirmed that no excursions occurred since the manufacture of PPQ lots.

No observations were made

(*This section was written by GB*)

Multiple incubators, freezers, and (b) (4) are installed throughout the Immunomedics facilty. I requested and reviewed the following temperature-controlled environment equipment temperature chart, qualification and/or requalification reports:

- Incubators E00170 and E00165
- Reference Standard -80 °C E00088
- Drug product 2-8 °C (b) (4) E00160
- Purified bulk 2-8 °C (b) (4) E00107 and E00105

No observations were made.

Temp. Controlled Vessels

(*This section was written by GB*)

Multiple temperature controlled vessels are installed throughout the Immunomedics facility. I requested and reviewed the following temperature controlled vessels temperature chart, qualification and/or requalification reports:

- (b) (4) E00162 and E00163
- Stability chambers, 25°C E00328 and 40°C E00329

No observations were made.

Laminar Flow Units

(*This section was written by MD*)

There are (b) (4) Laminar flow hoods in Grade C, Grade D and unclassified areas of the facility. They are requalified (b) (4) by a contractor named (b) (4) The requalification includes airflow velocity test, alarm test, aerosol challenge installation test, airborne particle count test and airflow smoke pattern test. The average intake velocity acceptance criteria should be within (b) (4) - (b) (4) fpm. I reviewed the last requalification of the laminar flow hood used for dispensing the drug substance intermediate and the results were within specification.

No observations were made

(b) (4)

(*This section was written by RC*)

Reuse of the (b) (4) has been assessed in small scale studies. The (b) (4) were (b) (4) and discarded after the facility (b) (4) and the lifetime studies of the (b) (4) were restarted in April, therefore there is very limited data. Review of the bioburden results of the (b) (4) prior to the facility (b) (4) included the following contaminated samples (too numerous to count or TNTC):

- (b) (4) pre-sanitization, lot (b) (4) TNTC
- (b) (4) lot (b) (4) TNTC

The microbiology results were not trended and no action was taken. In addition, several samples from the (b) (4) have resulted in high bioburden count (including TNTC).

Inspector Comment: This was an FDA-483 observation (Observation 9: No procedure is in place for (b) (4) intermediate (b) (4) trending of results.)

(*This section was written by GB*)
The (b) (4) lifetime protocols and existing data were reviewed. Production scale (b) (4) lifetime studies are currently underway using full scale performance monitoring. Detail information about (b) (4) storage and (b) (4) life cycle was reviewed.
Life cycle studies were reviewed for the (b) (4). which provided evidence supporting the longevity of (b) (4) reuses and includes monitoring for (b) (4) step yield, bioburden, and endotoxin. The master batch record list that the (b) (4) can be used for up to (b) (4) times or up to (b) (4) This (b) (4) usage was based to the (b) (4) manufacturer. The master batch record will be updated to correct the (b) (4) reuse life cycle as part of the open Document Change Order DCO # 17-532. To further support the (b) (4) life cycle, (b) (4) use logbook (previous look book M155, and current FRM-0226) were reviewed to confirm that the (b) (4) used did not surpass the (b) (4) lifecycle limit. The previous (b) (4) was ran (b) (4) times and the current (b) (4) has been running (b) (4) times, both were below the (b) (4) reuse lifecycle.

Equipment Cleaning
(*This section was written by RC*)
Most of the process is conducted using single-use bags. (b) (4) and media are purchase ready-to-use, therefore equipment cleaning is limited to bioreactors, (b) (4) the (b) (4) vessel used for (b) (4) and small parts. Small parts and equipment are cleaned in a pharmaceutical grade washer (b) (4) located in Room (b) (4) and (b) (4) and (b) (4). I reviewed SOP-0763 "Operation of the (b) (4) pharmaceutical grade washer" v1.0 effective August 3, 2018. I reviewed the cycle development and load configuration qualification study MF-0124-CQ.1. The study included a (b) (4) coverage of all equipment loads and assessment of removal after washing using (b) (4) Bioburden, conductivity, and bioburden were monitored from the rinse, and TOC was monitored from swabs. Worst-case locations were not identified by the (b) (4) coverage study as the (b) (4) was completely removed during the wash.

> *Inspector Comment: During interview with the cleaning SME I indicated that swabs should be taken from worst-case location and these locations could be identified by (b) (4) coverage followed by a partial washing cycle. This was not an observation.*

Cleaning validation for the equipment washer in the (b) (4) washer is currently being conducted using three consecutive runs. No interim results were available at the time of the inspection.

Cleaning is not validated or verified in the (b) (4), and in the product-contact section of the (b) (4) used for the (b) (4) step.

> *Inspector Comment: This was an FDA-483 observation (Observation 12: Cleaning of downstream equipment, including (b) (4) and product-contact parts of the (b) (4) (b) (4) is not validated or verified.)*

XII. Materials system

Storage/Distribution & Quarantine
(*This section was written by GB*)
The inspection team toured the warehouse (Building 410) on 8/6/2018 and 8/8/2018. Access to the warehouse is through a guarded door. The process of receiving materials was presented and is initiated, Per SOP-0707 (Receipt of GMP and Non GMP Materials for Warehouse in Building 410) and SOP-0265 (Receipt of Controlled and Non-Controlled Materials in Building (b) (4), at the loading dock. Here, packages are inspected for any damage, quantity checked. All materials are placed under quarantine. The material received is logged into the FRM-0071 ((b) (4) Receiving Log). If the materials are on a (b) (4) pallet, they are transferred to a (b) (4) pallet and the (b) (4) pallet is discarded. Copies of packing slip were made and a new receiving number is assigned. QA verifies the accuracy of the material report and labels to the certificate of analysis and issue a new control number.

While in the warehouse we requested a review of how raw materials are tracked into and out of the facility. The senior manager materials management of the warehouse, (b) (6) demonstrated the electronic system for tracking and storage of all raw materials. The system was tested by verifying the location and amounts available for two materials – (b) (4) (b) (4) (Cat. # (b) (4) internal part # (b) (4)), and (b) (4) (Cat. # (b) (4) internal part # (b) (4)). The system in-place is an excel sheet and while (b) (6) was able to find the amount on hand and the location of the (b) (4) However, he was unable to provide any information regarding the (b) (4) In addition, the warehouse was not properly mapped with only the storage racks having location assigned number. Materials received are off loaded and placed inside the warehouse segregated only by a chain on the floor. Materials under quarantine and not properly segregated and are stored side by side to released material. Furthermore, on 8/7/2018, en route to the current cell bank storage area, a barrel containing (b) (4) L of (b) (4) Cat # (b) (4) with a quarantine label was observed at the loading dock of Building (b) (4) Upon request, the barrel was destined for destruction after it was brought from Building 410 for testing. To verify this information, proof of traceability was requested for this barrel. Immunomedics was unable to trace the whereabouts of this (b) (4) (b) (4)

Training records of (b) (6) was requested, reviewed, and the training records showed that he was properly qualified.

These observations were noted and written as part of the 483 observation 5; "The firm lacks procedures for inventory audit trail and for tracking and reconciliation of raw materials used to manufacture the (b) (4) intermediate." In addition, verbal observation was provided that SOP-0707 is inadequate.

Sampling procudures during manufacturing of (b) (4) is described in SOP-0068, Sampling Procedures. The SOP describes how to collect samples from the (b) (4) through

the (b) (4) using sample bags, using (b) (4) and product container, and using (b) (4) in the biological safety cabinet. It also briefly notes how samples are delivered to QC lab. Additional information regarding the submission and recording of samples to the QC labs are described in SOP-0197, Submission of Samples to Quality Control. Both SOPs lack details from when samples are collected to the delivery of the samples to QC. Information that is lacking are: Time limits between collection and delivery of samples to the QC labs.

- Temperature requirement of the samples collected.
- Delivery location instruction.
- Delivery chambers instruction.

This was communicated to (b) (6) and he agreed that the information is lacking in the SOPs and opened a document change control (DCC-000468) to address these issues.

Sampling program of raw materials
(*This section was written by RC*)
I reviewed the sampling program for (b) (4) solution and found that the (b) (4) is never sampled. I asked the firm if the product was originally sampled and the sampling was discontinued after a risk assessment, but the product was never sampled.

> *Inspector Comment: This was an FDA-483 observation (Observation 4: The raw material sampling and testing program is inadequate.)*

DS Shipping Validation
(*This section was written by RS)*
The firm's SOP-0269 "Shipment of (b) (4) to (b) (4) " v2.0 eff 7/28/2018 describes the procedure for shipment of (b) (4) to (b) (4) . I reviewed the corresponding validation protocol, Document No. MF-0147-SV-01. I observed that the firm validated one batch of shipment with (b) (4) . The temperature of the bulk was recorded during the transit with (b) (4) strategically placed calibrated temptales. The data confirmed that the material remained at the recommended temperature (2 – 8 °C) during the transit.

I observed that the firm did not validate the shipment under different seasons. Mr. Mohit Gupta informed me that the shipment validation is still going on and they plan to carry out a second validation over the winter. Mr. Gupta also shared with me a draft of shipment mater plan, Drug Product Shipping Qualification Master Plan Immunomedics, Inc. Document No. VL-0015-MP-01, 8/13/2018. I reviewed the document and verified that it included acceptance criteria for shipping qualifications to the destinations including: (b) (4) (packager); (b) (4) and (b) (4) (warehouse); multiple locations in (b) (4) (distributors).

> *No observations were made*

XIII. Production system

a. Processes

Batch Record
(*This section was written by GB*)
I (GB) reviewed the batch records for the following (b) (4) batches:
(b) (4)

Batch records were provided in separate binders, which include both the upstream and downstream manufacturing processes. Each manufacturing process unit of operation was separated from each other and contained their own unique sequence lot number.
(b) (4)

In general;

- All BR were reviewed.
- Deviations (or events) were noted, and the reports on these events were reviewed. All were well-defined and appropriately investigated. None of them were determined to have an impact on product quality.
- Upstream manufacturing processes were reviewed in their entirety. No events or deviation were noted in this section, other than corrected sign off dates. Calculation errors were noted in the BR, which had been corrected (and countersigned) by a supervisor. The modified calculations were verified
- (b) (4) and (b) (4) sections were reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.
- (b) (4) section were reviewed in the their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.
- (b) (4) sections were reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.
- (b) (4) and (b) (4) sections were reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.
- (b) (4) section was reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.

- (b) (4) section was reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.
- (b) (4) section was reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.
- (b) (4) and dispensing of (b) (4) were reviewed in their entirety. No events or deviations were noted in this section, other than corrected calculations as described above.
- Formulated Bulk Drug Substance Formulation sections were reviewed in their entirety. No events or deviation were noted in these sections, other than corrected sign off dates.

Verbal observation was communicated to Immunomedics for the lack of entering information in a timely manner in the batch records. Specifically, while reviewing the batch record for (b) (4) *there were several pages that are were not used and were not crossed out, dated, and initialized.* (b) (6) *, Head of Downstream Production, acknowledge the missing information. He attributed the errors to the lack of manufacturing experience, due to the schedule* (b) (4) *earlier this year. In addition, he provided an open document change control form (DCO # 17-532) containing many of the changes discussed.*

Lots Made & Reprocessing

(*This section was written by GB)*

A list of all (b) (4) lots manufactured at Immunomedics was reviewed. In 2016, (b) (4) lots of (b) (4) were manufactured. In 2017, (b) (4) lots of (b) (4) were manufactured included the (b) (4) PPQ lots. In 2018, up to the current inspection, (b) (4) lots of (b) (4) have been manufactured in Immunomedics. Two lots (b) (4) were not purified due to a bioreactor contamination and one lot (b) (4) was terminated due to a cell growth issue in the bioreactor. No lot was reprocessing.

No observations were made.

Cell bank

(*This section was written by GB*)

We toured the room where the (b) (4) tanks used for storing the cell bank used in the manufacturing of (b) (4) are located. The (b) (4) freezers located in this room are used to store the MCB vials needed for (b) (4) Only personnel with proper clearance have access to the room. Each of the storage vessels is locked and the keys are kept with QA in separate room. Paper logbooks associated with each freezer identify what was retrieved/submitted, and for what purpose. SOP-C216 "Usage of the (b) (4) Storage Inventory System" was requested and reviewed. The SOP describe the operation of (b) (4) storage equipment, the process for storage of (b) (4) removal of (b) (4) and inventory check of cell banks, and the process for receiving and transfer to storage of (b) (4) shipment. Logbooks were reviewed for the disposition of all vials of (b) (4) MCB removed to date, and comparison to manufacturing records. All vials were accounted for. The SOPs for the Operation and maintenance of the (b) (4)

(b) (4) Freezers (SOP-C521) and Thawing of Cells From (b) (4) Storage (SOP-C503) were also reviewed.

I performed an inventory spot check on – E00162 for (b) (4) MCB located in rack # 8, drawer # 3, position # 20, #21, and # 3. The vials in # 20 and 21 were easily located and as expected from the (b) (4) log book, vial at potion # 3 was missing because it was already used.

No observations were made.

Purification & Formulation

(This section was written by MD)

RC and I (MD) observed the mock (b) (4) and filling carried out in the purification suite in Grade C area. We were accompanied by (b) (6) head of (b) (4) manufacturing and (b) (6) (b) (4) purification Technician. During the tour, we observed that (b) (4) Since it is an open process, environmental monitoring was carried out during this process.

Inspector's comment: This open process is inefficient and includes unnecessary steps. The procedure to prevent contamination of the (b) (4) intermediate after (b) (4) (b) (4) is inadequate. Thus, increases the contamination risk. This resulted in FDA-483 ion 13.

(This section was written by GB)

Purification steps were reviewed during the batch record review. In addition, the setup of the (b) (4) purification (b) (4) step was observed. Log books were requested and reviewed for the (b) (4) and the (b) (4) (b) (4) (b) (4) of all purification steps for all the PPQ lots were requested and reviewed.

(b) (4)

(This section was written by RC)

Most in-process intermediates are (b) (4) into disposable bags using sterile (b) (4) All solutions added to the bioreactor except for (b) (4) is (b) (4) at the point of use, and the (b) (4) are tested for integrity after use. All (b) (4) at (b) (4) at the point of use, except for the (b) (4) that is used to (b) (4) container used for (b) (4) and to conduct the (b) (4) integrity test.

Inspector Comment: Although the (b) (4) is product-contact and lack of (b) (4) at the point of use may result in contamination of the product, the (b) (4) is processed immediately to (b) (4) In addition, a deviation has

been initiated with a CAPA for (b) (4) of the (b) (4) at the point of use. This was not an observation.

Most (b) (4) connections are conducted aseptically inside a BSC that is monitored to Grade A.

(b) (4) is conducted using a (b) (4) I reviewed SOP-M671 "Operation of (b) (4) " v8.0 effective April 1, 2018 (b) (4) is conducted by (b) (4) This operation takes place in the Class D corridor (b) (4) The (b) (4) and the (b) (4) product in the (b) (4) tank are placed in the (b) (4) corridor and the end of the (b) (4) connected to the (b) (4) (b) (4) is (b) (4) between the corridor and the Class C (b) (4) room.

The (b) (4) is tested for integrity before and after use using a visual leak test as per SOP-M671. I reviewed documentation provided by the (b) (4) vendor (b) (4) regarding the appropriate procedures for integrity testing of the (b) (4) The vendor recommendations indicate that the (b) (4) can be tested post-use using a visual leakage test. The inspection team (RC and MD) inspected the (b) (4) integrity testing (b) (4) IT) during the mock (b) (4) conducted on August 9, 2018. The (b) (4) IT (b) (4) is conducted by (b) (4) to the (b) (4) and looking for (b) (4) .

<u>Inspector Comment</u>: During the (b) (4) IT the inspection team noticed that it is difficult to assess whether there are (b) (4) because the goggles of the operator had condensation in them. The operator ((b) (6)) indicated that a failed (b) (4) IT occurs if (b) (4) We could not get confirmation from the vendor that this is correct, however this was not an observation because (b) (4) may be indicative of (b) (4) (b) (4) The inspection team indicated throughout the inspection that the visual leak test is subjective and prone to data integrity issues. In addition, one of the CAPAs for deviation 18-053U indicated that equipment to conduct the (b) (4) IT had been purchased. Lack of (b) (4) integrity testing was one of the elements included in the data integrity breach and there is no assurance that all lots prior to the detection of the data integrity breach were adequately tested for (b) (4) integrity. <u>This resulted in FDA-483 observation 2.</u>

<u>Hold times</u>
(*This section was written by RC*)
The original (b) (4) did not included information on in-process holds and an information request was submitted asking for it. At the time of the inspection, the firm was conducting the first of three in-process hold validation studies at scale.

<u>No observations were made.</u>

Gowning & Qualifications
(*This section was written by RC*)
Prior to the facility tours, we read and understood the applicable SOP for gowning as follows:

- SOP-0077 "Gowning for entry into Grade C manufacturing areas" v5.0 effective August 3, 2018
- SOP-0078 "Gowning for entry into Grade D manufacturing areas" v5.0 effective August 3, 2018

In general, gowning includes multiple layers of gowning with scrubs for Class D areas and aseptic gowning for Class C areas.

> *Inspector Comment: Gowning may be excessive for a drug substance manufacturing facility. This was not an observation.*

b. Contamination/Mix-up

Pest Control
(*This section was written by MD*)

On 4/24/2018, Mr. Michael Levitt, Head of Manufacturing, provided me (MD) with an overview of the firm's pest control program, which is governed by SOP -0034 (Version 4.0, effective 7/20/2018) "Insect and Pest control program". The firm's pest control is outsourced to a contractor, (b) (4) . (b) (4) conducts (b) (4) checks on the devices deployed in the facility and provides reports of the findings to the firm. According to the SOP, the pest control plan is reviewed by QA to summarize all the data obtained during the past (b) (4) to assess whether trends appear and to assess gaps and possible changes.

- For rodents: 13 Tin Cats were placed inside the facility and 10 larger rodent bait stations were placed in the exterior of the facility
- 8 insect light trap (ILT) equipped with UV tubes (DEIV) are placed near the doors to destroy flying insects.

I (MD) requested and conducted a cursory review of the 8/03/2018 pest control report on 8/6/2018. The report states that all the rodent traps and insect light traps did not have any activity. However, large number of insects were observed in the light traps on 8/6/2018 (3 days after the inspection by (b) (4) Mr. Michael Levitt explained that all the insect and rodent traps must reach a certain threshold (See Exhibit MD-2: Pest control threshold) to report as "with activity". For example, 10 large filth flies must be present in the light trap, for the (b) (4) to report as "with activity". Although (b) (4) reported "no activity", more than 10 flies were observed just 3 days after cleaning the light traps. This resulted in verbal observation MD-1

Multi-product Manufacturing & Area Changeover

(*This section was written by RC*)

The facility is currently (b) (4) manufacturing the (b) (4) intermediate and it has been doing so since April 2017. Area changeover was not covered during the current inspection.

Microbial Control

(*This section was written by RC*)

I reviewed the bioburden results for all the (b) (4) batches manufactured in the facility. Most of the samples show no or low bioburden levels, except for the following samples:

- (b) (4) prior to sanitization: TNTC
- (b) (4) 186 CFU/100 mL
- (b) (4) 517 CFU/100 mL
- (b) (4) : 120 CFU/100 mL
- (b) (4) TNTC
- (b) (4) : 103 CFU/100 mL
- (b) (4) 31 CFU/100 mL

Additional samples showed bioburden recovery from the (b) (4). No limits or acceptance criteria were established for samples other than the (b) (4) and the bioburden results were not trended. Bioburden recoveries were mostly identified as *Achromobacter* and *Burkholderia*, with one incident of *Methylobacterium*.

> *Inspector Comment: This was an FDA-483 observation (Observation 9: No procedure is in place for (b) (4) intermediate (b) (4) trending of results.) During the inspection interviews it was indicated that the facility had not implemented action limits for sampling points other than (b) (4) and the results from those samples were not reviewed or trended. The bioburden results show several samples taken from the (b) (4) (b) (4) with bioburden recovery (including TNTC), however the results from the (b) (4) from the (b) (4) did not recovered any bioburden. There is no in-proces (b) (4) step (b) (4) The firm discovered in January 2018 that manufacturing personnel in (b) (4) purification had been (b) (4) the bioburden samples prior to submitting them to QC to prevent in-process OOS (refer to FDA-483 Observation 1). This practice was conducted only for in-process samples but not for other samples that were "for information only" and whose results were not trended. Morris Rosenberg, CTO of the firm told us verbally that from interviews with the employees at the time of the DIB discovery, the firm knew that the data integrity breach had stopped prior to the manufacture of the PPQ batches, however we could not assess the extent of the data integrity breach in terms of when it occurred or what aspects it included because all the relevant information was protected under attorney/client privilege and the firm refused to share the information with the inspection team. The bioburden results from the (b) (4) indicate that the (b) (4) was heavily contaminated during batch (b) (4) however the (b) (4) sample taken*

from this contaminated (b) (4) resulted in 0 CFU/100 mL. The probability of having no bioburden in the (b) (4) sample from the contaminated (b) (4) is very low, even taking into consideration the (b) (4) washes. Therefore, there is a reasonable probability that the lack of bioburden in the (b) (4) was due to sample manipulation and that the data integrity breach impacted the PPQ batches. Due to the uncertainty of the time lapse of the data integrity breach, it is not possible to assess whether the microbial data from any of the batches prior to December 2017 can be trusted. The firm initiated (b) (4) batches (b) (4) since the personnel involved in the data integrity breach were removed. Out of these (b) (4) batches, 2 of them (b) (4) and (b) (4) were aborted due to contamination of the (b) (4) Bioreactor and another one (b) (4) was rejected due to poor growth in the bioreactor. This was not an FDA-483 observation because the firm was consistently manufacturing the (b) (4) intermediate prior to December 2017. After the inspection was closed, it has been noted that one vial thaw does not result in a single lot numbers, and that if one vial resulted in OOS viability, the firm may thaw a second vial keeping the same product batch number (Refer to Exhibit RC-20, vials 201 and 200 thawed for batch # (b) (4) Recent results from batches manufactured after the facility (b) (4) show inconsistent cell viability; we cannot discard that poor cell viability was an issue prior to the (b) (4) but was covered by the data integrity breach.

XIV. Laboratory control

QC Chemistry Laboratory

(This section was written by RS)

Mr. Mohit Gupta provided me a list of the testing equipment in the QC analytical laboratory (**Exhibit RS-9**). Mr. Gupta informed me that the HPLC System 8, Equipment ID # E00312 was used for the in-process check (IPC), release test and stability test of the (b) (4) drug substance for the PPQ batches. I verified that the HPLV System 8 was qualified. I also verified that the firm has performed PM according to SOP-0715 "Operation and Maintenance of Alliance HPLC in QC Laboratory" v1.0 eff 6/12/18.

I reviewed the SOP-0307 "UV-Size Exclusion HPLC Analysis" v2.0 eff 8/3/2018. I verified that the procedure included all the necessary components to complete the analysis including (but not limited to); sequence list, system suitability requirements, and data analysis. The method was developed by Immunomedics Inc. but validated by a contract lab, (b) (4) I reviewed the method validation report, Determination of Purity and Identity of (b) (4) by SE-HPLC with UV Detection, Document No. STC-SP023-R-01, dated 1/2/2017. I verified that the method was validated for its intended purpose for determining the purity and identity of (b) (4)

I randomly selected to inspect QC assay results for (b) (4) batch ID # (b) (4) (lot (b) (4) I found that the sample was analyzed by Mr. (b) (6) (b) (6) Supervisor QC. In the QC lab, I observed that the firm uses Empower 3 Software that was validated to comply with 21CFR Part 11. I verified that the system has role based access

and requires unique user ID and password for the access. I requested Mr. (b) (6) to open and print the report for (b) (4) (lot (b) (4) I confirmed that the audit trail was active during the analysis of (b) (4). I reviewed the sequence list and data set. I did not find any issues with the report.

I reviewed the QC Samples Submission Log and verified that the sample for (b) (4) (lot (b) (4) was submitted to QC lab on 10/2/2017. I reviewed the BU/TS Reference, Sample and Standard Preparation Form (Appendix D, SOP # Q707 v17 eff 10/20/2017) to verify the lot numbers and expiry dates for reagents and standards used for the analysis of (b) (4) drug substance batch ID # (b) (4) I found the information appeared to be adequate and no issues noted.

I found that the firm uses same method for stability test. Mr. Ed Rossi, VP Process and Manufacturing Sciences informed me that the forced degradation study for (b) (4) drug substance was carried out by (b) (4) Mr. Rossi shared a report from (b) (4) Forced Degradation Screening Study, dated 7/5/2017. I reviewed the report and verified that it had all the necessary components required of a stability indicating method.

(This section was written by GB)
An assessment was made of the laboratory tests performed, the personnel involved, and the equipment used, throughout the production process of (b) (4) I toured the Quality Control laboratories and observed several assays being performed, including those for:

- Purity and impurities by CE-SDS (SOP-0330): Observed sample preparation and reviewed the generated data.
- (b) (4) Assay (SOP-0480): Observed sample preparation and reviewed the generated data.
- Titer by HPLC (SOP-0479): Observed sample preparation during personnel training,

While observing the performance of each assay, it was noted that all operators had an SOP to the appropriate page. All pipettes, equipment, and other critical components of the assay had identification number and their calibration schedule and results are tracked. (b) (4) used in the assay had stickers affixed containing type of (b) (4) made on date, expiration date, preparer and were all within their expiry. The laboratories themselves were neat and clean. Laboratory notebooks were readily available, well organized, and kept in place. Logbooks for all instruments were obtained and maintenance and qualification schedules were verified. Operators (when not involved in assessing samples) were queried regarding their implementation of the assay. The data reports were reviewed for each of the assays performed and all the results met their specifications of the samples tested.

During the (b) (4) assay, information regarding the (b) (4) used in the assay was requested. Ed Rossi, VP Process Sciences, described that the (b) (4) are purchased from ATCC as needed. The (b) (4) are cultured for up to (b) (4) passages and then discarded. Each

purchased lot are tracked and can be traced to the assay performed and the (b) (4) lot tested. The quality assurance of the (b) (4) are based on the CofA of ATCC, from information in the literature, and studies performed during the development (b) (4) at Immunomedics.

Information was also requested regarding the (b) (4) used during the identity testing of (b) (4) using SEC assay. The (b) (4) is a (b) (4) that bind specifically to (b) (4) and not to other molecules at Immunomedics. The qualification of the (b) (4) (b) (4) is currently ongoing and will be submitted to the (b) (4) in September 2018. Data provided for review were:

- SDS-PAGE of (b) (4) showing the its purity
- ELISA binding assay confirming its binding to only (b) (4) and to the (b) (4) other molecules.
- SEC data showing that shift seen when (b) (4) binds to (b) (4)

During the CE-SDS analysis, it was noted that the reference standard sample information during sample preparation was not entered correctly on FRM-0008. Upon request of the CofA of the reference standard, the correct information was entered and the incorrect was crossed-out, dated and initialed. In addition, during sample preparation, a (b) (4) aliquot of (b) (4) was made. This (b) (4) aliquot was placed in a (b) (4) which was not labeled. Futhermore, the SOP did not specify the amount of time the samples can stay at room temperature before running using the Maurice system. The analyst, (b) (6) informed me that samples could be held for up to (b) (4) at room temperature and there is assay validation data supporting it. However, the system validation report STC-SP011-R-01 did not have any stability data supporting leaving the samples at room temperature for up to (b) (4) (b) (6) Senior Manager of Quality Control, agreed to update and clarify the SOP.

This was a verbal observation communicated to the firm during the inspection for the lack of following SOP-0330 (Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS)).

Microbiology Laboratory

(*This section was written by MD*)

The QC microbiology laboratory performs bioburden and endotoxin testing of in-process samples, release samples and (b) (4) samples. In addition, QC microbiology lab performs environmental monitoring testing, documentation, and identity and method validation.

The two labs inspected were (b) (4) and (b) (4) and each room has (b) (4) laminar flow. Only the area under laminar flow is classified. Compendial organisms are stored (b) (4) at (b) (4) °C. BIs are stored at ambient temperature in the storage room. Bioburden plates are supplied ready to use and each lot and shipment is tested for sterility and growth promotion. The SOP Q621 "Suitability Test for media" (revision 21, effective 10/31/2016) describes the growth promotion and sterility tests for confirming the suitability of the media for microbiological use. I reviewed a recent (10/3/2018) growth promotion and sterility testing report. All the results met the

performance specifications. Although the SOP does not specify the sample storage time, (b) (6) (b) (6) Head of Microbiology stated that the samples may be stored up to (b) (4) prior to Bioburden and endotoxin testing. I (MD) recommended that they update the SOP to include sample storage conditions prior to testing.

> *Inspector's comment: I toured each of the individual laboratories and checked reagents/plates expiration date and storage conditions and incubator temperature. In addition, I observed the bioburden (b) (4) test for one of the in-process samples in the (b) (4) lab and I observed endotoxin testing for (b) (4) by gel clot assay in the (b) (4) lab. The bioburden testing and growth promotion studies are performed in the same BSC and incubated in the same incubators on different shelves. This resulted in verbal observation 2.*

I reviewed bioburden SOP Q601 and qualification for all in-process steps and release. All the samples including (b) (4) in-process and release is tested by (b) (4) method. In addition, I reviewed the SOP Q625 for Quantitation of Endotoxin by Gel-clot method.

I reviewed sample submission and recording procedures. The samples are submitted to QC as per SOP-0197, which describe the procedure for submission and recording of samples to QC analytical and Microbiology departments for testing. This SOP describes the information that needs to be recorded on the sample container and the samples must be accompanied by Material Specification Sheet (MSS).

OOS Investigations
(*This section was written by RC*)
I reviewed SOP-0162 "Out of Specification Investigations" v4.0 effective August 3, 2018. The SOP is internally inconsistent, for example the definition of "retesting" in page 6 indicates that retesting should only occur when there is a scientific rationale that potentially refutes the original result. However, page 7 indicates that "if the company believes there is possibility the laboratory test did have error, and the error was undetected, then the company may wish to perform a retest." *This was an FDA-483 observation (Observation 3: Retesting procedure for the (b) (4) (b) (4) intermediate is inadequate.)*

(*This section was written by GB*)
The overall method for dealing with OOS results (SOP-0162, Out of Specification Investigations) was requested for review. This SOP deals with Immunomedics lab generated out-of-spec results, regardless of the assay or the process stage. The investigation initiated per this SOP is immediately. However, a completion date and the ability of an extension is not indicated. The procedure does include description on the approval and closure of the investigation. The SOP is appropriate for its intended purpose in detailing the extent of the investigation required when spurious results are obtained, and quality oversight of the investigative results and any subsequent decisions. The event owner and QA conduct an assessment to decide if the event is escalated to a deviation as per SOP-0152 "Deviation Investigation", All impacted batches are

listed, a product impact justification is provided, material that needs to be segregated is identified, and recurrence of the issue are investigated.

The SOP-0162, lacks a clear time line for initiation, closing, and re-opening, and is inadequate. This was verbally communicated to Immunomedics. The lack of a clear time line for initiation, closing, and re-opening of OOS investigations are inadequate. In addition, there is a statement for retesting samples that is not clear which reads; "if the company believes there is a possibility the laboratory test did have error, and the error was undetected, then the company may wish to perform a retest." Immunomedics agree and initiated a document change order (# CDD-000464) on 8-13-2018 to clarify the retesting and to include a closing timeline.

The following OOS specific to the CE-SDS assay were reviewed:

- OOS 18-014: Samples tested by CE-SDS, cIEF, and IEF were not properly documented. The investigation determine that the analyst failed to request the appropriate forms to document the samples used. The data generated could not be analyzed. The root cause was determined to be human error and not following SOPs. Further investigation determined that this was not an OOS but rather an invalid assay and should have proceeded with SOP-0640 (Invalid Assay Procedure) since no data were generated. The OOS investigation was performed appropriately.
- OOS 18-004: Samples tested by CE-SDS were not properly prepared. The assay results did not visually comparable to the representative electropherogram. The investigation determine that the analyst inadvertently switched the samples with (b) (4) causing the samples to be too diluted. The root cause was determined to be human error and not following SOP. The samples were successfully re-tested and all system suitability and results were as expected. Further investigation determined that this was not a OOS but rather an invalid assay and should have proceeded with SOP-0640 (Invalid Assay Procedure). The OOS investigation was performed appropriately.
- OOS 17-015: Anomalous peaks observed in various injection using CE-SDS. Assay suitability was not met. The anomalous peak was also observed in the blank injection. The investigation determined that the root cause of the anomalous peak was due to a malfunctioning deuterium lamp. The corrective action was to replace the deuterium lamp. The OOS investigation was performed appropriately.
- OOS 17-008: Incorrect method use to run CE-SDS assay. The assay results did not meet system suitability criteria. The investigation determine that the analyst use the wrong method from the drop-down menu. The root cause was determined to be human error and unfamiliarity with the new SOP. The samples were successfully re-tested and all system suitability and results were as expected. The OOS investigation was performed appropriately.

- OOS 17-012 and 18-007: System suitability for the CE-SDS assay were not met. The assay results using the reference standard did not meet system suitability criteria. The investigation could not determine a root cause but speculated that it could have been a (b) (4) malfunction. The samples were successfully re-tested and all system suitability and results were as expected. The OOS investigation was performed appropriately.
- OOS 18-005: System suitability for the CE-SDS assay were not met. During the run, delayed peaks and current fluctuations were observed. The analyst, at the end of the run saw the presence of a white substance on the (b) (4) The investigation determined the root cause to be an equipment failure. The OOS investigation was performed appropriately.

Verbal observation was communicated to Immunomedics for the lack of following SOP-0330 (Capillary Electrophoresis Sodium Dodecyl Sulfate (CE-SDS)). See section QC Chemistry Laboratory above for more detail.

Reference Standards
(*This section was written by GB*)
SOP-0188, "Reference Standard Program", describe the procedure for the manufacture, qualification, control, storage and use of the reference standard prepared in house or procured commercially. It describes the types and uses, how a in-house primary and the working reference standard is prepared, the analysis of the reference standard, the characterization testing, the storage, stability studies, the qualification protocol, the requalification, and the monitoring of the reference standard. Initial requalification dates are (b) (4) for the (b) (4)
Stability is monitored and measured by Immunomedics. The stability testing program is conducted per SOP-0665, which dictates batch selection, storage conditions, validated analytical methods used, and acceptance criteria. The SOP was reviewed in its entirety and appeared to be comprehensive and appropriate. Training record of (b) (6) was requested to verify her training for SOP-0665 and confirm that she was trained.

No observations were made.

XV. Objectionable Conditions and Management's Response

Observation 1:

The quality control unit lacks authority to investigate critical deviations of approved procedures. Specifically, the discovery of a data integrity breach in February 2018 did not trigger a deviation. The scope of the data integrity breach included manipulation of bioburden samples, misrepresentation of the (b) (4) integrity test procedure in the batch record and backdating of batch records, including dates of analytical results.

Supporting Evidence and Relevance:
(*This section was written by RC*)
A data integrity breach (DIB) was discovered by the firm in January 2018. The inspection team had knowledge of the DIB because of a communication provided by the firm to the FDA on (b) (4) (Attachment RC-1) indicating "*concern about bioburden sampling and data collection*". At the beginning of the inspection (August 7, 2018), I (RC) asked the firm's management, including Morris Rosenberg, CTO and Mujtaba Ali, head of Quality, to provide additional information regarding the DIB; they indicated that the DIB had been discovered by analyzing historical bioburden data in January 2018, and that the extent of the breach included (b) (4) of in-process bioburden samples prior to submission to QC and wrong procedure used for the (b) (4) integrity test. I asked again on August 9, 2018 whether the only two procedures impacted by the DIB were the two indicated above, and Morris Rosenberg indicated that there had been also backdating of the batch records. Therefore, to my knowledge, the DIB included:

1. (b) (4) of bioburden samples: in-process samples were (b) (4) by the manufacturing operators prior to be submitted to the QC lab for analysis. The (b) (4) was conducted to prevent potential bioburden non-conformances of the samples. Only in-process samples were (b) (4) as other bioburden samples did not trigger non-conformances.
2. The (b) (4) integrity test (b) (4) IT) pre- and post-use was conducted without (b) (4) (b) (4) . The test was recorded in the batch record as conducted as specified. The procedure for the (b) (4) IT is to fill the (b) (4) and then monitor visually for the presence of (b) (4) The actual test prior to the DIB discovery was conducted without (b) (4) therefore if the (b) (4) had holes, the test would not have detected any failure in the integrity of the (b) (4)
3. Backdating the batch records. Operations in the batch records were not recorded when they were conducted. Instead, the operators recorded the operations later using the date when the operation was supposed to be recorded. Record backdating included information regarding manufacturing operations and input of analytical data.

I asked the firm for the investigation/deviation and the firm indicated that no deviation had been initiated. Dr. Rosenberg indicated that as soon as they found out the problem, they had a meeting with the board of directors and it was decided that all investigations regarding the DIB would be conducted with a lawyer and were therefore protected under attorney/client privilege. Dr. Rosenberg indicated that they could not provide me any documentation regarding the DIB because the information was protected.

Because no deviation was initiated and the firm refused to provide documentation regarding the DIB, I was not able to assess the extent of the DIB, including:

1. The dates during which the DIB occurred. Dr. Rosenberg indicated that although the firm did not discover the DIB until 2018 (and the responsible parties were working in the firm until 2018) they knew from the interviews conducted by the lawyers that the DIB ended

prior to the PPQ campaign, which was initiated August 1, 2017. The firm refused to provide access to the interview transcripts or any other information regarding the DIB. Bioburden data suggest that in-process bioburden (b) (4) results were manipulated during the PPQ campaign (refer to observation 2). In addition, Deviation report 18-009U (Exhibit RC-1, Conclusion 4) initiated on January 18, 2018 indicates that "*false low results are likely present in the historical product-related bioburden tests conducted*". Process validation report (MF-0119-PV-01-R; Attachment RC-3) that is specific to the PPQ batches refers to the lack of (b) (4) integrity test.

2. The operations impacted by the DIB: The letter submitted by the firm to FDA on (b) (4) (Attachment RC-1), cites as the only operation impacted by the DIB the (b) (4) of bioburden samples but did not disclose the lack of (b) (4) integrity testing that was also discovered in February 2018 (Exhibit RC-17, Deviation 18-053U). An update on the investigation was submitted to the FDA on (b) (4) (Attachment RC-2) also failed to disclose the lack of (b) (4) integrity testing. To my knowledge, no additional letters were submitted to FDA regarding the lack of (b) (4) integrity testing and the only mention of the issue is a note at the end of the process validation report (MF-0119-PV-01-R, Attachment RC-3) included in the (b) (4) When I reviewed Deviation 18-053U (Exhibit RC-17) during the inspection, I asked Dr. Rosenberg whether that was part of the DIB and he confirmed it but did not disclose any additional operation impacted by the DIB. Later, I asked Dr. Rosenberg if there was any other operation impacted by the DIB and he added the backdating of the batch records. I asked him if he could put the operations impacted by the DIB in writing and he said that those were the only three operations (see bullets above).

In summary, no verbal information could be verified during the inspection because the firm refused to provide information as all the documentation was protected under attorney/client privilege. The firm was reluctant to provide any writing confirmation of the information provided verbally. We were not able to verify which operations were impacted by the DIB nor the batches impacted by the DIB. The inspection team asked the firm to provide a list of all Process(b)(4) lots manufactured up to the inspection date. The firm provided the Process(b)(4) lot History (Exhibit RC-21), however, we later found that the list was incomplete because not every vial thaw resulted in a unique lot number, underestimating the rate of successful batches (for example, vial 201 was out of specification for cell viability, the culture was discarded and vial 202 was thawed; both vials thaws had the same lot number resulting in an underestimation of failed batches; Exhibit RC-20).

Management's Response:
(*This section was written by RC*)
I had multiple conversations with Dr. Rosenberg regarding the assessment of the DIB. I indicated that without any documentation, I could not assess the impact of the DIB.

On August 9, 2018 Dr. Rosenberg handed me a document and indicated that it was the information provided to the lawyers. However, the document was dated August 7, 2018 and was a written version of the verbal information already communicated. I indicated that to Dr. Rosenberg and asked him if I could keep a copy of the document. Dr. Rosenberg indicated that he preferred to keep the copy.

The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 2:

There is no assurance that samples and batch records from the (b) (4) intermediate process validation and commercial batches manufactured prior to February 2018 were not impacted by the data integrity breach. Interviews by Immunomedics to personnel involved in the event were conducted under attorney/client privilege and no additional documentation is available, therefore no assessment could be made during the prelicense inspection in support of (b) (4)

Supporting Evidence and Relevance:

(*This section was written by RC*)

During the pre-license inspection, the inspection team tried to assess the scope of the DIB that was discovered in January 2018. As indicated above, the firm refused to provide documentation related to their investigation of the event because it was protected. Consequently, there is no assurance that the DIB did not impact the PPQ or commercial batches or that the DIB was resolved. The DIB included backdating of the batch records, false information in the batch record regarding the (b) (4) integrity test, and (b) (4) of bioburden samples prior to handle them to the QC lab.

Dr. Rosenberg indicated that any issues related to the DIB has stopped prior to the PPQ campaign but we could not verify his claim. However, the following data suggests that the DIB was ongoing until its discovery in January 2018:

1. Review of historical bioburden data (Exhibit RC-2) shows that for multiple samples, bioburden was recovered from the (b) (4) but no bioburden was recovered from the in-process (b) (4) For example, during manufacturing of batch (b) (4) (b) (4) a sample collected on October 30, 2017 from the (b) (4) (b) (4) resulted in high bioburden recovery (TNTC), however, the (b) (4) collected from the same (b) (4) resulted in 0 CFU/100 mL. No in-process (b) (4) is conducted between the (b) (4) and the (b) (4) collection. The historical data show that prior to (b) (4) batch, bioburden had been recovered consistently from the (b) (4), but no bioburden was even recovered from the (b) (4) in the applicable batches, for example:

a. (b) (4) sample collected on October 3, 2017: (b) (4) bioburden was 35 CFU/100 mL; (b) (4) collected the same day did not recover bioburden
b. (b) (4) sample collected on October 10, 2017: (b) (4) bioburden was 186 CFU/100 mL; (b) (4) collected the same day did not recover bioburden
c. (b) (4) sample collected on October 17, 2017: (b) (4) bioburden was 120 CFU/100 mL; (b) (4) collected the same day did not recover bioburden
d. (b) (4) sample collected on October 24, 2017: (b) (4) bioburden was 29 CFU/100 mL; (b) (4) collected the same day did not recover bioburden
e. (b) (4) sample collected on October 31, 2017: (b) (4) bioburden was TNTC; (b) (4) collected the same day did not recovered bioburden
f. Post-(b) (4) sample collected on November 28, 2017: (b) (4) bioburden was 6 CFU/100 mL; (b) (4) collected the same day did not recover bioburden
g. Post-(b) (4) sample collected on December 2, 2017: (b) (4) bioburden was 103 CFU/100 mL; (b) (4) collected the same day did not recover bioburden
h. Post-(b) (4) sample collected on December 12, 2018: (b) (4) bioburden was 38 CFU/100 mL; (b) (4) collected the same day did not recover bioburden

The data presented above does not include bioburden recovered from the (b) (4) prior to sanitization or bioburden recovered from the (b) (4) because bioburden from those steps is expected to lower considerably after sanitization. When I discuss the bioburden results with Edmund Rossi, VP Process and Manufacturing Sciences he indicated that the bioburden from the (b) (4) did not show in the (b) (4) because It was eliminated during the (b) (4) washes. Although reduction in the bioburden recovered from the (b) (4) is expected due during the (b) (4) wash process, the data above show that bioburden was constantly present in the (b) (4) therefore it was not completely removed during the washes and should have been recovered from the (b) (4) However, bioburden was not recovered from the (b) (4) samples.

2. A similar pattern is found from samples collected from another (b) (4) For example, (b) (4) sample collected on October 12, 2017: (b) (4) bioburden was 517 CFU/100 mL; (b) (4) collected the same day did not recover bioburden.

3. Deviation report 18-009U (Exhibit RC-1, Conclusion 4) initiated on January 18, 2018 indicates that "*false low results are likely present in the historical product-related bioburden tests conducted.*" There is no mention of false low results impacting only batches prior to the PPQ campaign in August 2017.
4. It is not clear why if the DIB was conducted to avoid non-conformance results, the operators would have stopped manipulating the samples immediately prior to the PPQ campaign. In fact, the historical bioburden results show some bioburden recovery from in-process samples of clinical batches (samples taken in June 2017) but all in-process bioburden samples collected during the PPQ campaign and until December 2017 have bioburden results ≤ 1 CFU/100 mL, consistent with sample manipulation during testing.
5. Process validation report (MF-0119-PV-01-R; Attachment RC-3) specific to the PPQ batches, includes information regarding the lack of (b) (4) integrity test

In summary, the information provided above suggests that the DIB was ongoing during the PPQ campaign and possibly during the commercial campaign. However, the firm's management (Attachment RC-1) and Dr. Rosenberg indicated several times throughout the course of the inspection that data integrity had stopped before the PPQ campaign. There is no information to support this claim. In addition, there is no information to assess if the DIB involved additional data manipulation or batch record falsification as the firm refused to provide documentation regarding the DIB. The inspection team was not able to verify the verbal information provided by the firm's management.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 3:
Retesting procedure for the (b) (4) intermediate is inadequate. Specifically:

a. SOP-0162 "Out of Specification Investigations" indicates that "*if the company believes there is possibility the laboratory test did have error, and the error was undetected, then the company may wish to perform a retest.*" OOS Investigation report 18-001 shows that routine retesting was performed due to an initial OOS result.
b. SOP-0162 allows for retesting of microbiology samples. An OOS result for the (b) (4) in-process bioburden sample was recorded on 12/23/2017. A retest was conducted using a retain sample on 1/5/2018 and the results on 1/10/2018 were OOS (OOS 18-001). Initiation of a non-conformance report (NCR 18-009U) was delayed until the results of the retest were reported on 1/10/2018.

Supporting Evidence and Relevance:
(*This section was written by RC*)
Out-of-Specifications SOP-0162 (Exhibit RC-3) indicates that the company may wish to decide to retest any sample in the absence of a laboratory error. Retesting of a sample after an OOS result is inadequate unless there is an obviously assignable root cause. Otherwise, any OOS could be invalidated if after retesting, the second sample is within specification. In addition, microbiological samples that contain living organism should not be retested because samples after long-term storage are not representative of the original sample.

On August 13, 2018, the inspection team (RC and GB) interviewed Dough Stevens, Director of QC to address the statement in the OOS SOP. Dr. Stevens indicated that the firm never retested OOS samples without a documented lab error, with the only exception of samples with impossible results (results that do not make sense, for example a yield of 300 %) and reiterated that the firm never retested any sample without an assignable cause. However, a bioburden sample tested on December 18, 2017 resulted in an OOS on December 23, 2017. OOS investigation report 18-001 (Exhibit RC-4), initiated on January 3, 2018, indicated no obvious laboratory error; however, the firm did not initiate a not-conformance report, but submitted the sample for retesting on January 5, 2018. Eventually, one week after the results of the retest were obtained and were still OOS, non-conformance report NCR-0009U was initiated. The OOS investigation report reads in page 2: "*Due to the OOS results, a retest was performed using the retain sample provided by manufacturing*", indicating that retests are conducted routinely when a OOS is obtained, what is consistent with SOP-0162 and contradicts the information provided by Dr. Stevens during the interview on August 13.

In addition, the retest was conducted for a bioburden sample that had been stored at 2 to 8ºC for (b) (4) and was not representative of the original sample.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 4:
The raw material sampling and testing program is inadequate. Specifically:

a. (b) (4) solution (b) (4) supplied by (b) (4) has never been sampled and there is no assurance that the manufacturer can consistently provide material meeting specifications. The solution is (b) (4) -sterilized from the vendor and is added unfiltered to the cell culture bioreactors. Deviations 18-081U and 18-163U were initiated due to contamination in the (b) (4) bioreactors. In both cases, probable root causes included the (b) (4) addition assembly (b) (4) . Testing of an unused (b) (4) bag in inventory also resulted in a positive sample.

b. Product-contact (b) (4) used during cell culture of the (b) (4) intermediate are not tested for bioburden.

Supporting Evidence and Relevance:
(*This section was written by RC*)
Observation 4.a
Immunomedics outsource most of the (b) (4) media, and solutions used to manufacture the (b) (4) intermediate to (b) (4) this includes the (b) (4) solution that is added directly to the cell culture media during (b) (4) and production stages.

Prior to February 2017, the firm obtained (b) (4) mL) from (b) (4) (Exhibit RC-5). The Certificate of Analysis (CoA) for the (b) (4) included a certificate of (b) (4) but the firm included the (b) (4) bioburden in the raw material testing sampling plan with specification of NMT (b) (4) CFU/10 mL). On October 11, 2013 the firm initiated a change control (Exhibit RC-6) to remove bioburden the testing of (b) (4) based on acceptable bioburden results in three batches. On February 21, 2017, the firm initiated another change control (Exhibit RC-7) for an (b) (4) ((b) (4) Solution, supplied by (b) (4) . The new (b) (4) was from a different supplier, therefore the risk assessment used to eliminate bioburden testing from the (b) (4) raw material was not applicable. However, the firm did not review the incoming raw material sampling plan and bioburden of the (b) (4) (b) (4) Solution from (b) (4) was never included in the sampling plan. The material specification sheet from (b) (4) only includes a review of the supplier CoA and visual inspection (Exhibit RC-8).

The following events link contaminations of the (b) (4) bioreactor to (b) (4)

- (b) (4) Bioreactor E00064 was contaminated on May 16, 2018 (Deviation 18-081U; Exhibit RC-9). Liquid and swabs samples were taken as part of the investigation and a sample from valve XV070004 (b) (4)) was positive.
- (b) (4) Bioreactor E00063 was contaminated on July 27, 2018 (Deviation 18-163U; Exhibit RC-10). Liquid and swabs samples were taken as part of the investigation and a microbial growth was observed in the (b) (4) sample.
- Microbial growth was observed from an (b) (4) bag from the same lot of the (b) (4) used for the manufacture of the contaminated lots (Exhibit RC-11).

A summary of samples that resulted in microbial growth after the bioreactor contamination is included in Exhibit RC-9 (attachment within the exhibit).

The information above indicates that the (b) (4) Solution is a probable root cause of the contamination of the two (b) (4) bioreactors occurred in 2018. The contamination could have been prevented if bioburden of the (b) (4) solution had been part of the raw material sampling plan.

(*This section was written by MD*)
Observation 4.b
The firm's (b) (4) are supplied to all (b) (4) rooms and bioreactors. The (b) (4) testing are governed by SOP Q823 "Identification test for (b) (4)

(b) (4) " (Revision 7.0, effective 5/13/2016). However, microbial testing is not carried out at the firm and the supplier specification does not include microbial testing. The (b) (4) are purchased from (b) (4) and supplier specifications include only identity specifications (Exhibit MD-1). Since (b) (4) contact the product in the (b) (4) bioreactors, all the raw materials including the (b) (4) used in the manufacture, needs to be tested for bioburden. Such testing need to be implemented to prevent future contamination events.

Management's Response:
When I (MD) requested the microbial testing for (b) (4) used in the facility, Mike Levitt, Head of Manufacture stated that (b) (4) are (b) (4) at the point of use and the (b) (4) is tested for (b) (4) integrity. Therefore, they do not perform microbial testing on (b) (4) I stated that, in addition to (b) (4) microbial testing of (b) (4) is required to reduce the contamination risk. The management agreed to perform microbial testing on (b) (4)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 5:
The firm lacks procedures for inventory audit trail and for tracking and reconciliation of raw materials used to manufacture the (b) (4) intermediate. Specifically:

a. The firm does not keep records tracing the use of raw material. Raw material reconciliation cannot be conducted as discarded raw materials are not documented. During the tour to the manufacturing facility on 8/6/2018, the inspection team observed a (b) (4) L container of (b) (4) in the loading dock for destruction. The material could not be traced.

b. Warehouse raw material inventory list is kept in an Excel Spreadsheet that lacks history traceability. During the tour of the warehouse on 8/6/2018 Warehouse inventory cannot be located using the Excel Spreadsheet. Specifically, (b) (4) (catalog # (b) (4), Lot # (b) (4) was present in the warehouse, however the location and inventory could not be provided.

c. The warehouse is not adequately mapped for inventory purposes with floor plans. Items stored on the floor have no assigned location. In addition, quarantine and released items on the floor are kept side-by-side without a system in place to prevent the use of quarantined raw material.

Supporting Evidence and Relevance:
(*This section was written by RC*)
The warehouse does not have a traceable inventory system. The only manner to track material is through the batch record (looking at every single batch record and recording the material used). In addition, for (b) (4) purification, the batch record only lists the number of containers used but does not specify the volume or mass used. Tracing the raw materials through the batch record defeats the purpose of being able to account for material in case of errors or inconsistencies in the batch record.

(*This section was written by GB*)
On 8/7/2018, en route to the current cell bank storage area, a barrel containing (b) (4) L of (b) (4) (b) (4) Cat # (b) (4)) with a quarantine label was observed at the loading dock of Building (b) (4) . Upon request, I was informed that the barrel was destined for destruction after it was brought from Building 410 for testing. To verify this information, proof of traceability was requested for this barrel. Immunomedics was unable to trace the whereabouts of this (b) (4) In addition, the warehouse in Building 410 inventory management is not adequate to trace (b) (4) raw materials.

Without the proper capabilities for tracking and tracing raw material, potential safety issues due to raw materials would be difficult to trace. Furthermore, the lack of properly mapping the warehouse material location has the potential of increasing the risk that the wrong or quarantine materials could be transferred and used in the manufacturing of (b) (4) further potentiating a safety issue.

Management's Response:
(*This section was written by GB and RC*)
The firm acknowledged that the inability to trace the raw material was a weakness and they indicated during the inspection that they were planning to implement Great Plains. In order to have some traceability they proposed to print a dated copy of the Excel Spreadsheet every morning to keep in their files (Exhibit RC-24). The inspection team did not comment about that. The firm indicated at the inspection close-out that they understood the seriousness of the observation, that they actively migrating the excel inventory list to a new digital system, and that they would respond to the FDA.

Observation 6:
Differential pressure between GMP areas of different area classification is not adequately maintained and monitored. Specifically,

a. Air pressure in the GMP areas is not adequately maintained. For example, differential pressure between Rooms (b) (4) (Class C (b) (4) suite (b) (4) and (b) (4) (Class D corridor) was out of action levels in 37 out of 40 measurements between July 24, 2018 and August 1, 2018.
b. Continuous monitoring of pressure in the GMP areas has been installed in July 2018 and is undergoing qualification, however not all adjacent rooms with different air classification are alarmed for low pressure differential. For example, differential pressure between the Rooms (b) (4) (Class C (b) (4) suite (b) (4) and (b) (4) (Class D corridor) is not alarmed.

Supporting Evidence and Relevance:
(*This section was written by RC*)
The facility has a design with a (b) (4) to lower the risk of microbial contamination. Areas with higher risk (open operations) or higher criticality (last steps of the purification process) have higher pressure to prevent ingress of microorganisms in those areas.

The facility did not have a continuous monitoring system for pressure, temperature and humidity prior to July 2018. Pressure was recorded manually (b) (4) during manufacturing operations and recorded. I reviewed the data logs for the pressure differential between July 24 and August 1, 2018; the dates were chosen randomly as the last five days with recorded data prior to the inspection. The pressure differential results were out of action levels in over 25% of the measurements. Differential pressure between the (b) (4) suite (b) (4) (Room (b) (4) Class C) and the clean corridor (Room (b) (4) Class D) were out of action limit in 92% of the measurements (37 out of 40; Exhibit RC-12). The firm did not initiate a deviation.

In July 2018, the firm installed a continuous monitoring system for pressure, temperature, and humidity. The system is currently under qualification; however; not all adjacent rooms that have different classification are alarmed, including the (b) (4) suite (b) (4) (Room (b) (4) Class C) and the clean corridor (Room (b) (4) Class D; Exhibit RC-13). It is not clear whether the lack of alarm between these two rooms is related to their high number of excursions in the differential pressure.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 7:
The design of the facility is inadequate in that no drains are present in the purification rooms. In addition, there is no SOP for liquid containment and disposal after a catastrophic spill. All process streams downstream the (b) (4) Bioreactor are held in disposable bags.

Supporting Evidence and Relevance:
(*This section was written by RC*)
The design of the facility does not include drains in any of the purification areas, although some of these areas have (b) (4) points of use. In addition, all the manufacturing steps during clarification, capture, and purifications are conducted in single-use bags of up to (b) (4) L. During the purification tour I asked (b) (6) head of (b) (4) manufacturing, whether the firm had an SOP for liquid containment and disposal after a catastrophic spill and he indicated that there was none. Lack of a containment SOP in the absence of drains could result in large areas of the facility covered by liquids in case of a catastrophic spill and in a potential viral/microbial contamination.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 8:
There is no signed Quality Agreement between (b) (4) and Immunomedics Inc. (b) (4) is the supplier of cell culture media and all (b) (4) solutions (including (b) (4), and (b) (4) used for (b) (4) purification of the (b) (4) (b) (4) intermediate.

Supporting Evidence and Relevance:
(*This section was written by RC*)
The firm outsource most of the (b) (4) and solutions used to manufacture the (b) (4) intermediate from (b) (4) including (b) (4), cell culture media, solutions added to the media, (b) (4) solutions, and all (b) (4) for (b) (4) purification. Because many of the materials provided by (b) (4) are critical raw materials for the manufacture of the (b) (4) intermediate, failure on appropriate manufacture, analytical procedures, storage, and shipping may result in impact to the (b) (4) intermediate product quality. It is therefore necessary that the firm has an active oversight of the supplier and has established procedures to address the responsibilities of each party.

During the inspection, I was informed that there was a Quality Agreement between the two companies; however, when I asked to review the agreement, I was handed a copy of a final draft of the agreement (Exhibit RC-14). The draft did not have a date nor signatures from any of the involved parties (Immunomedics or (b) (4) The firm indicated that they had an audit program in place, however the firm does not have a clear understanding of the raw materials supplier by (b) (4) For example, on August 6, 2018 during the tour I asked the firm whether the (b) (4) supplied by (b) (4) was (b) (4) or (b) (4) (the label of the (b) (4) indicates that it is (b) (4) Quality (b) (4) tested as per USP Sterile (b) (4) It took the firm three days to respond to my question because they did not know the type of (b) (4) that the supplier was providing. On August 9, 2018 the firm indicated that they had called (b) (4) to question them about the (b) (4) and provided me with a presentation (Exhibit RC-15) that indicates that the (b) (4) is (b) (4) However, deviation 18-015 was initiated on February 15, 2018 because personnel were incorrectly referring to USP sterile packaged (b) (4) as (b) (4) In summary, it is not clear whether the company knows if they are using (b) (4) or (b) (4)

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 9:
No procedure is in place for (b) (4) intermediate (b) (4) trending of results. During the process validation (PPQ) campaign, bioburden levels in the (b) (4) were not trended and

inadequately high bioburden levels were not investigated. Low level bioburden (29 to 186 CFU/100 mL) was observed in the (b) (4) after sanitization in PPQ batches (b) (4) and the bioburden level increased to too numerous to count in PPQ batch (b) (4) No deviation was initiated.

Supporting Evidence and Relevance:
(*This section was written by RC*)
The firm has collected microbiology samples at several points of the manufacturing process since February 2017 (prior to the PPQ campaign). The firm has established in-process specifications for the in-process samples, such as (b) (4) The rest of the samples, including samples before and after sanitization of (b) (4) and samples from the load were for information only and did not have action or alert limits. On august 7, 2018, I requested a list of bioburden results for all samples collected during manufacturing (Exhibit RC-2) and a similar list covering the PPQ and commercial batches was also provided as part of the investigation of NCR18-009U (Exhibit RC-1; Exhibit RC-16). Both lists show an upwards trend of the bioburden in the (b) (4) after sanitization (PPQ batches, bioburden results in CFU/100 mL: 1, 35, 186, 120, 29, TNTC). I indicated that the data showed that the sanitization of the (b) (4) may be inadequate and had contaminated the (b) (4) I asked for the deviation resulting from the contamination event. However, no deviation had been initiated due to the upward trend of bioburden data or to the contamination of the (b) (4) I interviewed Dr. Edmund Rossi, VP Process and Manufacturing Sciences, regarding this event and he indicated that no deviation had been initiated because the data was not trended. Then, he indicated that, except for in-process samples, the bioburden data was not reviewed by QA, and that the microbiology department recorded the data and sent all the organisms for identification, but nobody did anything with the data. This statement was contradicted later by the Quality team, who indicated that all the bioburden data was reviewed.

In summary, the firm collected bioburden data but ignored the data and did not trend or use them. In the case of the (b) (4) lack of data trending resulted in contamination of the (b) (4) Because the low-level bioburden data was ignored by the firm, the firm did not realize that sanitization of the (b) (4) was not adequate, and this eventually resulted in a contamination of the (b) (4) It is not clear what the bioburden levels were in the in-process (b) (4) from the (b) (4) step because those samples were manipulated by (b) (4) them prior to sending them to the QC lab.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 10:
Deviation investigations and CAPA implementations are inadequate. For example, Deviation 18-053U was initiated after an internal audit concluded that the (b) (4) had not been adequately tested for integrity pre- or post- (b) (4) The deviation included the following deficiencies:

a. Lot number in the deviation form indicates "multiple lots" without specifying the potential lots impacted.

b. Product impact assessment includes the conclusion of a clinical Health Hazard Assessment, but no risk assessment on the presence of (b) (4) in the product is documented.

c. The CAPA section indicates that remediation included "… purchasing additional test equipment to evaluate the (b) (4) pre & post its use." However, at the date of the inspection no additional equipment has been purchased and no information about the CAPA is documented in the deviation.

Supporting Evidence and Relevance:
(*This section was written by RC*)
The review of the deviations indicates that the Quality Unit, not only fails to initiate deviations (refer to observations 1 and 9), but in addition the deviations are not conducted, documented, investigated and corrected properly. One example is NCR 18-053U (Exhibit RC-17); the deviation was initiated after a data integrity breach revealed that the (b) (4) integrity test had not been conducted. The deviation report lacks specificity and the information it is not accurate. The deviation (non-conformance report) was initiated on April 9, 2018 and closed the same day. Signature authority for approval included 1) Initiator: Anne Kelly, Sr. VP quality; 2) Department manager: Anne Kelly, Sr. VP quality; 3) Regulatory Affairs: (b) (6), 4) Quality Assurance: Anne Kelly, Sr. VP quality. Signature authority for closure was also Anne Kelly, Sr. VP quality. It is noted that the deviation was closed on April 9, before Regulatory Affairs signed on the deviation on April 10. The deviation report indicates that the date of the event was February 2018, however February 2018 was the date in which the event was discovered, and the event was ongoing for an undetermined period. Lots impacted by the deviation are not listed, instead there is a vague statement indicating "multiple lots", but no information on which lots or potential lots were impacted by the event. The event description indicates that the practice of not (b) (4) was widespread "*the practice during* (b) (4) *of* (b) (4) *in manufacturing was to visually observe for* (b) (4) *in the* (b) (4) *pre- and post-use without* (b) (4) Therefore, it appears that all lots prior to the discovery of the event were impacted.

The deviation report includes a Product Impact section (Section IV), however, the information included in this section is unrelated to product impact due to lack of (b) (4) integrity testing. The section refers to a Health Hazard Evaluation submitted to (b) (4) on March 1st (HHE, Attachment RC-4), 2018. The HHE was conducted to address a "*bioburden sampling procedure for the* (b) (4) *intermediate, that was not specified in out Master Batch Record*" and addressed patient exposure to pyrogens due to a hypothetical microbial contamination. No information regarding (b) (4) contamination is included in the HHE. In addition. one of the assumptions in the HHE to assess patient hazard is that "*All purification and sterilization steps and testing to include bioburden,* (b) (4) *and endotoxin reduction and sterile* (b) (4) *subsequent to the purification step were in full compliance.*" This assumption is incorrect as the (b) (4) were not tested for integrity.

The deviation report includes a CAPA section (Section V) that indicates that the event was remediated by February 2018 by "*purchasing additional test equipment to evaluate the* (b) (4) *pre- and post- use.*" However, the firm has not purchase any additional equipment to evaluate the (b) (4) integrity up to the time of the inspection closure. No CAPA documentation or tracking number are included in the deviation report.

On August 4th, 2018 an addendum was added to the deviation report. The addendum appears to be a summary update on the CAPAs for the deviation; however, no CAPA tracking number is included and the information. The person that prepared the addendum is not included, just an illegible signature at the end of it.

In summary, the deviation was opened and closed on the same day two months after the event was discovered. Most of the relevant information that should be part of the deviation is missing, including lots impacted, and impact to product quality. In addition, information related to corrective actions is incorrect.

The example above is one of many deviations that were inadequate. Most of the deviations forms are not filled, but they refer to an attachment that may be provided with the deviation. The attachments cannot be tracked and they are usually not signed. As examples, refer to deviation 18-116U (Exhibit RC-18) opened on June 20, 2018; all sections in this deviation are left blank and refer to attachment 1 from June 20th, 2018; however, the attachment provided with the deviation is dated August 3, 2018. An additional page provided with the deviation indicates that the initial version dated June 20, 2018 is not available.

Deviation 18-050U (Exhibit RC-19) was initiated on April 9, 2018; all sections in this deviation are left blank except for the final justification. The blank sections refer to attachment form dated June 21, 2018; however, the attachment provided with the deviation is dated July 10, 2018. It is noted that the information in the attachment indicates that cell expansion for lot (b) (4) was terminated and a second vial thaw was performed for the same lot number. The attachment indicates that recovery and expansion were also inconsistent following the second vial expansion. The deviation unveiled the following:

- The firm used the same lot number ((b) (4) for two independent cell vials (vials 200 and 201; Exhibit RC-20),
- A different deviation (18-081U; Exhibit RC-9) was initiated due to a contamination of the (b) (4) Bioreactor for the same lot ((b) (4)
- Inconsistent cell growth performance is a recurrent event; batch (b) (4) (b) (4) was stopped due to a cell growth issue. In addition, the second vial thawed for (b) (4) had lower than expected viability.

The fact that the two vial thaws (vial 200 and 201) were assigned the same lot number (b) (4) underestimates the number of failed recent manufacturing runs. The firm provided a Process Lot history (Exhibit RC-21) that shows that after (b) (4) (b) (4) in March 2018, (b) (4) batches were initiated, (b) (4) of them failed due to cell culture contamination and (b) (4) failed due to cell viability issues (60% failure rate); however, the discarded

expansion culture initiated from vial 200 due to poor cell viability was not included in the list. **The number of failed lots relative to started cultures (including the two cultures from lot (b) (4) is (b) (4) %; from these lots, (b) (4) % (b) (4) out of (b) (4) failed due to contamination of the (b) (4) Bioreactor and (b) (4) % (b) (4) out of (b) (4) failed due to poor cell viability. In addition, the culture initiated from vial 200 although was within cell viability specifications resulted in lower growth than expected viability (Deviation 18-050U; Exhibit RC-019, page 7); therefore, (b) (4) % of the vials thawed after (b) (4) resulted in poor cell viability/growth:**

- **Vial 201 (lot (b) (4) poor growth and culture discarded (Deviation 18-050U; Exhibit RC-019)**
- **Vial 200 (b) (4) note that this is the same lot): the viability of this vial was lower than previous runs but within AC (Deviation 18-050U; Exhibit RC-019)** (in addition, bioreactor contamination; culture discarded (Deviation 18-081U)
- Vial 199 (b) (4) ; going through purification at the time of the inspection
- (b) (4) **from vial 199 (b) (4) : poor growth and culture discarded (No deviation initiated)**
- Vial 197 (b) (4) ; pending purification at the time of the inspection
- (b) (4) from vial 197 (b) (4) ; bioreactor contamination; culture discarded (Deviation 18-163U)
- (b) (4) from vial 197 (b) (4) ; (b) (4) expansion in progress; unknown
- Vial 184 (b) (4) expansion in progress; unknown.

Cell viability from cultures prior to the facility (b) (4) is questionable due to lack of transparency regarding the data integrity breach; the percentage of failed lots cannot be traced because more than one vial may result in the same lot; in addition, a back-up culture is started from each vial, therefore failed vial thaws may have not been accounted for prior to the discovery of the DIB. Based on these rates, the firm does not appear to be able to consistently manufacture the (b) (4) intermediate. The inspection team was not aware of this information at the time of the inspection close-out.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA. Note that information regarding Deviation 18-050U was not communicated to the firm as the inspection team was not aware of the problem at the time.

Observation 11:

Deviation initiation and closing times are inadequate. Specifically:

a. SOP-0152 "Deviation handling" indicates that if the deviation cannot be completed by the assigned due date, a one-time extension can be requested to the QA unit. The following deviations were not closed by the due date and did not include an extension:
   i. 18-116U: deviation due date was 7/20/2018; deviation was open at the time of the inspection
   ii. 18-081U: deviation due date was 6/17/2018; deviation was open at the time of the inspection
   iii. 18-079U: deviation due date was 6/16/2018; deviation was closed on 8/3/2018
   iv. 18-050U: deviation due date was 5/9/2018; deviation was open at the time of the inspection
b. SOP-0152 "Deviation Handling" does not specify a time limit between time/discovery of event and deviation initiation. The following deviations were initiated more than one month after event discovery:
   i. 18-009U: investigation into bioburden OOS #18-001 for (b) (4) date of event was 1/10/2018, deviation was initiated on 3/27/2017.
   ii. 18-053U: (b) (4) related discrepancy; date of event was February 2018, deviation was initiated on 4/9/2017.

Supporting Evidence and Relevance:

(*This section was written by RC*)

Supporting evidence regarding time limits included in the SOP-0152 "Deviation handling" is included in Exhibit RC-22. Supporting evidence for deviations not closed on time are included in Exhibits RC-18 (Deviation 18-116U), Exhibit RC-9 (Deviation 18-081U), Exhibit RC-23 (Deviation 18-079U), Exhibit RC-1 (Deviation 18-009U), and Exhibit RC-17 (Deviation 18-053U). Note that Deviations are sometimes referred to as Non-conformance reports.

Management's Response:

(*This section was written by RC*)

The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 12:

Cleaning of downstream equipment, including (b) (4) and product-contact parts of the (b) (4) is not validated or verified. Non-conformance report 18-009 initiated due to a (b) (4) (b) (4) OOS bioburden sample includes as the primary root cause the (b) (4) contaminated during vendor (b) (4) testing.

Supporting Evidence and Relevance:

(*This section was written by RC*)

The firm does not have validated the cleaning of downstream equipment; cleaning verification is not conducted either. The firm's rationale was that cleaning validation or verification is not necessary because the facility is dedicated to (b) (4) intermediate. This is not sufficient because the cleaning protocol needs to be adequate to support microbial control of the product. The main root cause of a contamination (refer to Deviation 18-0009U, Exhibit RC-1) that resulted in an OOS and lot rejection was traced to a contaminated (b) (4) If the firm had had a validated cleaning procedure or had verified the sanitization of the (b) (4) prior to use, the OOS may have been prevented.

Management's Response:
(*This section was written by RC*)
The firm indicated at the inspection close-out that they understood the seriousness of the observation and they would respond to the FDA.

Observation 13:
The procedure to prevent contamination of the (b) (4) intermediate after (b) (4) is inadequate for a product stored 2 to 8ºC for up to (b) (4) Specifically, during a mock (b) (4) (b) (4) and dispensing of an (b) (4) intermediate surrogate conducted on August 9, 2018, the following was observed:

a. After (b) (4) the surrogate was transferred first to a single use (b) (4) L bag (SUB) and then from the SUB to (b) (4) The SUB was removed from its container and assembled in the Biologic Safety Cabinet (BSC) used for (b) (4) and dispensing. Multiple open-process manipulations were conducted to prepare the SUB, including (b) (4)

b. During the SUB preparation process, the end of the (b) (4) downstream the (b) (4) (b) (4) was observed to touch the operator's hands, the surfaces of the BSC, and the material placed inside the BSC.

c. Prior to filling the (b) (4) analytical samples were collected into (b) (4) The (b) (4) of the (b) (4) used to fill the (b) (4) and the (b) (4) (b) (4) are similar. In addition, the flow of the (b) (4) surrogate was not continuous and was difficult to control. As a result, the surrogate was spilled during the sampling process.

Supporting Evidence and Relevance:
(*This section was written by MD*)
The (b) (4) step, which includes (b) (4) are governed by SOP-0644 for the operation of (b) (4) (b) (4) and SOP-0059 for set up and use of the (b) (4) The (b) (4) (b) (4) step of the manufacturing is carried out in the BSC. Since the (b) (4) intermediate is stored at 2 to 8ºC for up to (b) (4), the contamination risk is high. For such high-risk drug substance intermediate, procedures to prevent contamination is inadequate. This open process is inefficient as it includes unnecessary steps such as (b) (4) In addition, the assembly of the SUB was

a challenge to the operator as it involves (b) (4) (b) (4) to the SUB (MD-2). These manipulations further increase the contamination risk as we witnessed the end of the (b) (4) downstream the (b) (4) touching the operator's hands, the surfaces of the BSC, and the material placed inside the BSC. The head of downstream manufacturing, (b) (6), head of downstream manufacturing who watched process with me (MD) and RC agreed with us. Although he has been on the job for 2 months, he stated that, this is the first time he has seen this process. This suggests that the lack of oversight from the management.

.

Management's Response:
RC and I (MD) communicated to the management that this process is inefficient and includes unnecessary steps. The management also agreed that the (b) (4) filling process is inefficient and stated that they will make the process more efficient by eliminating unnecessary steps.

XVI. General discussion with management
The following verbal observations/discussion items were communicated verbally to the firm during the inspection:

Verbal observations Written by RC:

RC-1: Deviations documentation is inadequate.
The deviation procedure SOP has a template to be filled when a deviation is documented. However, the only section of the template that is consistently filled is the title and deviation initiation. All information regarding description, product impact, and root cause investigation is left blank and it may be reference to an attachment. The dates or authors of the attachment are usually not traceable. Exhibits to support this deviation are included in the exhibits to 483-FDA observation 10.

RC-2: Environmental monitoring sampling is inadequate
The Environmental Monitoring program of the firm allows them to sanitize the area and then resample in case of an OOS. The resampling practice is inappropriate because it invalidates the first above-action-limit sample; in addition, since the resample is taken immediately after sanitization, the result would not be representative of the hygienic status of the area. This did not result in an FDA-483 observation because the initial results are documented in the EM result charts, the firm sanitizes the area after finding the initial excursion, lowering the risk to product contamination, and the firm has initiated a change control to initiate a deviation after the initial excursion.

Verbal observations Written by MD:

MD-1: Pest control system outsourced to (b) (4) and monitored by QA is inadequate. Although large number of inspects were observed (more than the threshold), (b) (4) reported no activity in insect traps.

This observation is an oversight by (b) (4) and QC. This did not result in an FDA-483 observation as there was no product impact. Thus, this observation was communicated as a verbal recommendation. I communicated to the firm that if there is a failure in the current pest control devices, the QC will not detect them. The firm agreed to monitor the pest control system managed by (b) (4) (See pest control section)

MD-2: Performing bioburden testing and growth promotion testing in the same BSC and, incubating the plates from bioburden assay and growth promotion studies in the same incubator increase the contamination risk of test samples.

Since, this observation does not impact the product quality, it was communicated as a verbal recommendation. The increased contamination risk of test samples may give rise false positives (See Microbiology Laboratory section).

XVII. Attachments

Attachment 1	Notice of Inspection FDA 482
Attachment 2	Inspectional Observation Form FDA 483
Attachment RC-1	Letter to (b) (4)
Attachment RC-2	Letter to (b) (4)
Attachment RC-3	Process Validation Report MF-0119-PV-R
Attachment RC-4	Health Hazard Evaluation, (b) (4)

XVIII. Exhibits

Exhibit 1	Individuals present at the opening of the inspection
Exhibit 2	Individuals present at the closing of the inspection
Exhibit 3	Organizational chart of Immunomedics

Exhibit RC-1	Non-Conformance Report 18-009U
Exhibit RC-2	Bioburden results of in-process samples
Exhibit RC-3	SOP-0162 v4.0 Eff August 3, 2018 "Out of Specification Investigations"
Exhibit RC-4	OOS Investigation Report 18-0001
Exhibit RC-5	(b) (4) mL
Exhibit RC-6	Change Control 13-521
Exhibit RC-7	Change Control 17-009P
Exhibit RC-8	Material Specification Sheet for (b) (4) Solution
Exhibit RC-9	Deviation Report 18-081U
Exhibit RC-10	Deviation Report 18-163U
Exhibit RC-11	Positive samples recovered from contaminated bioreactors
Exhibit RC-12	Differential Pressure Data from July 24, 2018 to August 1 2018
Exhibit RC-13	Form FRM-0267 v1.0 Eff August 4, 2018 " Differential Pressure Temperature and Relative Humidity Monitoring for Purification"
Exhibit RC-14	(b) (4) Quality Agreement, Final Draft for Execution
Exhibit RC-15	(b) (4) presentation, august 9, 2018

Exhibit RC-16	Purification Bioburden Data Evaluated during Investigation of 18-009
Exhibit RC-17	Non-Conformance Report 18-053U
Exhibit RC-18	Deviation Report 18-116U
Exhibit RC-19	Deviation Report 18-050U
Exhibit RC-20	Process (b) (4) Batches from vial thaw
Exhibit RC-21	Process (b) (4) Lot History, including disposition
Exhibit RC-22	SOP-0152 v3.0 Eff June 29, 2018 "Deviation Handling"
Exhibit RC-23	Deviation Report 18-079U
Exhibit RC-24	Excel Sheet for Immunomedics inventory

MD-1	(b) (4) specifications for (b) (4)
MD-2	Pest control threshold

RS-1.	SOP-0141 Management of regulated documents v2.0 eff 6/13/2018. (20 pages)
RS-2.	(b) (4) log sheets for (b) (4) . (6 pages)
RS-3.	Deviation # 18-1854, Recording data in a logbook on an uncontrolled form. (8 pages)
RS-4.	SOP-Q626 Monitoring of the USP (b) (4) system v9 eff 4/1/2013. (19 pages)
RS-5.	List of equipment for the manufacturing of (b) (4) drug substance. (3 pages)
RS-6.	SOP-C399 Preventive maintenance program for cell culture process equipment. (14 pages)
RS-7.	List of consumables for (b) (4) L Bioreactor. (2 pages)
RS-8.	List of consumables serviced during PM of the (b) (4) L bioreactor, equipment ID # E00060. (1 page)
RS-9.	List of testing equipment in QC analytical laboratories. (5 pages)

XIX. Signatures

Maria D. Candauchacon -S

Digitally signed by Maria D. Candauchacon -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000639745, cn=Maria D. Candauchacon -S
Date: 2018.09.26 16:44:51 -04'00'

Reyes Candau-Chacon, Ph.D., Microbiologist
CDER/OPQ/OPF/DMA

Madushini N. Dharmasena -S

Digitally signed by Madushini N. Dharmasena -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014260605, cn=Madushini N. Dharmasena -S
Date: 2018.09.27 01:30:37 -04'00'

Madushini Dharmasena, Ph.D., Staff fellow
CDER/OPQ/OPF/DMA

Gunther H. Boekhoudt -S

Digitally signed by Gunther H. Boekhoudt -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000605472, cn=Gunther H. Boekhoudt -S
Date: 2018.09.27 00:00:12 -04'00'

Gunther Boekhoudt, Ph.D., Staff fellow
CDER/OPQ/OBP

Rajiv R. Srivastava -S

Digitally signed by Rajiv R. Srivastava -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002112232, cn=Rajiv R. Srivastava -S
Date: 2018.09.27 07:28:24 -04'00'

Rajiv Srivastava, Consumer Safety Officer
ORA