DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Mark J. Kuenzi, Vice President, Quality Operations

FIRM NAME	STREET ADDRESS
Fujifilm Diosynth Biotechnologies USA, Inc.	101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance 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

1. There are no comprehensive risk assessments conducted at this multiproduct facility to justify the containment strategy and controls of manufacturing (b) (4) products using microbial and cell culture processes to prevent cross-contamination.

   Specifically,

   a. A formal risk assessment evaluating the cross-contamination risks of (b) (4) drug substance by other (b) (4) products (b) (4) : PDE = (b) µg/day, (b) (4) : PDE = (b) µg/day, and (b) (4) : PDE = (b) µg/day) manufactured in the same areas with shared product contact equipment has not been documented.
   b. The downstream purification areas and product contact equipment for manufacture of (b) (4) drug substance is shared with a (b) (4) product using a (b) (4) expression system (Molecule (b)). There is no formal risk assessment conducted evaluating any potential viral cross-contamination risks. (b) batch# (b) (4) (a post-PPQ run) was manufactured in the same suite after a campaign of (b batches of Molecule (b) was manufactured.
   c. Molecule (b) is classified as a Band C (b) (4) product) for cleaning, per RA-389.01, Revision 01 to Upstream and Downstream Risk Assessment for Facility and Safety Risk Assessment for Band C Molecule (b) . However, the same molecule is classified as Cleaning Band D (non-(b) (4) product) based on the List of FDBU Programs for CY 2020 2021 provided to the inspection team during the inspection.
   d. (b) (4) was assessed to have a PDE of (b) µg/day and deemed a Band D (non(b) (4) product. However, the PDE determination is not scientifically justified. There was no adequate risk assessment conducted evaluating cross-contamination risks for other products manufactured in the same manufacturing areas using shared product contact equipment.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE		Yun Wu, Staff Fellow Zhihao Peter Qiu, Supervisory Biologist Jacek Cieslak, Chemist Seneca Toms, Biotechnology Specialist	04/21/2021

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mark J. Kuenzi, Vice President, Quality Operations	
FIRM NAME Fujifilm Diosynth Biotechnologies USA, Inc.	STREET ADDRESS 101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

2. The (b) (4) manufacturing process is not adequately monitored and/or controlled to ensure the quality of the (b) (4) drug substance is not adversely affected.

Specifically,

a. On 04/15/2021, during observation of (b) (4) batch# (b) (4) step (b) (4) temperature of the (b) (4) stored in SUM-(b) (4) L was at (b) (4) °C. On 04/21/2021, during observation of (b) (4) batch# (b) (4), Bulk Fill, temperature of (b) (4) Retentate stored in SUM-5010 was at (b) (4) °C. However, it is stated in (b) (4), temperature during intermediate hold for (b) (4) and (b) (4) Retentate is at (b) (4) °C. Product temperature is not recorded or monitored throughout the process to ensure it is within the established limits.

b. Discoloration was observed in the (b) (4) -4018 (b) (4). The (b) (4) is shared with other products. The source of the discoloration is unknown. The (b) (4) was used for (b) (4) batch# (b) (4) (b) (4) step. SOPs and Work Instructions related to (b) (4) procedures do not include (b) (4) visual assessment after (b) (4)

c. A crevice of approximately 3 inches wide and 1 inch in height was observed under the seal within the (b) (4) in (b) (4) -4019. The (b) (4) had been used for (b) (4) batch# (b) (4) and going to be used for (b) (4) batch# (b) (4) step. SOPs and Work Instructions related to (b) (4) procedures do not include (b) (4) visual assessment after (b) (4)

d. Written procedures for manufacturing process are inadequate. On 04/15/2021, during observation of (b) (4) batch# (b) (4) step in Purification (b) (4) (Rm (b) (4)), employees were observed to install an additional valve to remove excess air from the hose connecting the SUM-(b) (4) L and the (b) (4). Installation of the valve to remove excess air is not specified in the batch record for this unit operation.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
		Yun Wu, Staff Fellow Zhihao Peter Qiu, Supervisory Biologist Jacek Cieslak, Chemist Seneca Toms, Biotechnology Specialist	04/21/2021

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mark J. Kuenzi, Vice President, Quality Operations	
FIRM NAME Fujifilm Diosynth Biotechnologies USA, Inc.	STREET ADDRESS 101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

3. Procedures of material management systems are not followed or are inadequate.

Specifically,

a. Four (4) vials of (b) (4) working cell bank (WCB) are unaccounted for in the PAS-X system. On July 17, 2020, as per FDBU-SOP-0358: Requesting Shipment, Acceptance, Receipt, Storage, Handling, Maintenance, and Shipping of Cell Banks, Revision 25, Effective Date: 10 July 2020, warehouse personnel completed a move transaction in SAP of (b) (4) WCB vials. Due to a damage to vial caps, additional 4 vials of WCB were obtained. Out of the total of (b) (4) vials, (b) (4) were used to inoculate (b) (4) shake flasks and 4 vials were discarded. However, the discard of 4 WCB vials not used during product manufacture was not recorded in PAS-X.

b. Expired materials were found in the SAP system in the warehouse. Some materials were expired more than 12 months ago. FDBU-SOP-0349: Handling of Rejected and Expired Raw Materials and Consumables, Revision 11, Effective Date: 27 February 2018 does not specify the time requirement for the expired product disposal.

c. An error message of "Power Failure" was observed on the Cryofreezer FZ-0439N used for (b) (4) (b) (4) WCB storage. The power failure occurred on 04/11/2021 and the error message had not been cleared on 04/14/2021. The FDBU-SOP-0255: BMS and DCS Alarm Response and Notification, Revision 15, Effective Date 18 December, 2020 is not clear who is responsible for clearing the alarm.

4. You failed to establish adequate cleaning and sanitization procedures for non-dedicated product contact equipment at this multiproduct manufacturing facility to prevent cross-contamination.

Specifically,

a. FDBU-SOP-0388: Changeover of Processing Equipment and Manufacturing Areas, Revision 32, Effective Date: 08 Nov. 2019 defines product contact equipment as any surface that comes into direct physical

contact with product proteins or a product intermediate. Shake flasks, fermenters and bioreactors used for inoculation, (b) (4) , or production of cultures that do not secret the product or the product intermediate directly into the media are not considered as product contact equipment. No swab samples were taken to demonstrate adequate cleaning.

b. FDBU-SOP-0388: Changeover of Processing Equipment and Manufacturing Areas, version 32, effective date: 08 Nov. 2019 and FDBU-SOP-0462: Cleaning Program for Process Equipment, Revision 09, Effective Date: 02 Apr 2020 allow equipment recleaning if a swab sample result failed to meet the acceptance criteria without conducting a root cause investigation. An investigation is only required if the swab sample result failed after the recleaning.

c. TOC recovery and degradation studies documented in CV218Recovery.00: Evaluation of Soil Recovery of Molecule (b) Approved 03/20/2019, were inadequate. On 04/16/2021, Scientist II, Bioassay Development with initials (b) (6) stated that there is no defined procedure for drying of the soiled coupons used in recovery study. The drying condition was unrepresentative of dirty hold times. In addition, the degradation study demonstrated that significant amounts of (b) (4) remained undegraded after (b) (4) treatment for (b) (4) There is no assurance that the cleaning procedures can effectively eliminate (b) (4)) activity or toxicity.

d. Process (b) (4) Cycles are used for Process Vessels that are deemed for "bioburden control" only. FDBU-SOP-0460: Validation and Re-validation of (b) (4) Procedures and Media Holds, Revision 08, Effective Date 19 Nov 2020, states that there is no requirement to requalify Process (b) (4) Cycles.

5. Discrepancies are not fully investigated to identify a root cause and corrective and preventative actions (CAPA) are not adequately implemented to prevent recurrence.

Specifically,

a. Excursions occurred during product validation are investigated as protocol events under FDBU-SOP-0457: Execution and Review of Qualification and Validation Documents. Section 4.6.7.1.2 states that if there is potential or unknown product impact, QA is consulted for further assessment according to FDBUSOP- 0432, Deviation/Event Reporting System. However, no formal investigations were conducted for the following protocol events:

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mark J. Kuenzi, Vice President, Quality Operations	
FIRM NAME Fujifilm Diosynth Biotechnologies USA, Inc.	STREET ADDRESS 101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

i. At least ten (10) Endotoxin testing results did not meet the Endotoxin System Suitability Test. You failed to conduct adequate investigations to identify the root causes.

ii. Under Protocol Event for (b) (4) three (3) Endotoxin Out of Specification results for in-process hold time studies were reported (PR206361, PR206365, and PR307208); however, no definitive root causes were identified. The firm concluded that the OOS results were "aberrant values" and the hold time studies were valid. No mediation action was taken.

iii. PR189569 was opened for two in-process samples ((b) (4) retentate and (b) (4) Load) failing to filter during bioburden qualification testing. A definitive root cause was not identified but was speculated to be prolonged sample storage at 2-8°C ((b) (4) and (b) (4), respectively). It was concluded that this event has no impact to product or process, without considering that the process hold time of (b) (4) Load is ≤(b) hr at 2-8°C. On 04/19/2021, Principle Process Scientist/Engineer, Group Lead with initials (b) , stated that the two in-process samples had been stored at 2-8°C for over a month before used for bioburden method qualification.

b. Events PR180216 and 196559 and deviation PR207669 were opened for excursions of personnel monitoring, in-process sample bioburden, and settle plate monitoring. Organisms recovered were identified to be (b) (4) The firm concluded the organisms were (b) (4) host organism, without considering the possibility of cross-contamination of host organism from other (b) (4) (b) processes.

6. Microbial control of the facility is inadequate. EM excursions were not investigated for root cause and CAPAs implemented were inadequate to control microbial contamination.

Specifically,

a. (b) (4) environmental and water monitoring summary reports from 2020 documented 30 events of action level *Paenibacillus spp.* (mostly *P. glucanolyticus*) recoveries from 57 monitoring sites, 5 events of alert/action level *Burkholderia* recoveries from 6 monitoring sites, and 4 events of mold recoveries from 5 monitoring sites. All of the excursions were assessed to be isolated incidents with no product impact. It was not taken into consideration that there may be a recurring, facility-wide microbial contamination.

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
SEE REVERSE OF THIS PAGE		Yun Wu, Staff Fellow Zhihao Peter Qiu, Supervisory Biologist Jacek Cieslak, Chemist Seneca Toms, Biotechnology Specialist	04/21/2021

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Mark J. Kuenzi, Vice President, Quality Operations	
FIRM NAME Fujifilm Diosynth Biotechnologies USA, Inc.	STREET ADDRESS 101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

For example, 5 *P. glucanolyticus* recovery events occurred between 02/22/2020-02/28/2020 from 10 monitoring sites in 4 different production suites including Purification (b), where (b) (4) was manufactured. On 02/18/2020 and 02/19/2020, *P. glucanolyticus* were recovered from (b) (4) in-process samples ((b) (4) and (b) (4) Load).

b. Events PR195075 and PR212557 recorded action level excursions of *P. glucanolyticus* recoveries from floor monitoring sites (b) (4) (TNTC), (b) (4) ((b) CFU) in Purification suites. The samples were taken within (b) (4) of room cleaning. (b) (4) cleaning of the rooms had been implemented under CAPA PR188746 in response to *P. glucanolyticus* recoveries in 2019. However, *P. glucanolyticus* continues to be the most prevalent environmental isolate in the facility. *Paenibacillus spp* has not been evaluated for disinfectant effectiveness.

c. Protocol Event PR195707 describes sub-alert level bioburden recoveries of *Paenibacillus glucanolyticus* ((b) CFU) and *Penicillium rubens* ((b) CFU) in (b) (4) Lot (b) (4) s a fungal species that produces penicillin (a beta lactam). A definitive root cause was not found but was attributed to sampling error that introduced contamination from the environment or personnel. It was justified that there was no impact to product or manufacturing because there are multiple (b) (4) steps to remove microbial contamination. However, the firm failed to consider the potential impact of residual *P. rubens* metabolites, e.g. penicillin, to product quality and patient safety, or the overall impact of fungal contaminations in the facility.

d. According to FDBU-STDP-0003, Microbial Control Strategy, Revision 03, Effective 29 Oct 2019, step (b) (4) an action limit of (b) (4) CFU/10 mL is set for in-process samples from upstream processes that occur in ISO 8 environment (fermentation, cell culture, and recovery). On 04/15/2021, when we toured the QC Microbiology Laboratory, QC scientist with initial (b) (6) stated that TNTC for bioburden is defined as > (b) (4) CFU/plate. According to TM-0046288, Bioburden Determination Using Total Aerobic Microbial Count and Total Yeast and Mold Count, Revision 05, Effective 23 Dec 2020, step (b) (4) sample volume less than (b) (4) mL must be directed by the client. There is no assurance that a sample exceeding the action limit can be detected.

7. Microbial (b) (4) hold time study was not adequately conducted.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mark J. Kuenzi, Vice President, Quality Operations	
FIRM NAME Fujifilm Diosynth Biotechnologies USA, Inc.	STREET ADDRESS 101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

Specifically,

a. Purification (b) (4) have a (b) (4) hold time and may be reused for a different process step within expiry. Connection between (b) (4) holding bag and the (b) (4) is not through an aseptic connection and the (b) (4) hold time study did not simulate the reuse condition.

b. Fungal (*Fusarium oxysporum*) contamination was observed from one of the worst-case (b) (4) used in the (b) (4) hold time study, with (b) CFU/10 mL recovered from (b) (4) sample and TNTC recovered from (b) (4) sample (action limit (b) CFU/10 mL). The study concluded that only the worst-case (b) (4) will have a hold time of (b) (4). All other (b) (4) will have a hold time of (b) (4).

8. Written procedures are not followed by manufacturing employees.

Specifically, on 04/15/2021, during observation of (b) (4) batch# (b) (4) step in Purification (b) (Rm (b) (4)), employees were observed to use non-(b) (4) tubes for endotoxin sample storage. FDBU-WI-0154: Work Instructions: Collection of Product Samples from the Manufacturing Area, Revision 06, Effective date: 29 May 2020, step 1.1 dictates that endotoxin testing samples are to be stored in pyrogen-free, (b) (4) capped containers. It was later observed that an employee checked in the samples onto LIMS system with the sampling location as Purification (b) (Rm (b) (4).

9. You failed to establish procedural controls for your electronic data acquisition systems to ensure that your data records are protected from unauthorized manipulation. For example,

a. The SoftMax Pro software (version 5.3 GxP) used to analyze in-process and release samples of commercial and non-commercial products in the QC Laboratories, including Endotoxin testing of (b) (4) (b) (4) allows analysts to save, delete, and rename data files outside of the approved file storage location (C:\AnalyticalGroup\SampleTesting).

b. Raw data from testing are auto-saved under the directory of C:\AnalyticalGroup\Data. However, technical review of the results and associated audit trail as governed by FDBU-SOP-0301: Data Recording and Review in the GMP Laboratory, Revision 22, effective date: 12 January 2021 is only conducted on

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Peter Zhihao Qiu, Division Director WO Building 22, Rm 5112 10903 New Hampshire Avenue Silver Spring, MD 20993 (301) 796-6655 Email: OPFBLAInspection483Responses@fda.hhs.gov	04/14/2021-04/21/2021
	FEI NUMBER 3000718852

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mark J. Kuenzi, Vice President, Quality Operations	
FIRM NAME Fujifilm Diosynth Biotechnologies USA, Inc.	STREET ADDRESS 101 J Morris Commons Ln
CITY, STATE, ZIP CODE, COUNTRY Morrisville, NC 27560	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

the file saved in the C:\AnalyticalGroup\SampleTesting folder by the analyst. There is no data and audit trail review associated with files stored in the raw data folder (C:\AnalyticalGroup\Data).

10. Manufacturing areas and equipment in the facility are not adequately designed, maintained, and labeled.

Specifically, during facility walk-throughs conducted during the inspection, we observed the following:

a. (b) (4) or processing (b) (4) are stored in the ISO 7 and ISO 8 corridors that limit personnel and material flows in the multiproduct manufacturing areas.
b. Multiple Use Status Tags did not have the correct information for manufacturing suites, processing steps and equipment status. For example,
   i. The manufacturing suite tag to Recovery (b) (4) for (b) (4) had the incorrect Room number ((b) (4)) and process steps ((b) (4)).
   ii. The Tag for VP-2661 indicated the vessel was "in use" and the content was (b) (4) Load. However, the actual status of the vessel was "not in use".
   iii. The dates and times on two (b) (4) and a (b) (4) used for in-process testing in Recovery (b) (4) and Purification (b) (4) were incorrect. The Room label on the (b) (4) in Recovery (b) (4) was also incorrect.
c. Deteriorated sealant at the ceiling was observed in Fermentation (b) (4) creating a gap that exposed the classified area to unclassified air above the ceiling.
d. A gap was observed between the floor and the door of the loading dock in the warehouse, allowing opportunities for pest to come into the facility.