DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/OPQ/OPMA/DBM, Attn: Zhihao (Peter) Qiu, Ph.D., Acting Director 10903 New Hampshire Avenue; White Oak Building 22, Room 5112 Silver Spring, MD 20993 (301) 796-6655| Email: OPFBLAInspection483Responses@fda.hhs.gov	03/02/2020-03/10/2020 FEI NUMBER 1000526871

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mr. Bryan Ball, Chief Quality Officer

FIRM NAME	STREET ADDRESS
Immunomedics, Inc.	300 The American Road
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Morris Plains, NJ 07950	Drug Substance Intermediate Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Observation 1

Procedures and controls designed to prevent microbiological contamination of the drug substance intermediate and related components are not established. Specifically,

a. There is no procedure, gowning requirements, and QA review of dynamic smoke studies performed for ISO 5 BSCs. The dynamic smoke studies performed within BSCs E00335 and E00076 did not simulate worst-case interventions and production conditions consisting of at least (b) (4) operators concurrently within the BSC unit, in which we observed during our review of vial thaw operations on 03/03/2020 within BSC 00335 for batch #(b) (4)

b. The (b) (4) filter is not (b) (4) sterilized and integrity tested on a routine basis to assure microbial control over the process. The (b) (4) used for sterilization of components is not tested for critical physical qualities on a routine basis for (b) (4)

Observation 2

The responsibilities and procedures applicable to the quality control unit are not in writing and fully followed. Specifically,

a. Final QA and microbiology review and approval of (b) (4) operations are not performed within a timely manner. For example:

   i. Final QA and microbiology release and approval for (b) (4) of the (b) (4) area after (b) (4) between 12/05 - 17/2019 was not completed until 03/06/2020 during the current inspection. This is despite conditional approval of (b) (4) and ongoing production operations since 12/17/2019.

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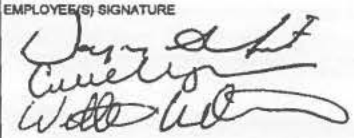
SEE REVERSE OF THIS PAGE		Wayne E. Seifert, Consumer Safety Officer Guerlain Ulysse, Consumer Safety Officer Willie Wilson, Lead Chemist Andrea Siegel, Biologist	03/10/2020

ii. Final QA and microbiology release and approval for (b) (4) of the Purification area after (b) (4) between 12/05 - 17/2019 was not completed until 03/06/2020 during the current inspection. This is despite conditional approval of (b) (4) and ongoing production operations since 01/27/2020.

b. Two operators were observed to have bare hands, bare forearms, and street clothes within the BSC E00335 unit during the review of dynamic smoke study videos, with two (2) out of (b) (4) prepared medium (b) (4) bottles, P/N: 53253, C/N: 1910003 within BSC E00335, while operators performed dynamic smoke studies. The (b) (4) area was then conditionally released for (b) (4) of production operations on 12/17/2019. There was no QA or microbiology evaluation of P/N: 53253, C/N: 1910003 medium bottles subsequently approved for usage in the inoculum preparation steps performed between 12/19 – 22/2019 for (b) (4) Large-Scale Production.

c. Chromatograms generated during (b) (4) on the (b) (4) process purification (b) (4) for (b) (4) purification are not electronically or manually indicated for review by the quality unit.

Observation 3

Standard operating procedures are inadequate and/or not followed. Specifically,

a. SOP-0126, Operation, Cleaning, Sanitization and Maintenance of the Biological Safety Cabinet, v6, Effective date 03/01/2020 provides instructions for verification of the Magnehelic gauges. Step 8.6.1 specifies to ensure the gauge or display is reading a positive differential pressure. Associated Form FRM 0225, Biosafety Cabinet Equipment Logbook, v4, Effective date 03/01/2020 provides a check box yes or no for the differential pressure as > 0. In a review of the current certification for the biological safety cabinet used for the bulk drug substance intermediate fill, (b) (4) conducted 10/18/2019, the certified differential pressure across the filter as measured by the magnehelic was (b) (4) An upper and lower limit from the certified state is not applied to routine magnehelic readings in support of manufacture to assure the certified state is maintained.

b. Equipment C208, E00498 - (b) (4) Plate Reader, Start Date: 6/20/2019 does not include a logbook entry for equipment usage and performance requalification performed on 12/11/2020. In addition, the equipment vendor personnel signed off as both running the validation test and verifying the same validation test reports for 12/2019. However, SOP-0917, Use and Maintenance of Molecular Devices (b) (4) Microplate Reader, Version 2, Effective Date: 09/23/2019 requires that the Lab Manger reviews, initials and dates the (b) (4) validation test.

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c. On 03/03/2020, sanitization of the cart used to transfer the seed culture to the (b) (4) liter bioreactor in cell culture was observed in (b) (4) C-300. A single wipe saturated with (b) (4) was used to sanitize the entire exterior of the cart in a back and forth motion, followed by a new saturated wipe with (b) (4) to sanitize the cart handle and two wheels, followed by another wipe saturated with (b) (4) (b) (4) to sanitize the two remaining wheels. SOP-0083, Sanitization of Equipment, Containers, and Components Entering a Controlled Environment, v6, Effective date 02/05/2020, Section 8 (wiping guidelines) specifies to saturate a wipe with sporicidal or sanitization solution and fold the sterile wipe into quadrants and wipe in a unidirectional motion with overlapping strokes. A new clean side of the sterile wipe should be used frequently. Once a wipe has been used on each side, a new sterile wipe should be obtained, and the steps repeated until sanitization is complete. The procedural process for sanitization of the cart was not followed.

d. SOP-0083, Sanitization of Equipment, Containers, and Components Entering a Controlled Environment, v6, Effective date 02/05/2020 describes the process of sanitizing carts into (b) (4) with associated form FRM-007, Decontamination of Equipment Entering Controlled Areas Logbook, v2, Effective date 02/05/2020 documenting the process. On 03/03/2020, LOG-20-00186 was reviewed to verify the sanitization of the cart used in transport of the seed culture to cell culture. The sanitization event could not be determined as form FRM-0007 does not provide the detail to distinguish sanitization activities. Furthermore, the logbook was incomplete for QA reviewed by on multiple pages, with each page of the logbook to be reviewed by QA upon completion, as verbally described by the firm. SOP-0641, Management and Issuance of Logbooks, v4, Effective date 12/20/2019 has no time interval for the QA review process.

e. SOP-0244, Test Methods and Remediation Procedure for HEPA Filters and Controlled areas, v3, Effective date 03/04/2020, Section 10.5, HEPA Filter Assessment and Repair, Step 1, states that the allowable repair size for a HEPA filter is no more than (b) (4) % of the total filter face area, and any one repair is limited to a lesser dimension not to exceed (b) (4) On 03/03/2020, ceiling HEPA filter C307-1 was observed with a patch greater than the limit, with HEPA filter M123-1 observed with sealant applied at the membrane frame interface, extending the length of one side. On 03/09/2020, ceiling filter 6 in area (b) (4) was observed with similar sealant applied at the membrane frame interface. The procedural process for rejecting and replacing a HEPA filter was not followed. In a review of the certification report for the filters, another filter C309-11 had an as-found issue with its supply air duct, with the duct secured, tested and found acceptable. There was no deviation investigation initiated to assess the aberrant air duct conduction on manufacturing activities.

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f. Section 7.5.8 of SOP-0149, Batch Record Review and Product Disposition, v4, Effective date 11/08/2019 states that there must not be any blank spaces in the batch record where entries are intended and that any steps not performed for any reason should be crossed out or have "NA" written next to them with a brief explanation given and initials/date. These procedures were not followed for the following executed batch record.

   i. Blank sections were not crossed out on pages 64 - 75 of MBR-0001 (Inoculum Preparation for (b) (4) Large-Scale Production) for C/N 1912014.

g. On 03/04/2020, clarified bulk harvest for (b) (4) Batch (b) (4) was re-filtered due to a leak in the (b) (4) bag (Deviation INV-20-134). The firm informed the Agency that (b) (4) intermediate lots derived from the re-filtered clarified bulk harvest will be placed on stability. However, the refiltration protocols MF-0220-PV-01, (b) (4) - Refiltration for Process Intermediates, dated 07/16/2019 and MF-0220-PV-01, Amendment A001, (b) (4) Refiltration for (b) (4) Filtration, dated 08/17/2019 do not contain details regarding the placement of re-filtered batches on stability.

h. During the master cell bank (MCB) thaw for Batch (b) (4) (vial (b) (4)) on 03/03/2020, the Agency observed that (b) (4) was used to wipe down the hemocytometer prior to the cell viability assessment. This process is not specified in SOP-0501, Determination of Total Non-viable and Viable Cell Count, v4, Effective date 10/30/2019 or in MBR-0001, Inoculum Preparation for (b) (4) (b) (4) Large-Scale Production, v1, Effective date 10/15/2019.

i. SOP-0600, Usage of the Cell Culture Equipment Log, v2, Effective Date 02/27/2019 states that the performer will initial and date each entry and that the cell culture department supervisor, on a regular basis, will review all information logged as each page becomes complete. These procedures are not consistently followed, and limited details are provided in SOP-0600 to ensure appropriate documentation and maintenance of equipment logbooks. For example, the last completed logbook (LOG-19-00646) for (b) (4) unit E00502 does not include the date at which the logbook was closed, with cell culture department and QA review signatures. Furthermore, pages 2 - 15 of LOG-19-00646 were left blank and were not crossed out or denoted with an "NA" to prevent the entry of information after the logbook closure.

j. SOP-0970 (b) (4) Cell Based Binding Assay, v4, Effective date 02/27/2020 (Step (b) (4) Preparation of Dilution), states that there is "No need to change tips during serial dilution except it's needed". This statement is unclear and provides inadequate guidance regarding the need to change pipette tips during the serial dilution of samples and plating.

k. Procedures that are routinely performed during the (b) (4) bulk filling operation are not described in SOP-0914, Operation of Bottling (b) (4) Purified Bulk, v4, Effective Date 02/10/2020, or documented in MBR-0021, (b) (4) Purified Bulk Filling, v6, Effective Date 02/6/2020. For example, during the mock (b) (4) bulk fill held 03/09/2020, the firm informed the Agency that the following activities are not conducted according to procedure or documented in the batch record.

   i. Routine inspection of tubing, connections and seals for defects (e.g., leaks) throughout the complete bulk fill set up and during the filling operations.

   ii. Visual inspection of the (b) (4) used as the container closure system for the intermediate drug substance for the absence of defects that may have a negative impact on the quality of the product.

l. Requalification for (b) (4) Cold Boxes and temperature-controlled refrigerators and freezers have not been performed in accordance to SOP-0247, Policy and Scheduling for Revalidation, v3, Effective date 08/03/2018. For example:

   i. Section 7 of SOP-0247, outline's requalification frequency for (b) (4) Cold Boxes as: Initially, (b) (4) and after repair/modification. However, the requalification for (b) (4) Cold Box, Equipment ID: E00160 was last performed on 04/18/2016. The (b) (4) Cold Box is used to hold (b) (4) Working and Primary Reference Standard.

   ii. Section 7 of SOP-0247 outline's requalification frequency for temperature-controlled equipment (incubators, baths, fridges, freezers) as: Initially (b) (4) and after repair/modification. However, requalification of Pharmaceutical Refrigerator with Freezer, Equipment ID #: E00158, which is used to hold (b) (4) was last performed on 10/31/2013. Additionally, the requalification of Laboratory Refrigerator, Room: M126, Equipment ID: E00188, which is used to hold medium and supplies, was last performed 05/18/2012.

m. According to SOP-0163, Change Control for the GxP Related Process, Equipment and Systems, v4, Effective date 01/31/2020, change controls are classified as temporary, permanent or emergency. The procedure and change control process does not include routine effectiveness checks based on change control classification.

Observation 4

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Appropriate controls are not exercised over computers or related laboratory and production systems. Specifically,

Electronic data obtained to support testing of upstream and downstream production processes or related equipment are not appropriately controlled. For example:

a. The following electronic files observed from the audit trails of the (b) (4) Filter Integrity Test Instruments have been aborted or discarded without documentation and review by the quality unit:

(b) (4)	Filter Integrity Test Instrument – Upstream Processing	
Product Name & Batch #	**Date/Time**	**Result**
(b) (4)	09/06/2019 (b) (4)	Fail Self-Test Failed
	09/14/2019	Manual Abort
	09/25/2019	Fail Self-Test Failed
	11/03/2019	Manual Abort

(b) (4)	Filter Integrity Test Instrument – Downstream Processing	
Product Name & Batch #	**Date/Time**	**Result**
(b) (4)	09/Feb/2020 (b) (4)	Manual Abort

b. QC analysts using Vi-Cell XR Analyzer for determination of cell culture density and percent viability for (b) (4) are granted advanced user privileges, which includes the following enable functions:

Menu Item	Normal	Advanced**	Administrator
Instrument/Log in sample/Save images	Disabled	Enabled	Enabled
Instrument/Log in sample/Print Results	Disabled	Enabled	Enabled

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Instrument/Log in sample/Export to Excel File	Disabled	Enabled	Enabled
Instrument/Log in sample/Add to multi-run file	Disabled	Enabled	Enabled
Instrument/Log in sample/Reanalyze	Disabled	Enabled	Enabled

***All QC analysts using the Vi-Cell XR Analyzer are granted advanced user access.*

According to the firm, aforementioned functions enabled for advanced and administrator users are more of a research and development (R&D) tool which allows users to store, open, save and reanalyze images of test run files, including under different parameters.

c. During the review of the Vi-Cell XR Analyzer (E00406) electronic data files, two unspecified test files were identified, Test-AA-26-2018.smp and Test.smp, that were logged within the system. However, there is no QA review or documented explanation for the unspecified test runs.

d. The current QC Supervisor and Previous QC Scientist from 04/2016 to 10/2019, was granted concurrent access to all three (3) user roles of: QC_Admin, Reviewer, and QC_Analyst, within Empower 3 Chromatography Data System between 03/27/2019 and 10/21/2019. In addition, she was assigned the user role of: QC_Manager since 10/2019. However, there is no procedure describing the user role, access privileges and responsibilities for a QC_Manager within the chromatography data system.

Observation 5

The (b) (4) process for bioreactors is a semi-automated process, with enhanced control and monitoring of the (b) (4) process performed by protocol and (b) (4) positioned near (b) (4) According to the protocol, at any point during the cycle, if it is observed that the minimum (b) (4) is not being obtained, upstream manufacturing will check manual hand valve positions and (b) (4) lines. If necessary, Upstream Manufacturing will make an adjustment that may include but is not limited to adjusting valves, the (b) (4) regulator and/or striking of (b) (4) The firm specified that interventions are routine in support of a successful (b) (4) cycle, with the process not always capable of meeting specification without human intervention.

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Observation 6

Facilities and equipment are not adequately maintained and inspected. Specifically,

a. The (b) (4) transfer hoses are not on a preventative maintenance schedule nor are they inspected for deterioration. Additionally, the (b) (4) hoses used in cell culture for the bioreactors are not on a preventative maintenance schedule nor are they inspected for deterioration.

b. Post (b) (4) the cell culture bioreactors are not visual inspected and documented as clean.

c. Gaps were observed at ceiling light frames and air returns within (b) (4) and cell culture suites, along with deteriorated sealant at ceiling tiles and at a (b) (4) ceiling interface.

Observation 7

Procedural controls are inadequate to assure the validated state is maintained. Specifically, hold times times in the purification process are not documented to assure the validated state is not exceeded.

Observation 8

Analytical method verification studies were not performed for the following procedures used during the lot release and stability testing of (b) (4) at Immunomedics Inc.:

a. pH according to SOP-0417, Operation and Maintenance of the Orion 4-Star Plus Benchtop pH/Conductivity Meter, v4, Effective date 04/30/2019
b. Visual appearance according to SOP-0481, Visual Appearance Testing of (b) (4) v2, Effective date 7/11/2018

The suitability of all testing methods, including compendial procedures, should be verified under actual conditions of use and documented.

Observation 9

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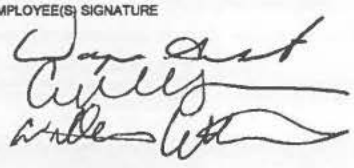
SEE REVERSE OF THIS PAGE		Wayne E. Seifert, Consumer Safety Officer Guerlain Ulysse, Consumer Safety Officer Willie Wilson, Lead Chemist Andrea Siegel, Biologist	03/10/2020

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The qualification of equipment has not been completed and procedural controls for use have not been established. Specifically,

a. (b) (4) Systems are used to acquire supplemental (b) (4) data for each (b) (4) cycle for the (b) (4) liter bioreactors. There is no procedural control for when the (b) (4) are calibrated and verified. Furthermore, other (b) (4) used in the acquisition of (b) (4) data have not been qualified.

b. (b) (4) incubators used to store medium (b) (4) bottles for production and laboratory operations have not been evaluated to determine whether the loaded chamber works within the specified limits of temperature through-out the chamber. This includes:

   i. Incubator, Serial #: IBRPO-1282, Location: Clean Room (b) (4) Equipment ID: E00164
   ii. Incubator, Serial #: IBRPO-1275, Location: (b) (4) Equipment ID: E00169

c. (b) (4) Refrigerators, Operating Range: 2 to 8 degrees Celsius, and Freezers, Operating Range: (b) (4) to -(b) (4) degrees Celsius, used to store components related to the drug substance intermediate, laboratory testing, and/or reference standards have not been evaluated to determine whether the loaded refrigerator/freezer works within the specified limits of temperature through-out the refrigerator/freezer. This includes:

   i. Laboratory Refrigerator, Model #: RGL2304A22, Equipment ID: E00188
   ii. Pharmacy Freezer, Model #:3672, Serial #: 808639-1145, Equipment ID: E00156
   iii. Pharmaceutical Refrigerator with Freezer, Serial #60813059, Equipment ID: E00158
   iv. Pharmacy Refrigerator, Serial #806413-23, Equipment ID: E00157

Observation 10

The (b) (4) Automated Cell Thawing System equipment ID: E00501 and E00502 in the (b) (4) (b) (4) area are not properly qualified to comply with their intended performance. Specifically, there is no sufficient assurance that (b) (4) master cell bank vials thawed using E00501 and E00502 would meet expected viable cell density and cell viability for commercial manufacture.

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