Food and Drug Administration Establishment Inspection Report

Date Assigned: 09/19/2023 **Inspection Start Date:** 05/29/2023 **Inspection End Date:** 06/09/2023

Firm Name & Address: Boehringer Ingelheim Biopharmaceuticals (China) Ltd. , 1090 Halei Road , Trade Zone Shanghai

Firm Mailing Address: 1090 Halei Road, Trade Zone, Shanghai ,Shanghai ,201203, China

FEI: 3015009021 **JD/TA:** **County:** **Est Size:** Unknown

Phone: **District:** CDER **Profiled:** Yes

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

Endorsement

A (b) (4) inspection of a drug substance and drug product manufacturing facility at Boehringer Ingelheim Biopharmaceuticals (China) Ltd., Shanghai, China, was conducted following a request by the Division of Biotechnology Manufacturing, OPMA, OPQ, CDER, under an eNSpect assignment # 260873. The inspection covered the (b) (4) drug substance and drug product manufacturing operations for (b) (4) mg/(b) (4) mL. The inspection was risk-based and conducted in accordance with applicable sections of CP 7356.002M Inspection of Licensed Therapeutic Drug Products, CP (b) (4) Inspections/Investigations, and ICH Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry. The profile classes covered are CBI (recombinant/non-recombinant protein drug substance of biologic origin) and SVS (Sterile-Filled Small Volume Parenteral Drugs).

The current inspection is the initial inspection of the facility and is limited to the manufacturing of (b) (4) drug substance and drug product in the (b) (4) Building (b) (4) of Boehringer Ingelheim Biopharmaceuticals (China) Ltd., located at 1090 Halei Road, Pilot Free Trade Zone, Shanghai, China. The inspection covered the firm Quality, Production, Materials, Facilities and Equipment, Laboratory Controls, and Packaging and Labeling systems, in order to assess the firm readiness for (b) (4) (also referred to as (b) (4) drug substance (DS) and drug product (DP) commercial manufacturing. A seven-item Form FDA 483 was issued to the firm at the end of the inspection on June 9, 2023, for the following observations: (1) The responsibilities and procedures applicable to the firm quality unit are not in writing and fully followed; (2) The firm has not established and followed appropriate visual inspection procedures designed to assure batches of (b) (4) products meet appropriate specifications and statistical quality control criteria as a condition for their approval and release; (3) Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed; (4) The firm failed to excise appropriate controls to protect the electronic data acquisition and/or manufacturing control systems used for (b) (4) drug substance and drug product manufacturing; (5) The current (b) (4) drug substance manufacturing practices present high risk for potential contamination; (6) Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications, do not always include appropriate conclusions and follow-ups; (7) Laboratory controls do not include the establishment of scientifically sound and appropriate standards designed to assure that components and in-process materials conform to appropriate standards of identity, strength, quality, and purity.

The section of this report entitled General Discussions with Management details other inspectional observations discussed with the firm management during the inspection. The firm management stated that Boehringer Ingelheim Biopharmaceuticals (China) Ltd. would provide a written response to the inspectional observations within 15 business days. No refusals were encountered, and no samples were collected.

(b) (4)

Endorsement Location:

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
	ET	Thuy T Nguyen	01/03/2024 08:24 AM ET

Food and Drug Administration Establishment Inspection Report

FEI: 3015009021 **Inspection Start Date:** 05/29/2023 **Inspection End Date:** 06/09/2023

Firm Name & Address: Boehringer Ingelheim Biopharmaceuticals (China) Ltd. , 1090 Halei Road , Trade Zone Shanghai

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

Registration Type

DRG Drug

Registration Dates

01/01/2024 01/01/2023 01/01/2022

Establishment Type

M Manufacturer

M Manufacturer

Industry Code

58 Human and Animal Therapeutic Biologic and Biosimilar Drugs

60 Human and Animal Drugs

District Use Code:

Food and Drug Administration Establishment Inspection Report

FEI: 3015009021 **Inspection Start Date:** 05/29/2023 **Inspection End Date:** 06/09/2023

Firm Name & Address: Boehringer Ingelheim Biopharmaceuticals (China) Ltd. , 1090 Halei Road , Trade Zone Shanghai

Inspection Basis: Compliance

Inspected Processes & District Decisions

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

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	01/19/2024	Voluntary Action Indicated (VAI)	Allen, Ekaterina	CDER-DIA

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	09/19/2023	Official Action Indicated (OAI)	Li, Zhong	CDER-DIA

Remarks:

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Food and Drug Administration Establishment Inspection Report

FEI: 3015009021 **Inspection Start Date:** 05/29/2023 **Inspection End Date:** 06/09/2023

Firm Name & Address: Boehringer Ingelheim Biopharmaceuticals (China) Ltd. , 1090 Halei Road , Trade Zone Shanghai

Products Covered

Product Code	Est Type	Description		Additional Product Description
(b) (4)	Manufacturer	(b) (4) Sterile Liquid	NEC Human - Rx/Single Ingredient	(b) (4)

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Li, Zhong	BUR	CDER	(b) (4)	Manufacturer	(b) (4)	120

Total Hours: 120

Food and Drug Administration Establishment Inspection Report

FEI: 3015009021 **Inspection Start Date:** 05/29/2023 **Inspection End Date:** 06/09/2023

Firm Name & Address: Boehringer Ingelheim Biopharmaceuticals (China) Ltd. , 1090 Halei Road , Trade Zone Shanghai

Inspection Result

EIR Location **Trips Num**
2023-033A

Inspection Summary
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The section of this report entitled General Discussions with Management details other inspectional observations discussed with the firm management during the inspection. The firm management stated that Boehringer Ingelheim Biopharmaceuticals (China) Ltd. would provide a written response to the inspectional observations within 15 business days. No refusals were encountered, and no samples were collected.

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals: No refusal

Samples Collected

Recall Numbers

Related Complaints

Food and Drug Administration Establishment Inspection Report

FEI: 3015009021 **Inspection Start Date:** 05/29/2023 **Inspection End Date:** 06/09/2023

Firm Name & Address: Boehringer Ingelheim Biopharmaceuticals (China) Ltd. , 1090 Halei Road , Trade Zone Shanghai

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

FDA 483 Responses

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

Response Type	Response Mode	Response Date	Response Summary

TABLE OF CONTENTS

I. SUMMARY

A (b) (4) inspection of a drug substance and drug product manufacturing facility at Boehringer Ingelheim Biopharmaceuticals (China) Ltd., Shanghai, China, was conducted following a request by the Division of Biotechnology Manufacturing, OPMA, OPQ, CDER, under an eNSpect assignment # 260873. The inspection covered the (b) (4) drug substance and drug product manufacturing operations for (b) (4) mg/(b) (4) mL. The inspection was risk-based and conducted in accordance with applicable sections of CP 7356.002M "Inspection of Licensed Therapeutic Drug Products," CP(b) (4) Inspections/Investigations," and ICH Q7 "Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry." The profile classes covered are CBI (recombinant/non-recombinant protein drug substance of biologic origin) and SVS (Sterile-Filled Small Volume Parenteral Drugs).

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Trade Zone, Shanghai, China. The inspection covered the firm's Quality, Production, Materials, Facilities and Equipment, Laboratory Controls, and Packaging and Labeling systems, in order to assess the firm's readiness for (b) (4) (also referred to as (b) (4) drug substance (DS) and drug product (DP) commercial manufacturing. A seven-item Form FDA 483 was issued to the firm at the end of the inspection on June 9, 2023, for the following observations: (1) The responsibilities and procedures applicable to the firm's quality unit are not in writing and fully followed; (2) The firm has not established and followed appropriate visual inspection procedures designed to assure batches of (b) (4) products meet appropriate specifications and statistical quality control criteria as a condition for their approval and release; (3) Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed; (4) The firm failed to excise appropriate controls to protect the electronic data acquisition and/or manufacturing control systems used for (b) (4) drug substance and drug product manufacturing; (5) The firm's current (b) (4) drug substance manufacturing practices present high risk for potential contamination; (6) Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications, do not always include appropriate conclusions and follow-ups; (7) Laboratory controls do not include the establishment of scientifically sound and appropriate standards designed to assure that components and in-process materials conform to appropriate standards of identity, strength, quality, and purity.

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II. ADMINISTRATIVE DATA

(*This section was written by ZL.*)

Inspected firm:	Boehringer Ingelheim BioPharmaceuticals (China) Ltd.
Location:	1090 Halei Road, Pilot Free Trade Zone, Shanghai, 201203, China
Mailing Address:	1090 Halei Road, Pilot Free Trade Zone, Shanghai, 201203, China
Phone:	(+) 86-21-20584258
Dates of inspection:	May 29 - June 2, 2023 & June 5 - 9, 2023
Days in the facility:	10

FMD-145 and official regulatory correspondence should be sent to:

Name:	Dr. Yuguo Zang
Job Title:	General Manager, Boehringer Ingelheim BioPharmaceuticals (China) Ltd
Address:	1090 Halei Road, Pilot Free Trade Zone, Shanghai, 201203, China
Phone:	(+) 86-21-20600007
E-mail:	yuguo.zang@boehringer-ingelheim.com

Participants:

Zhong Li, Ph.D., Sr. Pharmaceutical Quality Assessor, CDER/OPQ/OPMA/DBM/B1 (ZL)
Leiyun Boone, Ph.D., Lead Biologist, CDER/OPQ/OBP/DBRRIV (LB)

Yiwei Li, Ph.D., Supervisory Chemist, CDER/OPQ/OPMA/DPMAIV/PMB10 (YL)

Each investigator wrote his/her assigned corresponding sections of this report, as identified with his/her initials. In addition, each investigator provided a written narrative of his/her objectionable conditions listed on the Form FDA 483. Ms. Anji Shen, Head of Quality System, accompanied me (ZL) during the entire inspection.

At the beginning of the inspection on May 29, 2023, the FDA inspection team presented Inspector Credentials to Dr. Yuguo Zang, General Manager, who identified himself as the most responsible person at Boehringer Ingelheim Biopharmaceuticals (China) Ltd. (hereafter referred to as "BICN" or "the firm"). Immediately after, the firm presented an overview of the firm's history, locations, organization, quality control laboratories, warehouses, utilities, and (b) (4) DS/DP and associated manufacturing processes [**Exhibit ZL-01**]. Individuals from the firm present at the opening meeting are shown in [**Exhibit ZL-02**]. A (b) (4) representative, Mr (b) (4) attended the opening meeting. The inspection team then proceeded to conduct a walk-through inspection of the firm's DS and DP manufacturing facilities, located at the (b) (4) Building,1090 Halei Road, Pilot Free Trade Zone, Shanghai, China.

During the inspection's closeout meeting on June 9, 2023, a Form FDA 483 (**Attachment 1**) was issued to Dr. Yuguo Zang, General Manager. In addition to Dr. Zang, the individuals present at the closeout meeting are shown in [**Exhibit ZL-03**]. Mr. (b) (4) also attended the closeout meeting.

During the inspection, the Covid-19 self-assessment as directed by ORA Field Alert #57 was performed by the FDA investigators daily, and the precautions as described within this alert were discussed with the firm at the pre-inspection teleconference and at the opening meeting.

The inspection team used the Agency's authority under Section 704(a)(4) to request records from the firm in advance of the on-site inspection on April 24, 2023, following procedures described in the FDA Staff Manual Guide SMG9004.1 *Policy and Procedures for Request Records in Advance or in lieu of a Drug Inspection* (Effective August 25, 2017). On May 12, 2023, Boehringer Ingelheim Biopharmaceuticals (China) Ltd. submitted the requested documents.

III. HISTORY

(*This section was written by ZL.*)

Boehringer Ingelheim (also referred to as BI) is a family-owned global corporation and was founded in 1985 in Ingelheim, Germany. The company has more than (b) (4) employees worldwide with 180 affiliated companies worldwide and net sales of (b) (4) EUR. In June 2013, Boehringer Ingelheim started a manufacturing facility in Shanghai, known as Boehringer Ingelheim Biopharmaceuticals (China) Ltd., which is one of the four biopharmaceutical manufacturing sites of Boehringer Ingelheim in the globe (other sites are located in Fremont CA, USA; Biberach, Germany; and Vienna, Austria, respectively).

Boehringer Ingelheim Biopharmaceuticals (China) Ltd. provides Chemistry, Manufacturing and Control (CMC) services for Clinical Trial Applications (CTAs); supplies materials for toxicology studies, Phases I, II, and III clinical trials; and manufactures products for commercial

markets. No non-pharmaceutical activities are carried out by the firm. Only medicinal products for human use are manufactured at the site. The biopharmaceutical products produced are the active ingredients of (b) (4) (*e.g.*, (b) (4) cell lines). No antibiotics (*e.g.*, penicillin or penicillin-related compounds) or preparations, steroids/steroid hormones, cytotoxins, non-medicinal products, highly toxic products, sensitizing products, or immunosuppressive drugs are manufactured in the facility. Based on the (b) (4) technology platform, BICN provides production volumes of (b) (4) and (b) (4) cell cultures and the corresponding harvest, purification, sterile fill and finish, secondary packaging, and quality analysis capabilities. BICN offers the abovementioned services through two operating sites in Shanghai, China.

- Halei Road site: No. 1090 Halei Road, Pilot Free Trade Zone, Shanghai, 201203, China (D-U-N-S Number: 544325726°)

  The Halei Road site has a total area of about (b) (4) m^2, with about (b) (4) m^2 currently occupied while the remaining land is for future expansions. The (b) (4) building of (b) (4) m^2 is composed of DS production, DP production, quality control (QC) laboratories, and storage areas. The (b) (4) DS production line has been in operation since May 2017. The sterile liquid vial DP fill & finish line has been in operation since May 2018. The Halei Road facility houses (b) (4) capable of providing commercial supplies of the market products.

  The (b) (4) floor of the (b) (4) building consists of storage areas for raw material and excipients, cell banks, bulk DS, finished DP, and the QC sampling suite. The (b) (4) floor of the (b) (4) building is used for DS production, including (b) (4) (class C, ISO 7), cell culture with capacities up to a (b) (4) scale (class D, ISO 8), downstream processing (class D, ISO 8), and (b) (4) purification (class C, ISO 7). Production areas for DS are designed as a multi-product facility utilizing (b) (4) technologies. There are (b) (4) zones on the (b) (4) floor: Zone (b) (4) Zone (b) (4) has been in operation since May 2017. Zone (b) (4) was later introduced in October 2020.

  Zone (b) (4) Upstream areas include a Media Preparation room (b) (4) rooms (b) (4) a Cell Culture room (b) (4) Downstream areas include a (b) (4) room (b) (4) an (b) (4) Purification room (b) (4)

  Zone (b) (4) Includes a Cell Culture room (b) (4) and a (b) (4) room (b) (4)

  The (b) (4) floor of the (b) (4) building is used for DP production and QC laboratories. DP production on the (b) (4) floor includes filling, visual inspection, and packaging. The DP filling process utilizes a (b) (4) (Grade A) with filling/stoppering/capping machines. QC labs on the (b) (4) floor include Protein Analytics labs, an Instrument lab, a Microbiology lab, a Sample Management lab, and a Stability Sample Management lab.

- Lishizhen Road site: No. 257 Lishizhen, Road, Pilot Free Trade Zone, Shanghai, 201203, China (D-U-N-S Number: 554551086°)

  The Lishizhen Road site is about three kilometers away from the Halei Road site and consists

of several buildings including a DS production area for preclinical and Phase VII clinical material supply, a technical transfer lab, QC laboratories, storage areas, secondary packaging lines for commercial products, and administration buildings. Since its operation in 2014, several biopharmaceutical products have been produced and released from this site for uses in clinical studies worldwide.

The site has a total floor area of about (b) (4) m^2, including the area designated for BICN of about (b) (4) m^2. The non-biopharmaceutical operations at the site belong to Boehringer Ingelheim Shanghai Pharmaceuticals Co., Ltd., which currently does not have an FDA Establishment Identification (FEI) number. The DS Production area for biopharmaceutical operations include an (b) (4) room (class C, ISO 7), a cell culture area of capacities up to a (b) (4) scale (class D, ISO 8), a downstream processing area (class D, ISO 8), and a (b) (4) purification room (class C, ISO 7). Production areas for DS are designed as multi-product facilities utilizing (b) (4) technology. The QC labs in Lishizhen Road site have a floor area of about (b) (4) m , including a raw material lab, a microbiology lab (Endotoxin test, DNA test), a sample management lab, and a stability sample management lab. The secondary packaging production area is of (b) (4) m^2 and is currently used for the secondary packaging production of the commercial products for China's market. The area of the warehouse is about (b) (4) m^2 and is used for raw material and excipient storage and finished product (for China's market) storage.

(b) (4) DS and DP are manufactured at the BICN facility, located at 1090 Halei Road, Pilot Free Trade Zone, Shanghai, China. Production of (b) (4) starts with manufacture of the master cell banks/working cell banks in (b) (4) Further processing occurs in BICN (b) (4) Building (b) (4) from cell cultivation steps to final aseptic filling steps. Quality Control testing is performed at the (b) (4) (b) (4) site.

As of May of 2023, there are about (b) (4) persons employed at the BICN facility including quality (b) (4) production (b) (4) and QC (b) (4) The firm's office hours are (b) (4) Production hours are (b) (4) (b) (4)

Annual FDA drug registration is complete and current for the 2023 calendar year.

IV. INTERSTATE (I.S.) COMMERCE

(*This section was written by ZL.*)

This inspection was a (b) (4) inspection and interstate commerce was not evaluated. The inspection was limited to the (b) (4) DS and DP in the (b) (4) Building of Boehringer Ingelheim Biopharmaceuticals (China) Ltd. (b) (4) , located at 1090 Halei Road, Pilot Free Trade Zone, Shanghai, China. The (b) (4) DS and DP manufactured at the site are (b) (4)

V. JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

(*This section was written by ZL.*)

The firm currently has no approved commercial products for distribution in the United States

markets.

VI. INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

(*This section was written by ZL.*)

According to the firm's organizational chart, Dr. Yuguo Zang, General Manager, is the most responsible individual at the site. See [**Exhibits ZL-01** and **ZL-04**] for Organizational Charts and [**Exhibit ZL-05**] for persons interviewed by the FDA inspection team.

VII. FACILITY INSPECTION WALK THROUGH

(*The following was written by ZL.*)

In the morning of May 29, 2023, FDA investigators (ZL, LB, and YL) accompanied BICN staff on a general walk-through inspection of the firm's DS and DP manufacturing facility at Halei Road site, No. 1090 Halei Road, Pilot Free Trade Zone, Shanghai, 201203, China. The inspection team started the walk-through inspection in the warehouse areas located on the (b) (4) floor of the (b) (4) building (b) (4) which include: finished DP (b) (4) (b) (4) a raw material (b) (4) (b) (4) bulk DS (BDS) storage (b) (4) rooms (b) (4) a DS (b) (4) room (b) (4), a general ambient storage area (b) (4) a receiving area (b) (4) a pallet washing room (b) (4) a quarantine area (b) (4) a cell bank storage room (b) (4) a QC raw material sampling area (b) (4) and a rejected-goods room (b) (4) Mr. (b) (6) Supply Chain Management specialist, provided an overview of the firm's warehouse operations to the FDA inspection team. During the walk through, I (ZL) noted and pointed out to the firm's subject-matter-experts (SMEs) that (b) (4) tape was placed around an emergency exit door to the exterior of the warehouse [**Exhibit ZL-06**]. I (ZL) expressed my concern to the firm that the tape conceals potential door seal issues and can provide shelters for insects. This was communicated to the firm's management as a verbal discussion item (ZL-11) during the closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

In the afternoon of May 29, 2023, the FDA inspection team conducted a general walk-through inspection of the firm's DS downstream process (DSP) areas located on the (b) (4) floor of the (b) (4) building, which include: DS Gowning Room (b) (4) CNC/ grade D), Corridor (b) (4) (b) (4) grade D), a (b) (4) grade D), DSP storage room (b) (4) grade D), (b) (4) Room (b) (4) grade D), (b) (4) Purification Room (b) (4) grade D), (b) (4) (b) (4) grade D), (b) (4) Purification Room (b) (4) grade C), IPC/Documentation Room (b) (4) grade D), DSP Storage Room (b) (4) grade D), Washing (b) (4) grade D), Clean Equipment (b) (4) grade D), Open Bin 1 (b) (4) grade D), Weighing Room (b) (4) grade D), and (b) (4) Room (b) (4) grade D). Ms. Wenxiu Nie, Head of Downstream, provided an overview of the (b) (4) downstream manufacturing processes to the FDA inspection team. During the walk through, I (ZL) observed a QC analyst performing routine environmental monitoring (EM) of the (b) (4) Purification Room (b) (4) grade D). I (ZL) noted and pointed out to the firm's SMEs the following deficiencies in the EM operation: (1) The analyst was observed wiping the viable air sampler with a (b) (4) wipe immediately before placing an EM plate inside the sampler and taking the viable air samples; (2) There are no routine EM samples taken inside the (b) (4) grade D). These were communicated to the firm's management as a verbal discussion item (ZL-02) during the closeout meeting on June 9, 2023.

In addition, I (ZL) noted and pointed out to the firm's SMEs the cracked or separated caulk beads that were applied to seal the joints or seams between the wall and floor in Room (b) (4) [**Exhibit ZL-07**]. I (ZL) expressed my concern to the firm about the lack of adequate facility maintenance. This was also communicated to the firm's management as a verbal discussion item (ZL-11) during the closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

In the afternoon of May 29, 2023, the FDA investigators also conducted a general walk-through inspection of the upstream process (USP) areas in (b) (4) which include: Zone (b) (4) Upstream Cultivation (b) (4) grade D), (b) (4) grade C), (b) (4) grade C), Washing Room (b) (4) grade D), Clean Equipment (b) (4) grade D), Media Preparation (b) (4) grade D), Open Bin2 (b) (4) grade D), Weighing Room (b) (4) grade D), Transfer Room (b) (4) grade D), Zone (b) (4) Upstream Cultivation (b) (4) grade D), and IPC for Upstream (b) (4) grade D). Ms. (b) (6) Upstream Managers, provided an overview of the (b) (4) upstream manufacturing processes to the FDA inspection team.

In the morning of May 30, 2023, FDA investigators (ZL, LB, and YL) conducted a general walk-through inspection of the firm's DP manufacturing facility located on the (b) (4) floor of the (b) (4) building (b) (4) which includes: Corridor (b) (4) CNC), (b) (4) grade D), (b) (4) grade D), Washing (b) (4) grade D), Washing (b) (4) grade D), (b) (4) (b) (4) grade D), Filling Room (b) (4) grade D), and Inspection (b) (4) CNC). The thawing of bulk drug substance (BDS) for a DP Batch # (b) (4) was in-progress in the (b) (4) room (b) (4) Mr. Jerry Yu, Head of DP Production, provided an overview of the (b) (4) DP manufacturing processes to the FDA inspection team.

In the afternoon of May 30, 2023, the FDA inspection team (ZL, LB, and YL) conducted a general walk-through inspection of the firm's QC laboratories located on the (b) (4) floor of the (b) (4) building, which include: a Sample Receiving area (b) (4), a Stability Storage room (b) (4) an Instrument Lab (b) (4) a Particle Lab (b) (4) a Protein Analytics lab (b) (4) and a Balance room (b) (4) Mr. (b) (6) QC Managers, provided an overview of the firm's QC lab (non-microbiology) operations to the FDA inspection team.

In the afternoon of May 30, 2023, I (ZL) conducted a general walk-through inspection of the firm's QC microbiology laboratories, which include a Preparation room (b) (4) an Incubation room (b) (4) and an Endotoxin Testing room (b) (4) Ms. (b) (6) QC Microbiology Manager, provided me (ZL) with an overview of the QC microbiology lab operations. In Lab (b) (4) I (ZL) observed a QC microbiologist performing bacterial endotoxin kinetic chromogenic assay (BET) on in-process control (IPC) samples for (b) (4) DS Batch #s (b) (4) and (b) (4) While reviewing the BET test records, I (ZL) noted and pointed out the following deficiencies: (1) The certificate for a Limulus Amebocyte Lysate (LAL) Kinetic-QCL Bulk Kit (b) (4) catalog # (b) (4) used for the assay was received with a recipient listed as "… *Dummy Customer CN*" [**Exhibit ZL-08**], indicating a lack of quality oversight of GMP documentation; (2) The firm's QC electronic data review procedure, BI-VDQ-56773 (effective 12 May 2023, version 6.0), does not explicitly require a determination whether any repeated or aborted analyses/runs occurred during the testing [**Exhibit ZL-09**]. These were communicated to the firm's management as verbal discussion items (ZL-09 and ZL-04, respectively), during the

closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

In the morning of May 31, the FDA investigators (ZL, LB, and YL) observed the (b) (4) loading for (b) (4) DP Batch # (b) (4) in the DP filling room (b) (4) Mr. Jerry Yu, Head of DP Production, provided an overview of the (b) (4) loading and (b) (4) decontamination processes to the FDA team. Deficiencies in the firm's (b) (4) set-up were noted [see the discussion for FDA-483 **Observation 3A** in the Objectionable Conditions section for details]. In addition, we (ZL & YL) observed the firm operators not applying appropriate aseptic techniques during the (b) (4) loading operation. Specifically, the following deficiencies were observed: (1) Production operators were observed touching working bench, production batch records, pens, trash bags, and (b) (4) The operators did not sanitize their gloves before they proceed to operate (b) (4) (2) Production operators were observed placing a package on the working bench and wiping the flat surface of the package. The operator proceeded to place the wiped/cleaned surface on the working bench to wipe/clean another surface before the package was placed (b) (4) (3) Production operators did not fold or change the (b) (4) wipes after each cleaning stroke when they were observed sanitizing tools such as flashlights or removing particles from the (b) (4) gloves. These were communicated to the firm's management as verbal discussion items (ZL-01) during the closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

In the afternoon of May 31, 2023, I (ZL) observed the DS bioburden reduction for (b) (4) DS Batch # (b) (4) in the (b) (4) Purification Room (b) (4) Ms. Wenxiu Nie, Head of Downstream, provided me (ZL) with an overview of the processes for (b) (4) formulation, bioburden reduction (b) (4) and aliquot into DS storage bags. According to Ms. Nie, the routine EM monitoring performed by QC does not always occur during the operations. There were (b) (4) operators in the (b) (4) Purification Room during the operation. I (ZL) expressed my concern to the firm's SMEs that its EM program appears to lack adequate dynamic monitoring for the DS and DP manufacturing areas. This was communicated to the firm's management as a verbal discussion item (ZL-02) during the closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion. I (ZL) then proceeded to Cultivation-(b) (4) Room (b) (4) and observed the installation of a (b) (4) bioreactor (b) (4) for DS Batch # (b) (4) Mr. (b) (6) USP Manager, provided me (ZL) with an overview of the (b) (4) setup process. In the afternoon of May 31, 2023, I (ZL) also observed the BDS (b) (4) for (b) (4) DP Batch # (b) (4) in the (b) (4) Room (b) (4) on the (b) (4) floor of the (b) (4) building. Mr. Jerry Yu, Head of DP Production, provided me (ZL) with an overview of the DS (b) (4) operations.

On June 1, 2023, the FDA investigators (ZL and YL) observed the filling-line aseptic setup and filling/capping operations for (b) (4) DP Batch # (b) (4) in the DP filling room (b) (4) on the (b) (4) floor of the (b) (4) building (b) (4) Mr. Jerry Yu, Head of DP Production, provided an overview of the aseptic setup and filling processes to the FDA team. Deficiencies in the firm's aseptic filing line setup operations were noted [see the discussion for FDA-483 **Observation 3B** in the Objectionable Conditions section for details]. In addition, we (ZL & YL) observed the firm operators not applying appropriate aseptic techniques during the setup operations. Specifically, the following deficiencies were observed: (1) The exterior surfaces of

the (b) (4) ports were not wiped with sterile wipes each time before connecting the stopper bag to the (b) (4) port; (2) During intervention activities, production operators were observed having (b) (4) gloves (b) (4) over exposed vials (b) (4) the filling (b) (4) (3) Production operators were observed using long tweezers to manipulate the non-sterile exterior of the stopper bag. The operators then used the same tweezers to move the sterile stoppers from the inside of the stopper bag into the stopper bowl. These were communicated to the firm's management as verbal discussion items (ZL-01) during the closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion. In addition, I (ZL) noted and pointed out to the firm that, during the routine environmental monitoring following the filling activities, not all sanitized or non-sterile equipment surfaces above the sterile filling and stoppering components (direct and indirect product-contact) on the filling line were adequately sampled. For example, microbiological surface samples were not taken from the stopper bowl, stopper pick-up device, (b) (4) holder, and handle of the transition plate between the (b) (4) and (b) (4) (b) (4) and a sensor arm above the (b) (4) These were communicated to the firm's management as a verbal discussion item (ZL-02) during the closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

In the afternoon of June 1, 2023, I (ZL) observed (2) QC microbiologists performing EM plate reading in the Incubation Room (b) (4) and another QC microbiologist performing Bioburden testing in EM Lab (b) (4)

On June 5, 2023, I (ZL) conducted a general walk-through inspection of the firm's clean utilities that are used for the (b) (4) DS and DP manufacturing, which include: (1) (b) (4) Building (b) (4) Room (b) (4) Room (b) (4) Room (b) (4) HVAC Rooms (b) (4) (2) Central Utility Building (CUB): (b) (4) Room (b) (4) BMS Control Room (b) (4) Room (b) (4) and (b) (4) (b) (4) Generation System (b) (4)

In the afternoon of June 5, 2023, FDA investigators (ZL and LB) accompanied BICN staff on a walk-through inspection of the firm's facilities at Lishizhen (LSZ) Road site (No. 257 Lishizhen, Road, Pilot Free Trade Zone, Shanghai, 201203, China) that are used for the (b) (4) DS and DP manufacturing, which include: Warehouse Receiving Areas (b) (4) a (b) (4) Warehouse (b) (4) (b) (4) a Raw Material (b) (4) Storage building (Biolab Room (b) (4) and a Cell Bank Storage Room (b) (4) During the warehouse walk through, the FDA investigators noted and pointed out to the firm's SMEs that the entrance to the truck loading dock had holes on each side of the sliding door [**Exhibit ZL-10**], indicating a potentially deficient facility maintenance program and lack of quality unit's oversight. This was communicated to the firm's management as a verbal discussion item regarding facility maintenance (ZL-11) during the closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

In the afternoon of June 5, 2023, I (ZL) also conducted a general walk-through inspection of the firm's QC laboratories at the LSZ site, which include: a Sample Receiving/Storage and Stability lab (b) (4) a Microbiology lab (b) (4) and a Raw Material lab (b) (4)

During the walk-through of the labs, I (ZL) observed a QC analyst performing Container Closure Integrity Testing (CCIT) using a dye ingression method.

In the morning of June 6, 2023, I (ZL) observed the (b) (4) passage for Batch (b) (4) in (b) (4) Lab 2 (b) (4) I (ZL) noted and pointed out the following deficiencies in the operations to the firm's SMEs: (1) There is no non-viable particles (NVP) monitoring during the open operation inside the biosafety cabinet (BSC); (2) There is no post-opeation microbiological sampling of the working surface inside the BSC; (3) The fingerprint collection of operators was not done properly (*e.g.*, without rolling on the contact plate) during post-operation personnel monitoring. These were communicated to the firm's management as verbal discussion items regarding EM (ZL-02) during the closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

After the observation of the passage operation on June 6, 2023, I (ZL) observed QC sampling of (b) (4) Utility in Zone (b) (4) Upstream Cultivation (b) (4) suite (Room (b) (4) I (ZL) also performed an additional walk-through inspection of (b) (4) Room (b) (4) grade D) and (b) (4) grade D). I (ZL) noted and pointed out to the firm's SMEs that the (b) (4) room is full of (b) (4) for (b) (4) bags, which does not facilitate proper and effective cleaning and disinfection of the floors and equipment (*e.g.*, (b) (4) (b) (4) [**Exhibit ZL-11**]. This was communicated to the firm's management as a verbal discussion item regarding facility cleaning and disinfection (ZL-10) during the closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

In the morning of June 7, 2023, I (ZL) observed a QC microbiologist performed sterility test (by (b) (4) method) of a (b) (4) harvest sample in Sterility Testing Room (b) (4). In addition, the FDA investigators (ZL, LB, and YL) performed an additional walk-through inspection of QC Instrument Lab (b) (4) A deficiency in the firm's practice in integration of chromatographic analyses was noted [see the discussion for FDA-483 **Observation 7B** in the Objectionable Conditions section for details].

VIII. QUALITY SYSTEMS

Deviation Procedure(s)
(This section was written by LB.)

Deviation is handled according to 028-BIS-00491 "Deviation Management" version 1.0, a global SOP describing the roles, responsibilities, process, and documentation in deviation handling. On 5/30/2023, Mr. (b) (6) Senior QC Scientist, provided an overview of the firm's deviation management. GMP discrepancies are defined as event or deviation. Discrepancy with no or low impact on compliance and/or conformity is defined as event. Deviation is defined as a confirmed discrepancy with a potential impact on the compliance and/or conformity. Deviations are classified as minor or major. Minor deviations are those have low potential impact on the compliance and conformity, and major deviations are those have potential impact on the compliance and conformity, or product quality. The defined timeline at the firm is (b) (4) (b) (4) for deviation initiation and (b) (4) for investigation closure.

In addition, two reference documents 028-BIS-00491-RD02 and RD03 (version 2.0 for both) provide additional requirements and a technical guide for deviation management within BioBU,

such as the procedure for deviation investigation, risk assessment, timelines and extensions etc. canceling and reopening a deviation, timeline to extend the Required Actions/Corrections (RAC), the GOTrack deviation management, and deviation record.

No objectionable conditions were noted.

Deviations

(*The following was written by ZL.*)
The firm provided lists of the process, facility, and equipment deviations associated with the manufacture of (b) (4) DS and DP in the (b) (4) Building (b) (4) (b) (4) manufacturing facility since the initiation of the process performance qualification (PPQ) for US market [**Exhibit ZL-12**], under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection. A total of (163) deviations were reported. Throughout the inspection, the FDA inspection team requested and discussed various deviation investigations with firm's SMEs. I (ZL) requested and reviewed the following deviation investigations with the firm's SMEs:

Deviation #	Deviation description
679736	HL RD,DSP, Water leakage was found in the ceiling of corridor (b) (4)
680196	HL RD,DSP, (b) (4) The results of some cleaning validation items failed the acceptance criteria
732857	HL RD, USP, (b) (4) filter integrity test of exhaust filter1 can't be completed per program
758737	HL RD,USP (b) (4) of (b) (4) lost power for 14 minutes in process (b) (4)
778973	HL RD, USP, (b) (4) , filter integrity test of exhaust filter1 can't be completed per program
805686	HL RD, USP, (b) (4) filter integrity test of backup exhaust can't be completed per program
830545	HL RD,FF (b) (4) Temperature for room (b) (4) is over the limit.
918978	HL RD, F&F (b) (4) The (b) (4) filter's FIT failed 3 times
919434	HL RD, Cleaning Validation, Criteria not met for Loading Pattern (b) (4) of (b) (4)
988374	HLRD, DSP, the ground was damaged ir (b) (4)
995211	HL RD, DSP, (b) (4) Storage Temperature out of upper limit (b) (4) °C)
996957	HL RD,DSP, Water leakage was found in the ceiling of corridor (b) (4)
996984	HL RD, USP, (b) (4) Exhaust filter integrity test can't be completed per program
1004126	HL RD, USP, (b) (4) medium (Lot# (b) (4) filter integrity test failure
1008294	HLRD, USP, (b) (4) Exhaust 1 and Exhaust 2 filter testing failure for (b) (4)
1039778	HL RD, F&F, (b) (4) Production preparation was temporarily stopped
1039987	HLRD, DSP, (b) (4) wrong (b) (4) was used to (b) (4)
1041126	HL RD,DSP (b) (4) A pump tube with scratch was used in Q step Flow kit test
1052646	HL RD, USP, (b) (4) Exhaust filter integrity test can't be completed per program
1067296	HL RD, USP, (b) (4) exhaust filter integrity test can't be completed per program
1088013	HL RD, USP, (b) (4) Exhaust filter integrity test can't be completed per program

1101663	HL RD, USP, (b) (4) exhaust filter integrity test can't be completed per program
1125921	HL RD, USP, (b) (4) filter integrity test failed
1126378	HLRD, USP, (b) (4) Filter integrity test failed three times during (b) (4) solution preparation
1127114	HL RD, USP, (b) (4) Exhaust filter integrity test failed
1129556	HL RD, DSP (b) (4) the first filter instead of the second was tested for FIT
1130688	HL RD, USP, (b) (4) Exhaust filter integrity test failed
1132396	HLRD,DSP (b) (4) ,operator interfere with pressure sensor of installed flow kit
1125921	HL RD, USP, (b) (4) filter integrity test failed
1213591	HL RD, F&F, (b) (4) Capper failure cause production stop
1256644	HL RD DSP (b) (4) Wrong flow kit method was used for (b) (4)
1261178	LSZ RD,QC (b) (4) Disconnect the network of W010 record on KAYE system
1295099	HL RD, DP, Media Fill, (b) (4) media fill was not executed within the scheduled period
1343058	HL RD,FF (b) (4) Glove integrity test report curve breakpoints not retest
1376059	HL RD,USP, (b) (4) filter integrity test of (b) (4) um medium filter failed.
1553118	HL RD, F&F, (b) (4) failure cause production stop
1596535	HL RD USP Room (b) (4) Ceiling Leakage

Three (3) deviations, PR#s 670736, 996957, and 1596535, were initiated for the ceiling water leaks found in the DS manufacturing areas [**Exhibit ZL-13**]. There was no microbiological surface sampling of the impacted areas taken before and after repair to ensure the effectiveness of the cleaning and disinfection. This concern was communicated to the firm's management as a verbal discussion item (ZL-05) during a closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion. In addition, during the discussion of the deviation investigations, I (ZL) noted and pointed out to the firm's SMEs that all (18) deviations associated with the filter integrity test (FIT) failures [**Exhibit ZL-14**] had been initially classified as "*Minor*" deviations. I (ZL) stated it to the firm that these deviations can have potential adverse product impact and should have been classified as major deviations to ensure prompt, thorough, and effective investigations. Ms. Anji Shen, Head of Quality System, acknowledged my concern.

(*The following was written by LB.*)
I requested and reviewed the following deviations and events with SMEs.

Deviations:

- 887526: (b) (4) WCB did not meet acceptance criteria
- 914036: (b) (4) bag leakage during (b) (4) process
- 976982: (b) (4) The number of filters (b) (4) for (b) (4) step was below low limit
- 754985: Bag leakage during (b) (4) process
- 778973: (b) (4) ,filter integrity test of exhaust filter1 can't be completed
- 956048: (b) (4) leakage occurs in the tube during (b) (4)

- 958896: (b) (4),liquid spilled from protective casing of (b) (4) BDS during BDS transfer
- 967427: (b) (4) and (b) (4) speed out of range
- 988118: (b) (4) bag leakage detected during DS aliquotation
- 995248: (b) (4) datalogger disconnect from temperature sensor of cell bank shipper
- 1132398: (b) (4) cell bank Storage SCADA data loss
- 1459175: (b) (4) leakage detected during (b) (4)
- 1146626: leakage was found from the (b) (4) port on (b) (4)
- 703552: (b) (4) leakage of (b) (4) prior (b) (4) formulation
- 707682: liquid seeped on (b) (4) in batch (b) (4)
- 711625: Leakage found during performing blank run of (b) (4)
- 779260: (b) (4) Leakage happened at the DS bag during DS (b) (4)
- 978311: (b) (4) bag (b) (4) connection leakage found during (b) (4) load
- 1316207: (b) (4) Leakage occurs in a (b) (4) bag of the BDS before (b) (4)
- 1375826: (b) (4) Leakage found when prepared to adjust diluted spike (b) (4) bag
- 1460384: (b) (4) leakage detected on DS bag during DS aliquotation
- 1465035: (b) (4) Leakage detection on (b) (4) bottleneck of (b) (4)
- 1488176: (b) (4) connection leakage at rear of (b) (4) during (b) (4)
- 1488199: (b) (4) Leakage found around bag outlet when finishing (b) (4) transfer
- 1321753: (b) (4) intermediate (b) (4) out of range in (b) (4)
- 804025: (b) (4) The (b) (4) transfer tube was leaked during DS aliquotation
- 1605347: (b) (4) the temperature exceeded normal operating range
- 1459175: (b) (4) leakage detected during (b) (4)
- 805685: (b) (4) equipment defined in MBR can't be used for harvest

Events:

- 754985: bag leakage during (b) (4) process
- 1095204: (b) (4) bag leakage
- 1100190: (b) (4) Q Cyc1 product bag leakage
- (b) (4) The "overpressure detected" alarm occurs during the (b) (4) of (b) (4) transfer due to bubbles.
- (b) (4): before sampling it was found material particles at the dead angle at the bottom of the bag were not completely dissolved and continues to stir for (b) (4) to completely dissolve.

Several deviations and events related to leakage were found to have inadequate risk assessment and corrective actions, including deviations PR# 707682, 804025, 1038242, 1274193, and 1308704, and events PR# 754985, 1095204, and 1100190 [**Exhibit LB-09**]. The deficiencies led to **FDA 483 Observation 6A**. See **section XV OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE** for more information.

(*The following was written by YL.*)

I (YL) requested and reviewed the following deviation investigations with the firm's SMEs:

Deviation Number	Deviation description
1580781	HL RD, USP, (b) (4) Partial MFCs/win data loss of (b) (4) Medium (b) (4)
1576646	HL RD,DS USP, The calibration master data is inconsistent with process range.
1577789	HL RD USP (b) (4) MFCS/win partial information loss.
1550874	HL RD, DP/FF, (b) (4) & Capper, the calibration master data is inconsistent with actual process parameter.
1457828	HL RD, E&T, (b) (4) alarms cannot be notified to production in real time by the SCADA system.
1422557	HL RD, E&T, (b) (4) SCADA Power Air Switch Disconnect and Data Loss.
1410823	HLRD,DSP,BD test report lost.
1396591	HL RD,FF, (b) (4) Real-time data not displayed after modbus communication failure.
1388326	QA observed that working copy of cleaning record was not used for GMP operation during oversight
1388328	HL RD, USP, (b) (4) QA observed that working copy of room cleaning record was not used for GMP operation during oversight
1344482	HL RD,DSP, (b) (4) test data of (b) (4) cycle2 is displayed as illegal (b) (4)
1302594	HL RD, USP, (b) (4) MFCS/win lost 5h36min55s data in (b) (4) of (b) (4)
1302571	HL RD, DSP, part of electrical data in (b) (4) was lost and cannot be read.
1277580	LSZ RD,E&T,EMS: EMS data is lost.
1159536	LSZ RD,USP The EMS monitoring data of refrigerator RE-6107 in room (b) (4) is loss.
1136273	HL RD,DSP (b) (4) test data of (b) (4) is displayed as illegal.
1132398	HL RD USP (b) (4) cell bank Storage SCADA data loss
1089063	HL RD USP (b) (4) cell bank Storage (b) (4) incubator SCADA data loss.
1003302	HL RD,USP, (b) (4) MFCS/win can't record audit trail from (b) (4) and (b) (4)
950814	HL RD, QC, (b) (4) the (b) (4) failed in raw data, but it was manually transferred as passed.

758755	HL RD, E&T, SCADA Cabinet 24V Power Down and Data Loss
1583609	HL RD,DP,(b) (4) AQL result of individual defect (Major A Defects) was over limit.

Based on the deviation reports, data loss events were reported on multiple computerized systems. Specifically, five deviations (PR# 758755, 1089063, 1132398, 1422557, and 1457828) reported data loss on SCADA system while five deviations (PR# 1003302, 1302594, 1577789, 1580781, and 1277580) documented data loss on MFC/win and EMS systems. Although CAPAs were implemented to address the identified causes of the data lost, it appears that no comprehensive risk assessments were conducted to evaluate the entire computerized systems. In addition, it appears that the firm did not implement data back-up mechanisms to ensure adequate security of the data.

*The observed deficiencies led to **FDA 483 Observation 4D**.*

Change Control Procedure(s)
(*This section was written by YL.*)

Change Control (CC) is handled according to 028-BIS-00484 version 1.0, effective 02, Nov 2020, a global SOP describing the roles, responsibilities, process, and documentation in change control handling. Change control covers changes in computerized systems, process, product, manufacturing, quality control and distribution of medical devices, DP, vaccines, and DS as well as any components thereof including but not limited to cell banks, starting materials, raw materials, packaging materials, excipients.

No objectionable conditions were noted.

Change Controls

(*The following was written by ZL.*)
The firm provided lists of the process, facility, and equipment change controls associated with the manufacture of (b) (4) (also known as (b) (4) DS and DP in the (b) (4) Building (b) (4) manufacturing facility since the initiation of the process performance qualification (PPQ) for US market [**Exhibit ZL-15**], under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection. A total of (163) change control (CC) requests were reported.

(*The following was written by LB.*)
I requested and reviewed a list of change controls. Selected items as shown below were further discussed with SMEs.

- CC-2020-0082: Introduction of (b) (4) DS manufacturing process into (b) (4) (b) (4) area.
- 864798: Introduction of (b) (4) and support equipment in GMP operation
- 926379: Update (b) (4) range, addition amount and (b) (4) in MBR
- 952163: To introduce new Lot WCB of (b) (4) project for commercial production.
- 1255096: (b) (4) step can be directly loaded without titer results in some cases
- 1256718: Covid-19 temporary release the current complaint flow kit for downstream

- 1386082: (b) (4) Adjust supplement day and remove amount limit of (b) (4) addition
- 1456309: USP Introduce new (b) (4) Bag for (b) (4) production
- 1460567: Allocate (b) (4) DS batch (b) (4) to be used for US commercial DP.

No objectionable conditions were noted.

(*The following was written by YL.*)

I requested and reviewed a list of change controls. The following items were further discussed with SMEs.

- 816188: 2021 Facilities & Utility (b) (4)
- 876992: Adjust the lower limit of the maximum (b) (4) speed of the Filler（O1-A-6808-FF）
- 880878: Introduce bag integrity test system into (b) (4) USP.
- 914019: 2021 Extend AHU Preventive Maintenance Interval
- 934904: Upgrade Building Management (BMS) / Environment Monitoring System (EMS)
- 947111: Fill & Finish (b) (4) room introduce a Glove Tester and PC for (b) (4) glove integrity test
- 941391: Introduction of (b) (4) Pressure Monitoring System in DP
- 1199154: HL RD DSP add a (b) (4) as backup for (b) (4) system
- 122456: Add Solutions in 105-SOP-000087 RA-04 for partial pipeline shortages
- 1261106: Covid-19 Temporary CC for Extension of Equipment Periodic requalification
- 1253423: Temporary extend the preventive maintenance workorder completion date.
- 456309: Introduce new (b) (4) Bag for (b) (4) production.
- CC-2020-0116: Introduce one new (b) (4) new Kaye ValProbe loggers
- CC-2020-0134: (b) (4) Project: implement an additional Visual Inspection area in (b) (4) including equipment and (b) (4)

No objectionable conditions were noted.

Annual Product Review
(*This section was written by LB.*)

The BioPharma Global SOP (BGS) document 099-BGS-00132 "APR/PQR within BioBU" Version 4.0 describes the procedure for Annual Product Reviews/ Product Quality Reviews. Document 099-BGS-00132-RD01 version 2.0 provides a template for compilation of the product review reports. The review is typically performed annually. It covers the summary test results of (b) (4) DS and DP and lists other quality related matters such as critical manufacturing parameters, quality failures, change controls, rejects, product complaints and recalls, deviations, CAPAs, and summary of on-going stability studies.

I requested and reviewed the latest annual product review report 028-PQR-AB46910 Version 1.0, covering the period of 12/26/2021 to 12/25/2022. The APR was performed for (b) (4) lots intended for China market. A total of (b) (4) DS lots were manufactured, of which (b) (4) were released and (b) (4) were pending review. A total of (b) (4) DP lots were manufactured, of which (b) (4) were released and was aborted due to COVID lockdown. No adverse quality trends were observed.

No objectionable conditions were noted.

Stability

(*This section was written by LB.*)

Document 099-BGS-01156 "Stability Testing in BioBU" version 1.0 is a global SOP describing the standard process and general approaches for performing stability studies throughout the product life cycle. Stability studies are performed according to specific stability protocols and the study results are summarized in stability reports. Following the general principles outlined in the global SOP, the local SOP document BI-VQD-56890-S "Stability Management at Quality Control Biopharmaceuticals China" Version 7.0 provides detailed guidelines for managing the firm's stability program.

On 5/31/2023, I inspected the QC sample management and stability areas. Room (b) (4) houses stability chambers of (b) (4) °C, 5°C, 25°C, and 40°C. Ms. (b) (6) from QC provided an overview of firm's stability program. Briefly, the Stability Team is responsible for planning stability studies and creating protocols with specified batch number. QC stability samples from production are labeled and placed into respective chambers by Stability Team. Stability information such as storage condition, time points, and sample amount is entered into LIMS, which will automatically create testing notifications before each timepoint.

Protocols 105-T-001933_P-01 and 105-T-001934_P-01 are used for (b) (4) DS and DP long-term stability studies, respectively. The protocols specify the sampling and testing plans and require that at least 1 commercial batch per year is placed on annual stability. I confirmed that for year 2023, one batch each of the DS (b) (4) and DP (b) (4) were placed on stability. The DS stability is performed at long-term condition (b) (4) °C to (b) (4) °C) for up to 60 months, and the DP stability is performed at long-term condition of 5 ± 3°C for up to 48 months. Stability samples are stored in containers representative of those used for the DS/DP commercial use. The DP stability samples are stored in inverted positions.

No objectionable conditions were noted.

Internal Audits

(*This section was written by LB.*)

Document 028-OCS-00353 "Internal Quality Audits at Boehringer Ingelheim" Version 5.0 (document number BI-VQD-10413) is a global SOP that governs the general process for internal quality audits (self-inspections) at BI. The List of Applicable Processes (028-OCS-00353-RD01) and Audit Universe Template (028-OCS-00353-RD02) are used when preparing for internal audits, and the audit plans are prepared following a risk-based determination of audit frequency and area etc. The risk assessment is performed (b) (4) via the Risk Assessment Template 028-OCS-00353-RD03. The audits include 4 types: regular audits, process audits, for-cause audits, and support audits. Upon completion, an audit report is prepared summarizing the audit findings and associated CAPA plan. The audit findings are trended by area at minimum on a (b) (4) basis.

No objectionable conditions were noted.

Quality Agreements and Contractor Qualification
(*This section was written by LB.*)

I reviewed the quality agreement document 099-QAA-02608 "BICN-(b) (4) CMB-QAA-commercial" Version 4.0 between the firm (b) (4) DS and DP manufacturer) and (b) (4) holder of (b) (4) This agreement describes the responsibilities of the firm and (b) (4) with respect to the quality of (b) (4) DS and drug product. I also reviewed the quality agreement 099-QAA-00180 Quality Agreement between BI BP China / (b) (4) Version 3.0, between the firm and (b) (4) (referred to as (b) (4) . The high-bay warehouse (room (b) (4) and a (b) (4) (Room (b) (4) at (b) (4) are (b) (4) (b) (4)

The contractor qualification is governed by the global SOP document 099-BGS-00011 "Management of Supplier/Manufacturers in BioBU" Version 5.0. It covers the material suppliers, service providers, and equipment and computer systems suppliers. The SOP describes how to assess and manage the quality of the contractor suppliers and manufacturers. Based on the risk of the intended use and impact on product quality, suppliers are categorized into 3 categories: Category 1, 2, and 3, with Category 1 having the highest risk/impact. Quality audits are performed at least (b) (4) for Category 1, and (b) (4) for Category 2 and "certified" Category 3 suppliers. Qualification is typically initiated due to supplier change, new product introduction, quality issues, new regulatory requirement, client requests, or business and supply needs. Initial qualification of suppliers for excipients, (b) (4) derived materials, and primary packaging materials require (b) (4) batches to be tested. The QC testing results are compared to those from the suppliers CoA or the material specifications. Re-qualification of the suppliers may be needed in cases of quality or compliance issue, inactive status, or significant changes for example. I reviewed the most recent supplier qualification report #1544189 for (b) (4) (b) (4) that was performed in 2/2023, for which the prior 2 audits were performed in (b) (4) (PR# 290861) and (b) (4) (PR# 943892).

No objectionable conditions were noted.

(*The following was written by ZL.*)
During the inspection, I (ZL) requested and performed a cursory review of the following quality agreements:

- **099-QAA-01119** "Quality Assurance Agreement between Boehringer Ingelheim and (b) (4) for all (b) (4) products (*e.g.*, (b) (4) (version 2.0, effective 19 Oct 2022)
- **099-QAA-03693** "Quality Assurance Agreement between Boehringer Ingelheim and (b) (4) for all (b) (4) products (*e.g.*, (b) (4))" (version 2.0, effective 02 Aug 2022)
- **099-QAS-02971** "Participation Agreement between BioChina and (b) (4) for Rabbit Pyrogen Testing (USP151)" (version 1.0, effective 26 Mar 2020)

I (ZL) also requested and reviewed periodic reviews and associated audit reports for the following material vendors and service providers:

- (b) (4) Bioindicator vendor

- (b) (4) DP Filling System Assembly vendor
- (b) (4) vendor
- (b) (4) Inoculation/passages sterile components vendor
- (b) (4) Rabbit Pyrogen Test provider
- (b) (4) HVAC and clean environment
- (b) (4) (b) (4) maintenance/test vendor

My review revealed that the firm currently does not perform any audit of the contractor service providers that are responsible for the firm's HVAC and clean environment maintenance and testing, including HEAP filter integrity testing for the firm's DS and DP manufacturing facilities. Specifically, only a verification of adherence to BI's QMS was performed for the service provider, (b) (4) [**Exhibit ZL-16**]. I (ZL) pointed out to the firm that its documented supplier qualification failed to include a comprehensive assessment and associated site audit of the service provider's capability to perform the critical validation services. I (ZL) expressed my concern to the firm that its quality unit had not fully exercised its responsibilities regarding the critical service contractors' qualification. I (ZL) stated to the firm that it is essential that the firm selects a qualified contractor and maintains sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant. This concern was communicated to the firm's management as a **verbal discussion item** (ZL-06) during a closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

Product Complaints/Returns Procedures
(*This section was written by LB.*)

Product complaints are handled according to the SOP document BI-VQD-58203-S "Handling of Technical Product Complaints" version 7.0. Complaints include those from client and health authority. Complaints are managed in Global Complaint Management System GOTrack per BI-VQD-58203-S-AD01. An overview of the complaint investigation and CAPA process is described in BI-VQD-58203-S-AD02 version 2.0. Complaints are trended (b) (4) In 2021, there were 4 complaints including 1 for bottle/vial defect (change control PR830309 was initiated for this) and 3 complaints for primary packaging/plastic cap off. In 2022, there was 1 complaint due to primary packaging/plastic cap off.

The SOP document BI-VQD-165636-S "Quality return Process" version 1.0 describes the process for handling product returns. According to the return product evaluation procedure, the returned products are either reprocessed/reworked per BI-VQD-56900-S or rejected per BI-VQD-55284-S. The evaluation will take into consideration of the nature of the product, transport and storage conditions, product quality concerns etc. Return records are documented in paper records using form BI-VQD-165636-S-FO01 Return Goods Information Record. No returns were reported in 2022.

No objectionable conditions were noted.

Training
(*This section was written by LB.*)

The firm's training is governed by SOP document BI-VQD-57732-S "Training Program" version 8.0, which describes the assessment procedures, structure, and scope of GMP training. On 6/6/2023, Mr. (b) (6) (QS Scientist) provided an overview of the firm's training program. There are 3 types of training, including initial training, continuous training, and training on demand. Training requirements for each employee are assigned per role or function in a training matrix which includes initial training, continuous training, and training on demand. Employees are required to complete all necessary training prior to perform GMP operations. Training methods include instructor led, on-the-job/operational, and document based (read and understand). Training documents are maintained electronically in LOS (Learning One Source) system and/or in paper records. Training effectiveness is assessed upon completion and is documented on BI-VQD-57732-S-FO01 Training Form.

I requested and reviewed the training records of Ms. (b) (6) and Mr. (b) (6) for harvest unit operation, Ms. (b) (6) and Ms. (b) (6) for binding ELISA assay, and Mr. (b) (6) for CZE assay.

No objectionable conditions were noted.

(*The following was written by ZL.*)
Throughout the duration of the inspection, I (ZL) requested and reviewed the several BICN employees' training records for their GMP and job-function specific training.

No objectionable conditions were noted.

BPDR, Recall, AE Procedures
(*This section was written by LB.*)

Product recalls are handled according to BI-VQS-57736-S "Handling of potential market actions (recalls) in BioPharma China" version 5.0. Quality issues triggering recalls are investigated covering the impacted products/areas, root cause and immediate action and applicable CAPA, prior to determining the market action plan/ recall strategy. Mock recalls are implemented per client's requirement. No recalls were reported during 2022.

No objectionable conditions were noted.

Document Control Procedures
(*This section was written by YL.*)

Document control procedures are handled according to BI-VQD-55047-S Version 4.0 effective 11 May 2023 "Vault Quality (Veeva) – General Vault Quality (Veeva) Rules, Hierarchy, Categories, Creation and Management of Controlled Documents in BioPharma China" and BI-VQD-58199-S Version 11.0 effective 13 Jan 2023 "IDEA for CON – General IDEA Rules, Hierarchy, Categories, Creation and Management of Controlled Documents in BioPharma China". The procedures described the hierarchy of controlled documents at BI Biopharma China and specifies the creation and management process of controlled documents such as SOPs, Working Instructions (WIs) and Process Description in Vault Quality or IDEA for CON.

No objectionable conditions were noted.

Computerized Systems

(*The following was written by YL.*)

The following procedures I reviewed provide guidance in the management of the firm's computerized systems:

BI-VQD-04122-S-AD02 Points to consider for Computerized Systems effective date 01/20/2023

027-BIS-00061 System Backup and Restore/Recovery effective date 04/01/2020

028-BIS-00522 Operational Use of Computer Systems effective date 11/02/2020

BI-VQD-168579-WI Working Instruction for Electronic Data Archiving effective date 05/19/2023

BI-VQD-56773-S Electronic Data Review in QC effective date 05/12/2023

BI-VQD-55525-S QA oversight to QC effective date 03/14/2023

During the inspection, deficiencies were observed with respect to software's use and data backup in the firm's Quality System.

*[see the discussion for **FDA 483 Observation 4** in the Objectionable Conditions section for details].*

(*The following was written by ZL.*)
The firm provided a list of GMP computerized systems, under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection [**Exhibit ZL-17**]. Throughout the inspection, the FDA inspection team (YL, LB, and ZL) requested and discussed various computerized systems, which are used for (b) (4) DS and DP manufacturing, with the firm's SMEs. Deficiencies in the validation and control of these electronic data acquisition and manufacturing control systems were noted [see the discussion for **FDA 483 Observation 4** in the Objectionable Conditions section for details].

I (ZL) also requested and reviewed procedure BI-VDQ-56773 (effective 12 May 2023, version 6.0), which governs the firm's Quality Control reviews including electronic data review. I (ZL) noted and pointed out to the firm that the procedure revealed that the audit trail review procedure does not explicitly require a determination whether any repeated or aborted analyses/runs occurred during the testing. In addition, I (ZL) noted and pointed out to the firm additional deficiencies in the firm's computerized system controls: (1) The firm currently does not have an IT group that is independent of production, engineering, and QC labs. The system administrators for the firm's computerized systems are designated to the staff of the firm's Engineering & Technology (E&T) department, which is responsible for the validation and calibration of the process equipment and analytical instrument at the site. I (ZL) expressed my concern to the firm that the system administrators, responsible for control of the records generated by the computerized systems, are also corresponding functional area (validation) managers responsible for the content of the generated records; (2) There appears be a lack of documented evidence in the firm's computerized system validation (CSV) reports reviewed during the inspection that each system had been fully validated for data backup/transfer and retrieval. These concerns were

communicated to the firm's management as **verbal discussion items** of additional deficiencies ragarding data governance (ZL-04) during a closeout meeting on June 9, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

(The following was written by LB.)
Unicorn and Empower computerized systems are used in data collection, processing, and storage for (b) (4) manufacturing and QC testing, respectively. I requested and reviewed a user list with access levels for Unicorn and Empower. The Unicorn user list showed a "Default" Administrator account without specific user ID. On 6/5/2023, I followed up with Ms. (b) (6) (DSP Manager) regarding the Unicorn "Default" Administrator account, and I was told that the account was shared by (b) (4) mployees **[Exhibit LB-03]**. In addition, each of these (b) (4) employees has an additional account under their specific user IDs, including one Administrator, two Power users, and one User. For the Empower user list **[Exhibit LB-04]**, one QC analyst involved in routine QC testing was shown to have multiple levels of user privileges, including Coordinator, Sign2, User_AH1, and User_Data_Import. Document BI-VQD-04122-S-AD02 "Points to consider for computerized systems" version 4.0 (an associated document of BI-VQD-04122-S entitled Specific Data Integrity Requirements in BioPharmaceuticals) requires that individual login credentials be used with no shared accounts, and that the number of user accounts should fit to the intended use of the system. Deficiencies in user access controls for Unicorn and Empower led to FDA 483 **Observation 4A** (items 1 and 2). Refer to **Objectionable Conditions** section below for more details.

IX. FACILITY AND EQUIPMENT

A. Facilities

HVAC & Building/Alarm Management Systems
(*This section was written by ZL.*)

On May 31, 2023, Mr. (b) (6) Head of Engineering & Technology (E&T), provided me (ZL) with an overview of the firm's HVAC (Heating, Ventilation, and Air Conditioning) system and cleanroom HEPA (high-efficiency particulate air) filter certification program for the (b) (4) DS and DP manufacturing facilities [**Exhibit ZL-18**], governed by the following procedures:

- **BI-VQD-55342** "Operation of AHU & MAU for Ha Lei Road Site" (version 8.0, effective 04 May 2023)
- **BI-VQD-58814** "Testing of HVAC HEPA Filter for HL RD Site" (version 5.0, effective 07 May 2022)

There are (b) (4) HVAC systems serving GMP areas at the site. (b) (4) make-up air units (MAU) provide 100% fresh air for (b) (4) Labs (b) (4) and Microbiology Lab independently. (b) (4) MAUs provide fresh air for (b) (4) cleanroom recirculation air-handling units (AHU) [serving for USP (b) (4) area (grade C), USP production area (grade D), DSP production area (grade D), USP storage area (grade D), DSP storage area (grade D), DSP (b) (4) purification area (grade D), (b) (4) purification area (grade C), DP filling area (grade C)]. The fresh air ratio is above (b) (4) %. The MAUs and recirculation AHUs draw the air into the building and pass through a (b) (4) filter (Removal Efficiency rating "Em" according to (b) (4) % ≤ Em <

(b) (4)%) and a (b) (4) filter (Removal Efficiency rating "Em" according to (b) (4) % ≤ Em). The air temperature and relative humidity (RH) is adjusted to ((b) (4) °C and (b) (4)% RH) and additionally filtered by HEPA (H14) type filters before entering the individual manufacturing area. The DP filling line is situated inside a (b) (4) (ISO 5) with a Grade C background. Pressure differences between different classifications or between classified area and unclassified area, are maintained at (b) (4) - (b) (4) Pa. A Building Management System (BMS) is utilized to control and monitor the HVAC systems and environment.

According to SOP BI-VQD-58814, HVAC systems are routinely tested for air change rates (grade C ≥(b) (4) air changes per hour; grade D ≥(b) (4) air changes per hour), differential pressures, and HEAP filter integrity (leak testing). The tests are performed (b) (4) for all HEPA filters in Zones (b) (4) My review of the HEPA testing procedure revealed that it stipulates that the acceptance criterion for the HEPA filter leak test using (b) (4) is not more than (b) (4) (≤(b) (4)) percent of the upstream challenge (refer to Section 4.4.3.3). This would deem a measured value of (b) (4)% acceptable. However, according to FDA 2004 Guidance for Industry "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice", "*a single probe reading equivalent to 0.01 percent of the upstream challenge would be considered as indicative of a significant leak and calls for replacement of the HEPA filter or, when appropriate, repair in a limited area.*" I (ZL) stated it to the firm that a test result equivalent t (b) (4) percent should prompt a replacement of the HEPA filter, especially for the ones used in the critical, aseptic process areas. This was communicated to the firm's management as a **verbal discussion item** (ZL-06) during the closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

The following documents associated with the HVAC systems and qualification, which had been requested and submitted under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection, were briefly reviewed during the inspection with the firm's SMEs:

- **106-E-011712-VSR** "Validation Summary Report of Cleanrooms: Grade D and Grade C" (version 1.0, effective 16 Apr 2018)
- **106-E-011776-VSR** "Validation Summary Report of GMP HVAC Systems: Grade D and Grade C" (version 1.0, effective 12 Apr 2018)
- **106-E-011712-VSR06** "Validation Summary Report of Periodic Requalification for HVAC and Cleanrooms of HL RD Site" (version 1.0, effective 22 Dec 2022)
- **106-E-032658-VSR** "Validation Summary Report of Cleanrooms for (b) (4) Project" (version 1.0, effective 29 Mar 2021)
- **106-E-032659-VSR** "Validation Summary Report of GMP HVAC Systems for (b) (4) Project" (version 1.0, effective 29 Mar 2021)
- **106-E-032658-VSR04** "Validation Summary Report of Periodic Requalification for HVAC and Cleanrooms of HL RD Site (b) (4) Area)" (version 1.0, effective 28 Oct 2022)

During the inspection, I (ZL) also requested and reviewed the following documentation associated with the HVAC system routine testing:

- (b) (4) Clean Room Test Report by (b) (4) approved 15 Feb 2023

On May 31, 2023, Mr. (b) (6) Senior Process Engineer, and Mr. (b) (6) QA Specialist, provided me (ZL) with an overview of the firm's alarm management systems [**Exhibit ZL-19**], governed by the following procedures:

- **BI-VQD-57759** "Handling of GMP Relevant Alarms in BioPharma China" (version 13.0, effective 12 May 2023)
- **BI-VQD-56775** "Standard Operating Procedure for MS System in Halei Road Site" (version 10.0, effective 28 Apr 2023)
- **BI-VQD-57811** "Standard Operating Procedure for SCADA System in Halei Road Site" (version 13.0, effective 28 Apr 2023)

An Environment Monitoring System (EMS) is utilized to monitor, record, and store the cleanroom environment parameters (differential pressure, temperature, and humidity) data and alarms. Standalone Supervisory Control and Data Acquisition (SCADA) systems are used to collect and monitor process equipment related alarms and parameters data. According to SOP BI-VQD-57759, all alarms need to be acknowledged by an E&T staff in (b) (4) after the alarms occurred. The alarm affected department needs to complete the relevant impact assessment within (b) (4) After an alarm is initiated, a determination is made as to whether a deviation is to be initiated. All alarm events are required to be closed within (b) (4) (b) (4) During the inspection, I (ZL) requested and performed a cursory review of the following documentation associated with the GMP alarms:

- **105-TR-002356** "Automation System Alarm Trending Report for 2022" (version 1.0, effective 14 Apr 2023)

I (ZL) also requested and reviewed the EMS room pressure, temperature, and humidity monitoring data for DP Filling Room (b) (4) DS (b) (4) Purification Room (b) (4) DS (b) (4) Purification Room (b) (4) and (b) (4) Lab 1 (b) (4) for the period of the inspection, with the firm's SMEs.

Environmental Monitoring
(*This section was written by ZL.*)

On June 2, 2023, Mr. (b) (6) QC Microbiology Manager, provided me (ZL) with an overview of the firm's Environmental Monitoring (EM) program, governed by the following procedures:

- **BI-VQD-56735-S** "Environmental Monitoring in Bio China" (version 19.0, effective 15 Mar 2023)
- **BI-VQD-54238-S-AD02** "Halei Road Site Routine Environmental Monitoring Sampling Plan and Layout" (version 22.0, effective 30 Mar 2023)
- **BI-VQD-58941-S** "Trending Analysis of Environmental Monitoring Data" (version 6.0, effective 26 May 2023)
- **BI-VQD-55310-S** "Test Methods of Microbiology and Particle for Environment Control" (version 13.0, effective 25 May 2023)

- **105-SOP-000504** "Identification Test for a Microbial Strain" (version 4.0, effective 15 Aug 2022)
- **105-SOP-001347** "In-house Flora Build-up and Management in Shanghai Site" (version 5.0, effective 26 May 2023)
- **105-RA-000064** "Environmental Monitoring Site Selection Rationale for all clean area in (b) (4) Site" (version 3.0, effective 18 Jul 2022)

The following documents associated with the EM Trending Reports, which had been requested and submitted under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection, were reviewed with the firm's SMEs during the inspection:

- **105-TR-002183** "Environmental Monitoring Trending Report of Halei Site Clean Rooms: (b) (4) (version 1.0, effective 01 Apr 2022)
- **105-TR-002250** "Environmental Monitoring Trending Report of Halei Site Clean Rooms: (b) (4) " (version 1.0, effective 08 Aug 2022)
- **105-TR-002321** "Environmental Monitoring Trending Report of Halei Site Clean Rooms: (b) (4) " (version 1.0, effective 09 Mar 2023)

According to SOP BI-VQD-58941-S, EM trending analyses for the prior (b) (4) EM data are performed (b) (4) I (ZL) also requested and reviewed the following EM excursions with the firm's SMEs:

- Action Limit Excursions: DV# 1011261; DV# 1123300; DV# 1444151; DV# 1463701
- Alert Limit Excursions: OOL-E-2021-04; OOL-E-2021-09; OOL-E-2021-10; OOL-E-2021-11; OOL-E-2021-21; OOL-E-2021-22; OOL-E-2021-23

According to SOP BI-VQD-56735, environmental monitoring of the firm's DS and DP manufacturing areas in (b) (4) is performed as follows:

Clean Areas	Area Function	Active Viable Air (CFU/m³)	Contact Plates (CFU/plate)	Settle Plates	Total Particles
Grade C	(b) (4) purification, Filling	(b) (4)			
	Corridors (b) (4) Storage, Washing				
Grade D	(b) (4) Media Preparation, (b) (4) purification, Cell culture				
	Corridors (b) (4) Storage, IPC				

Clean Areas	Active Viable Air	Surface Monitoring**	Settle Plates	Finger DAB	Total Particles
(b) (4)	(b) (4)				

LAF for aseptic process	(b) (4)
LAF for Non-aseptic process	
Weighing Booth	

* set-up, (b) (4) of fill; ** contact plate or swab

Deficiencies in the firm's environmental monitoring of aseptic processing areas following aseptic assembly of filling components and aseptic filling operations were noted [see the discussion for **FDA 483 Observation 3C** in the Objectionable Conditions section for details]. In addition, the following deficiencies regarding the firm's EM program that are not included on the Form FDA 483 were noted: (1) There is no microbiological surface sampling for all DP F&F (fill & finish) grade C and grade D areas except for the DP filling room (b) (4); (2) There is no microbiological surface sampling for all DS grades C/D (b) (4) (b) (4) equipment washing areas, storage areas, and IPC areas; (3) There is no EM sampling for all Grade C/D (b) (4) (4) Microbiological surface sampling taken in the grade C/D areas does not include floor drains, sinks, and utilities (refer to Page 13 of 20 in SOP BI-VQD-54238-S-AD02); (5) There are no EM sampling points in the (b) (4) processing area (also refer to **FDA 483 Observation 5**); (6) There is no passive air monitoring (settling plates) in the Grade C/D manufacturing areas; and (7) There appears to be a lack of scientifically sound justification and/or historical data for relatively low EM sampling frequencies (*e.g.*, (b) (4) (b) (4) for grade C support areas and (b) (4) for grade D support areas), considering the high volumes of manufacturing activities in the firm's DS/DP manufacturing areas. I (ZL) expressed my concerns to the firm that inadequate EM sampling (locations and frequencies) can have a significant adverse impact on the reliability and accuracy of the firm's EM data and overall assessment of the state of environmental control of the DS/DP manufacturing facilities. The EM program should provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness. These were communicated to the firm's management as **verbal discussion items** (ZL-02) during the closeout meeting on June 09, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

Facility Cleaning & Sanitization
(*This section was written by ZL.*)

The firm's facility cleaning and sanitization program for (b) (4) DS and DP manufacturing facility is governed by the following procedures:

- **099-BGS-02652** "Implementation of a New Disinfectant & Cleaning Agent" (version 2.0, effective 28 Sep 2020)
- **BI-VQD-54196-S** "Cleaning and Disinfection of GMP relevant areas within BioPharma China" (version 11.0, effective 11 Nov 2022)
- **099-BGS-00012-RD07** "List of approved cleaning agents I disinfectants - site Shanghai" (version 13.0, effective 27 Apr 2023)

- **BI-VQD-54196-S-AD0l** "Details on cleaning & disinfection in BioPharma China" (version 17.0, effective 12 May 2023)
- **BI-VQD-54196-S-AD04** "Routine and Intensive Cleaning/Disinfection Plan for Halei Road Site" (version 15.0, effective 12 May 2023)
- **BI-VQD-53809-S** "Operation of Weighing Booth" (version 7.0, effective 24 May 2023)
- **BI-VQD-56228-S** "Operation Procedure for Biosafety Cabinet (BSC)" (version 9.0, effective 23 May 2023)
- **BI-VQD-54809-S** "Standard Operation Procedure of (b) (4) (version 10.0, effective 24 Feb 2023)

SOP BI-VQD-54196-S stipulated cleaning and disinfection procedures for GMP-relevant areas including grade C, grade D, and CNC areas. There are no designated grade A or B rooms in the facility. Cleaning and disinfection procedures of LAF (laminar airflow) units and (b) (4) are managed by relevant equipment SOPs. During the walk-through inspection, I (ZL) requested and reviewed the cleaning & sanitization logbooks for the clean rooms in (b) (4) On May 31, 2023, Mr. (b) (6) Cleaning Supervisor, provided me (ZL) with an overview of the routine facility cleaning and sanitization/disinfection operations.

On June 2, 2023, Ms. (b) (6) QC Scientist, provided me (ZL) with an overview of the firm's disinfectant efficacy studies (DES). The following DES reports, which had been requested and submitted under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection, were reviewed with the firm's SMEs during the inspection:

- **106-STU-013849-R** "Report of Microbiological Efficacy Testing of (b) (4) with ATCC strain; BICN" (version 2.0, effective 29 Apr 2021)
- **106-STU-013867-R** "Report of Microbiological Efficacy Testing of (b) (4) with In-house Isolates" (version 4.0, effective 28 Dec 2021)
- **106-STU-013868-R** "Report of Microbiological Efficacy Testing of (b) (4) with In-house Isolates" (version 4.0, effective 28 Dec 2021)
- **106-STU-013869-R** "Report of Microbiological Efficacy Testing of (b) (4) with ATCC strain; BICN" (version 3.0, effective 29 Jun 2021)
- **106-STU-013870-R** "Report of Microbiological Efficacy Testing of (b) (4) with ATCC strain; BICN" (version 3.0, effective 29 Jun 2021)
- **106-STU-013871-R** "Report of Microbiological Efficacy Testing of (b) (4) with In-house Isolates" (version 4.0, effective 28 Dec 2021)
- **599-D-015623-R** "Microbiological Efficacy Validation of (b) (4) with ATCC strains" (version 1.0, effective 06 Jul 2018)
- **106-STU-038514-R** "In-house Isolates Efficacy Study of (b) (4) (version 1.0, effective 27 Dec 2021)

Deficiencies in the firm's disinfectant efficacy studies were noted [see the discussion for **FDA 483 Observation 3E** in the Objectionable Conditions section for details]. In addition, the

following deficiencies regarding the firm's facility cleaning and sanitization/disinfection program that are not included on the Form FDA 483 were noted: (1) The cleaning staff does appear to be fully aware of the requirements of documentation and verification in that the treated surfaces are wetted and remain wetted for the contact time(s) validated in the DES; (2) The current equipment SOPs do not require the use of a sporicidal agent during the routine disinfection of process equipment in the grade C/D areas, such as (b) (4) and LAF weighing booths, *etc.*; (3) The firm's DES does not adequately support the sanitization procedures for the antimicrobial and sporicidal effectiveness of the disinfectants and sporicidal agents for all representative manufacturing surfaces in the (b) (4) manufacturing facility. For example, leather of chairs and sealants on the walls were not included in the studies. In addition, the floor materials unique to the (b) (4) facility are excluded in the BI's global DES program (refer to 099-BGS-02652); (4) The DES failed to establish the disinfectant expiration limits by subjecting the materials tested for the actual use and storage conditions at the (b) (4) facilities; and (5) The firm lacks in-situ data to demonstrate the effectiveness of the firm's facility cleaning and disinfection program due to the inadequate microbiological surface sampling taken during the routine EM (also refer to Verbal Discussion item ZL-02). I (ZL) stated to the firm that a sound cleaning and sanitization program is needed for controlled environments used in the manufacture of biological DS and sterile DP to prevent the microbial contamination of these products. These concerns were communicated to the firm's management as **verbal discussion items** (ZL-10) during the closeout meeting on June 09, 2023. Firm's management understood the concerns and had no specific comments during the closeout discussion.

B. (b) (4) ***Utilities***

(*This section was written by ZL.*)

On May 31, 2023, Mr. (b) (6) Maintenance Service Manager, provided me (ZL) with an overview of the firm's the firm's GMP (b) (4) utilizes, governed by the following procedures:

- **BI-VQD-58776-S** (b) (4) Generation & Distribution Systems Operation" (version 10.0, effective 28 Apr 2023)
- **BI-VQD-58793-S** (b) (4) Generation & Distribution Systems Operation" (version 8.0, effective 28 Apr 2023)
- **BI-VQD-58289-S** (b) (4) Generation & Distribution Systems Operation" (version 5.0, effective 26 Apr 2022)
- **BI-VQD-56769-S** (b) (4) Distribution Systems Operation" (version 6.0, effective 14 Nov 2022)

(b) (4)

(b) (4)

The qualification and routine monitoring of the (b) (4) utilities are governed by the following procedures:

- **028-OCS-00182** "Validation of Equipment" version 4.0, effective 01 Jan 2019)
- **099-BGS-00137** "Qualification of (b) (4) Distribution Systems" (version 2.0, effective 17 Jul 2019)
- **BI-VQD-55792-S** (b) (4) Grades at Shanghai Site: Designation, Specification, Use, and Testing Frequency" (version 16.0, effective 10 Mar 2023)
- **BI-VQD-56746-S** "Quality Monitoring of (b) (4) (version 17.0, effective 10 Mar 2023)

The (b) (4) are tested against the current USP, and European Pharmacopoeia (Ph.Eur.), and Chinese Pharmacopoeia (Ch.P.) requirements, in accordance with SOP BI-VQD-55792-S as follows:

(b) (4)	Microbial and Endotoxin	Chemical testing
	(b) (4)	

(b) (4)

The (b) (4) are tested in accordance with SOP BI-VQD-56746-S as follows:

(b) (4)	Airborne Microbe	Particles	Humidity/Moisture	(b) (4) Content
	(b) (4)			

The following documentation associated with the (b) (4) utility qualification and routine monitoring, which had been requested and submitted under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection, were reviewed with the firm's SMEs during the inspection:

- **106-E-011589-VSR04** (b) (4) System: Validation Summary Report of (b) (4) Distribution System" (version 1.0, effective 01 Apr 2021)
- **106-E-011590-VSR04** "Requalification of (b) (4) Distribution System for (b) (4) Project" (version 1.0, effective 06 Nov 2020)
- **106-E-011591-VSR04** "Validation Summary Report of (b) (4) System" (version 1.0, effective 24 Apr 2017)
- **106-E-011597-VSR02** "Validation Summary Report of (b) (4) System" (version 1.0, effective 08 May 2019)
- **106-E-011594-PQR02** "Requalification of (b) (4) Distribution System" (version 1.0, effective 13 Apr 2020)
- **106-E-011595-PQR02** "Requalification of (b) (4) Distribution System" (version 1.0, effective 13 Apr 2020)
- **106-E-011596-PQR02** "Requalification of (b) (4) Distribution System" (version 1.0, effective 13 Apr 2020)
- **105-TR-002180** "HL Road site Trending Report of (b) (4) System 2021"
- **105-TR-002239** "HL Road site Trending Report of (b) (4) System 2021-07 to 2022-06"
- **105-TR-002317** "HL Road site Trending Report of (b) (4) System 2022"
- **105-TR-002187** "HL Road Site Trending report of (b) (4) Systems 2021"
- **105-TR-002319** "HL Road site Trending Report of (b) (4) Systems 2022"

My review of (b) (4) utility qualification reports revealed that the firm had not tested (b) (4) content (b) (4) in the distribution systems for the (b) (4) delivered to the firm's (b) (4) DS/DP manufacturing facilities. I (ZL) expressed my concern to the firm that it had not adequately qualified all critical (b) (4) utilities used for the manufacture of (b) (4) DS and DP. This concern was communicated to the firm's management as a **verbal discussion item** (ZL-03) during the closeout meeting on June 09, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

C. Equipment Maintenance & Calibration

SOPs and Logbooks
(*This section was written by LB.*)

I reviewed the following SOPs related to equipment maintenance and calibration:

- **BI-VQD-56700-S** "Maintenance in BioPharma China" Version 11.0.
- **BI-VQD-58227-S** "Calibration in BioPharma China" Version 12.0

The SOP for equipment maintenance (BI-VQD-56700-S) defines the required maintenance activities, management of maintenance planning, execution, and documentation. A risk-based approach is used to assess the preventive maintenance needs based on equipment classification and frequency of use for example. Maintenance cycles with fixed dates are used in maintenance planning and scheduling. All firm's maintenance activities including planned (preventative) and unplanned (corrective) are managed through Computerized Maintenance Management System (CMMS). A maintenance management review is performed on a (b) (4) basis based on equipment classification to evaluate the overall status of the maintenance program and to assess trends.

Equipment calibration is governed by document BI-VQD-58227-S, Version 12.0. The SOP for equipment calibration describes the overall calibration management and defines the associated applicability and responsibilities. A risk-based approach is used to perform Criticality Risk Assessment (CRA) based on equipment classification. The planning, execution, and documentation of initial and ongoing calibration activities.

Logbooks are managed according to SOP document 099-BGS-00032 "Logbooks in BioBU" Version 4.0, including logbook issuance, revision, filling, review, and archiving. Both paper-based and electronic logbooks are used at the firm.

No objectionable conditions were noted.

Out of Tolerance (OOT)
(*This section was written by LB.*)

I did not review equipment related Out of Tolerance. During review of qualification reports for (b) (4) and (b) (4) no deviations or Out of Tolerances were noted.

No objectionable conditions were noted.

D. Equipment Qualification

(The following was written by ZL.)
On June 1, 2023, Mr. (b) (6) Validation Manager, provided me (ZL) with an overview of the firm's process equipment qualification program, governed by the following procedures:

- **028-OCS-00182** "Validation of Equipment" (version 5.0, effective 01 Jun 2019)
- **106-O-016908-VMP-RD01** "Periodic Requalification/Revalidation" (version 6.0, effective 28 Dec 2022)

According to SOP 028-OCS-00182, "equipment may consist of simple standardized components, interdependent equipment, systems that include automation, instrumentation, integrated process control and supervisory computerized controls [*e.g.*, laboratory instrumentation, embedded controls, Programmable Logic Controller (PLC), Supervisory Control and Data Acquisition (SCADA) and Distributed Control Systems (DCS)]." Periodic reviews of the equipment operating history including changes and deviations in performance, maintenance, and security are performed with frequencies of (b) (4) Periodic requalification that includes the specific performance test(s) are required for certain equipment and systems are defined in SOP 106-O-016908-VMP-RD01, along with frequencies. In the BioChina Shanghai site, periodic requalification is performed for the following systems: cleanrooms, LAF (laminar airflow) units, (b) (4) and (b) (4)

The firm provided two lists of the major process equipment used for the manufacturing of (b) (4) DS and DP, respectively, along with corresponding qualification document numbers and completion dates [**Exhibits ZL-20 & 21**], which had been requested and submitted under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection. During the inspection, the FDA investigators requested and reviewed the qualification documentation for the following process equipment or systems.

Incubators/freezers/(b) (4)
(*This section was written by LB.*)

SOP document 028-OCS-00182 "Validation of Equipment" Version 5.0 describes the process and requirements for the firm's equipment qualification. A risk-based approach is used to categorize standard equipment and determine the qualification requirement.

(b) (4) that is used to perform (b) (4) WCB vial thaw. On 6/1/2023, I discussed the qualification of (b) (4) with Ms. (b) (6) Upstream Manager). Qualification included installation, operation, and performance qualification. The qualification results are documented in report O1-A-2201-TH: "Validation Report of (b) (4) version 1.0. During OQ phase, vial thaw was compared between (b) (4) and a water bath, and no significant differences were observed based on the notes in the report.

On 6/5/2023, I discussed the qualification of (b) (4) with Mr. (b) (6) (E&T Manager). The discussion covered (b) (4) which were (b) (4) The qualifications included empty load test, full load test, power off, (b) (4) and dynamic

simulation test. Requalification of (b) (4) are required (b) (4) The initial qualifications were performed in 2018 for (b) (4)

No objectionable conditions were noted.

(b) (4) process equipment
(This section was written by LB.)

The firm uses (b) (4) controlled by (b) (4) during (b) (4) harvest process. The manufacturing Zone (b) (4) have (b) (4) system in each area. On 6/7/2023, I discussed the qualification of (b) (4) system with Mr. (b) (6) (b) (6) (E&T Manager) and reviewed the qualification reports for (b) (4) System O2-A-3101-FX, including IOPQ as documented in 106-E-032772-IOQR "Installation and operational qualification report of (b) (4) system" V1.0 and 106-E-032772-VSR "Validation summary report of (b) (4) System" version 1.0. The qualification covered the communication between (b) (4) and controlling system, access control verification, audit trail verification, backup and recovery verification, media filtration and harvest operation verification.

No objectionable conditions were noted.

(b) (4) Bioreactors (b) (4)
(*This section was written by YL.*)
During the inspection, I (YL) performed a cursory review of the following equipment qualification with the firm's SMEs:

- (b) (4) O1-A-2801 (b) (4) Latest Re-Qualification, 106-E-010531-IOQR03, 2023/3/20
- O2-A-2801 Latest Re-Qualification, 106-E-032776-IOQR03, 2023/2/28

No objectionable conditions were noted.

(b) (4)
(*This section was written by YL.*)

- (b) (4) System, O1-A-5101 (b) (4)
- System, O1-A-5102
- System, O1-A-5301
- System, O1-A-5401

During the inspection, I (YL) performed a cursory review of the following equipment qualification record(s):

106-E-011715 (b) (4) 1 (b) (4) Executed Requalification Pre-requisite Check 03/21/2023
106-E-011715 2 Executed Installation Qualification 03/21/2023
106-E-011715 3 Executed Operational Qualification 03/21/2023
106-E-011715 3 (b) (4) Operational Qualification Discrepancy of Unicorn

System 03/21/2023

No objectionable conditions were noted.

(b) (4)
(*This section was written by LB.*)

(b) (4) for (b) (4) steps and (b) (4) are (b) (4). The lifecycle limits are set at (b) (4) for (b) (4) (b) (4) for (b) (4) for (b) (4) and (b) (4) for (b) (4). The (b) (4) number is traced in paper logbooks. I requested a list of the (b) (4) usage since 2020, and discussed with Ms. (b) (6), DSP Manager on 6/5/2023. Each lot purification typically used (b) (4) (b) (4) of (b) (4) of (b) (4) of (b) (4). The usages of all the (b) (4) were all within the respective (b) (4) limits.

Concurrent validation of (b) (4) lifetime is performed according to the principles outlined in the SOP document BI-VQD-03560 "Process Validation in BioPharma" Version 9.0 as part of the (continued) process validation. (b) (4) are performed periodically to evaluate (b) (4) performance. (b) (4) are performed to evaluate cleaning effectiveness after (b) (4) and periodically afterwards according to the corresponding protocols. On 6/1/2023, I reviewed the online (b) (4) profiles for (b) (4) in Unicorn system with Ms. (b) (6) (DSP Manager). (b) (4) lifetime validation has been completed in 2022. I requested and reviewed the following lifetime validation protocols and reports:

- **106-P-032406-P01** Version 2.0 (b) (4) lifetime and storage protocol
- **106-P-032406-R01** Version 1.0 (b) (4) lifetime and storage report
- **106-P-032406-P02** Version 2.0 (b) (4) lifetime and storage protocol
- **106-P-032406-R02** Version 1.0 (b) (4) lifetime and storage report
- **106-P-032406-P03** Version 2.0 (b) (4) lifetime and storage protocol
- **106-P-032406-R03** Version 1.0 (b) (4) (b) (4) lifetime and storage report
- **106-P-032406-P04** Version 2.0 (b) (4) (b) (4) lifetime and storage protocol
- **106-P-032406-R04** Version 1.0 (b) (4) (b) (4) lifetime and storage report

No objectionable conditions were noted.

(*The following was written by ZL.*)
During the inspection, I (ZL) reviewed the following validation records, which were provided under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection, with the firm's SMEs:

- **106-P-032406-R01** (b) (4) Lifetime and Storage including Cleaning (commercial scale) (version 1.0, effective 13 Feb 2020)

- **106-P-032406-R04** (b) (4) Lifetime and Storage including Carry-over (commercial scale) (version 1.0, effective 29 Mar 2023)
- **106-P-032406-R03** (b) (4) Lifetime and Storage incl. Carry Over (commercial scale) (version 1.0, 29 Mar 2023)
- **106-P-032406-R02** (b) (4) Lifetime and Storage incl. Carry Over (commercial scale) (version 1.0, 29 Mar 2023)

No objectionable conditions were noted.

Laminar Flow (LAF) Units & Bio-Safety Cabinets (BSC)
(*This section was written by ZL.*)

I (ZL) requested and performed a cursory review of the following equipment validation records with the firm's SMEs:

- (b) (4) Requalification of BSC (O1-A-2201-LF) in (b) (4) Lab (b) (4) (approved 15 Feb 2023)
- (b) (4) Requalification of BSC (O1-A-2101-LF) in (b) (4) Lab (b) (4) (approved 15 Feb 2023)

No objectionable conditions were noted.

(b) (4)
(*This section was written by ZL.*)

I (ZL) requested and performed a cursory review of the following equipment validation record(s) with the firm's SMEs:

- **106-E-015020-PR01** "Filling Line: O1-A-6801-WS: Periodic Review for (b) (4) (version 1.0, effective 25 May 2023)
- **106-E-015020-VSR04** "Filling Line: O1-A-6801-WS: Qualification Report for (b) (4) (version 1.0, effective 10 Feb 2023)

During the inspection, I (ZL) noted and pointed out to the firm that, according to Validation Master Plan (VMP) # 106-O-016908-VMP-RD01, periodic requalification is not required for the (b) (4) The initial or the last qualification of the equipment for the format of (b) (4) mL) vials used for (b) (4) DP was conducted in April of 2018. I (ZL) stated to the firm that a periodic paper review does not provide adequate assurance that the critical equipment fully functions properly over the time after the initial equipment performance qualification (PQ). For example, a cumulative impact of minor changes as well as wear and tear of equipment or dynamic changes in (b) (4) functional performance may not be detected by deviations and change controls. This concern was communicated to the firm's management as a **verbal discussion item** (ZL-03) during the closeout meeting on June 09, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

(b) (4)
(*This section was written by ZL.*)

I (ZL) requested and performed a cursory review of the following equipment validation records with the firm's SMEs:

- **106-E-015021-VSR08** "Requalification Report for (b) (4) O1-A-6802-SZ" (version 1.0, effective 2023/1/31)
- **106-E-015021-PR04**, "Periodic Review for (b) (4) O1-A-6802-SZ" (version 1.0, effective 2023/1/12)

A deficiency in the audit trail review of the (b) (4) validation data for the (b) (4) (b) (4) was noted [see the discussion for **FDA 483 Observation 4E** in the Objectionable Conditions section for details].

(b) (4)
(*This section was written by ZL.*)

I (ZL) requested and performed a cursory review of the following equipment validation records with the firm's SMEs:

- **106-E-011702-PR04** "Periodic Review for (b) (4) O1-A-6504-AV" (version 1.0, effective 03 Jan 2023
- **106-E-011702-PR04** "Requalification Report for (b) (4) O1-A-6504-AV" (version 1.0, effective 03 Jan 2023

A deficiency in the audit trail review of the (b) (4) validation data for the (b) (4) was noted [see the discussion for **FDA 483 Observation 4E** in the Objectionable Conditions section for details].

(b) (4)
(*This section was written by ZL.*)

During the inspection, I (ZL) requested and reviewed the following documentation regarding the (b) (4) qualification:

- **129-SR-007616** "(b) (4) mg/Vial (b) (4) mg/ml): V14: Determination of the (b) (4) Concentration in vials filled at (b) (4) Bl China" (version 1.0, effective 28 Jan 2021)
- **518-STU-030894-R01** "(b) (4) mg/Vial (b) (4) mg/ml): VOS: (b) (4) Study (b) (4) ml (b) (4) ml vial (b) (4) mg/ml, data up to (b) (4) " (version 5.0, effective 05 Dec 2022)
- **106-E-004267-PR04** "Periodic Review for (b) (4) (O1-A-6851-IO/O1-A-6852-IO)/(b) (4) (O1-A-6804-(b) (4) (version 1.0, effective 12 Jan 2023)
- **106-E-004267-VSR07** "Requalification Report for (b) (4) (O1-A-6851-IO/O1-A-6852-IO)/(b) (4) (O1-A-6804-(b) (4) " (version 1.0, effective 30 Aug 2022)

The firm provided the following documentation related to Air Flow Pattern Visualization (Smoke Studies), under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection:

- **028-BIS-00475** "Air Flow Pattern Visualization (Smoke Studies)" (version 1.0, effective 31 Jan 2020)
- **106-E-015574-VAP02-A02-R** "Smoke Study Script for Aseptic Vial Filling Line" (version 1.0, effective 27 APR 2023)
- **106-E-015574-VSR02** "Validation Summary Report of Smoke Study Requalification for Aseptic Vial Filling Line" (version 1.0, effective 27 APR 2023)
- **106-E-015574-VSR02-A01** "Video Review Summary" (version 1.0, effective 27 APR 2023)
- **106-E-015574-VSR02-TC01-R** "Executed Test Case - Smoke Study Requalification for Aseptic Vial Filling Line" (version 1.0, effective 27 APR 2023)

During the inspection, I (ZL) discussed the above smoke studies with firm's SMEs. Deficiencies regarding the studies were noted [see the discussion for FDA 483 **FDA 483 Observations 3A & 3B** in the Objectionable Conditions section and the **verbal discussion item** (ZL-01) in the GENERAL DISCUSSION WITH MANAGEMENT section for details].

Filler/Capper
(*This section was written by ZL.*)

I (ZL) requested and performed a cursory review of the following equipment validation records with the firm's SMEs:

- **106-E-015022-ICFT-R** "Filling Line: O1-A-6806-FF, O1-A-6805-FF: Installation and Operational Qualification Report for Filler/Capper" (version 1.0, effective 19 Oct 2017)
- **106-E-015022-RT-R** "Filling Line: O1-A-6806-FF, O1-A-6805-FF: Performance Qualification Report for Filler/Capper" (version 1.0, effective 12 Apr 2018)
- **106-E-015022-VSR05** "Filling Line: O1-A-6806-FF, O1-A-6805-FF: Validation Summary Report for Filler/Capper" (version 1.0, effective 12 Apr 2018)
- **106-E-015022-PR03** "Filling Line: O1-A-6806-FF: Periodic Review for Filler" (version 1.0, effective 09 May 2023)
- **106-E-015022-VSR05** "Filling Line: O1-A-6806-FF, O1-A-6805-FF: Qualification Report for Filler/Capper (b) (4)" (version 1.0, effective 28 Feb 2023)

A deficiency in the requalification of the capping machine was noted [see the discussion for **FDA 483 Observation 3D** in the Objectionable Conditions section for details].

E. Equipment Cleaning, Sanitation/Sterilization
(*This section was written by ZL.*)

On June 5, 202, Mr.(b) (6) Process Validation Manager, provided me (ZL) with an overview of the firm's process equipment cleaning validation program [**Exhibit ZL-22**], governed by the following procedures:

- **BI-VQD-03317-S** "Cleaning Validation Procedure" (version 6.0, effective 30 Jan 2023)
- **106-C-029654-VMP** "Halei Road Site: Site Cleaning Validation Master Plan" (version

4.0, effective 23 Feb 2023)

- **106-C-029654-VMP-A01** "Implementation Plan and Cleaning Validation Status" (version 4.0, effective 23 Feb 2023)

Manufacturing processes at Halei Road site are based on (b) (4) technology (b) (4) systems (b) (4). (b) (4) and product-dedicated (b) (4) materials are applied for the product (API-containing solution) contacting surfaces for all DS and Drug Product manufacturing processes. Pre-sterilized equipment and consumables are used (*e.g.*, sterilization by (b) (4) can be applied instead of sterilization by (b) (4) (b) (4) product-dedicated (b) (4) for DS manufacturing, including (b) (4) are cleaned and sanitized. Small pieces of equipment such as spinner vessels or glass bottles are (b) (4)

There are mainly (b) (4) types of cleaning operations utilized at the BICN facility: (b) (4) he status of the cleaning validation for both DS and DP manufactures including corresponding cleaning procedures is summarized in the document 106-C-029654-VMP-A01. The initial cleaning validation has been completed as of June 9, 2023, and the next periodic review is due by Jan 28, 2024.

The following documentation associated with the process equipment cleaning validation, which had been requested and submitted under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection, were reviewed with the firm's SMEs during the inspection:

- **106-C-029654-P01** "Robustness and Effectiveness Check of Cleaning procedures (b) (4) Method)" (version 5.0, effective 01 Jun 2023)
- **106-C-029654-P02-A01** (b) (4) Cleaning Robustness; DPM (b) (4) New loading Pattern CC-2020-0102 (Protocol)" (version 1.0, effective 01 Sep 2020)
- **106-C-029654-R02** "Cleaning Robustness, Cleaning and Dirty Hold Time Validation at Bl China, Halei Road site, Shanghai (Report)" (version 1.0, effective 28 Jan 2021)

No objectionable conditions were noted.

X. MATERIALS SYSTEM

Storage/Distribution & Quarantine
(*This section was written by LB*)

The firm's material management regarding storage, distribution, and quarantine are governed by the following SOPs:

- **BI-VQD-57276-S** "Control of incoming goods including returns" Version 12.0
- **BI-VQD-56281-S** "Material issue and material return" Version 8.0
- **BI-VQD-54813-S** "Warehouse management" Version 25.0.

An overview of the material management program was provided as part of the pre-requests. It covered the processes for material receiving, material issuance, and return of remaining materials. The materials are received and examined by the warehouse staff. Material information is put into GBS system and labeled with firm's material labels. The shipping packages are cleaned and removed, and the received goods are moved to BI pallets for storage under respective conditions. The receiving area adjacent to the loading dock in room (b) (4) is CNC grade equipped with temperature and humidity control. QC is notified with material sampling plan to perform incoming tests and will release the materials for distribution based on the testing results. Materials during receiving and QC testing are assigned with "quarantine" status in GBS system. Expired and rejected materials are discarded per request forms. On May 29, 2023, I inspected the reject area located in room (b) (4) of the (b) (4) building (b) (4) (b) (4) and reviewed the request forms for reject materials submitted on 4//28/2023 and 5/22/2023.

No objectionable conditions were noted.

Inventory & Vendor Qualifications
(*This section was written by LB*)

Document O99-BGS-00011 "Management of Suppliers Manufacturers in BioBU" Version 5.0 describes the procedure for supplier selection and qualification. Materials undergo initial categorization to Category 1 (high impact to product quality), Category 2 (significant impact to product quality), and Category 3 (all others) prior to initiating the qualification plan. Vendor qualification is done through a change control and is typically not product specific. A risk assessment is performed first to determine the need for qualification. The qualification team and pre-requisites are defined to initiate the change control process. Re-qualification may be needed if there are significant changes or if the supplier status is inactive or blocked, for example, due to compliance issues.

No objectionable conditions were noted.

Specification & Sampling Plan
(*This section was written by LB*)

Materials sampling plan is defined in 105-SOP-000216 "Sampling Management of Raw Materials." I requested and reviewed the specifications for the following materials. The specifications match those submitted in the (b) (4)

- **105-SPEC-000183** Testing Specification of (b) (4) Version 3.0
- **105-SPEC-000212** Testing Specification of (b) (4) Version 6.0
- **105-SPEC-000214** Testing Specification of (b) (4) Version 6.0

No objectionable conditions were noted.

XI. PRODUCTION SYSTEM

A. DS PROCESSES

Manufacturing Process

(*The following was written by LB.*)
(b) (4) is (b) (4) cells. The manufacturing process of (b) (4) DS (DS) includes the upstream cell culture and harvest, and downstream purification steps. The upstream process consists of (b) (4) The downstream process consists of (b) (4) followed by (b) (4) and filling of the DS. The DS manufacturing facility includes (b) (4)

(*The following was written by ZL.*)
The firm provided a flow diagram of the manufacturing process for (b) (4) (b) (4) DS with sampling points, (b) (4) points, and hold points, under the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 704(a)(4) [21 U.S.C. 374(a)(4)] in advance of the current onsite inspection [**Exhibit ZL-23**]. The process validation is described in the validation master plan (VMP) below:

- **106-P-041872-VMP** (b) (4) Manufacturing Process Validation Master Plan (ex-China" (version 1.0, effective 27 Feb 2023)

According to the VMP, a periodic review is performed (b) (4)

Batch Records
(*This section was written by LB.*)

The firm's batch record review is performed according to BI-VQD-58217-S "Manufacturer's Release Procedure of GMP Batches" version 14.0. The document describes the procedure and requirements for reviewing batch record, and related QC testing and deviations. QP (qualified person) performs final batch disposition review according to document BI-VQD-58217-S-FO14 "Batch Disposition Checklist for DS" version 3.0.

Paper-based batch records are used for (b) (4) media, and (b) (4) DS manufacturing. (b) (4) is used for adjusting the (b) (4) DS formulation after (b) (4) step. I requested and reviewed the executed batch record for (b) (4) (lot # (b) (4) manufactured on 5/21/2023 (expiry (b) (4)

On 6/1/2023, I reviewed the executed batch record with SMEs, including the upstream process for batch (b) (4) with Mr. (b) (6) USP Manager) and downstream batch records for (b) (4) with Ms. (b) (6) DSP Manager). The review covered the entire unit operations from vial thaw to bulk DS filling. I verified critical process controls and operational conditions for each step. Process was run according to the conditions described in the (b) (4) One deviation (PR# 1388540) occurred during the (b) (4) step due to computer power outage.

The firm stated that the run continued as controlled by the process method and thus the deviation did not result in any loss of the raw data. The firm also stated that not all equipment have an uninterrupted power supply (UPS) yet but they do plan to install UPS for computers. No other deviations were noted during the batch record review. The step yield for each unit operation was (b) (4)-(b) (4)%, and the overall process yield was (b) (4)%.

No objectionable conditions were noted.

Lots Made & Reprocessing
(*This section was written by LB.*)

A list of all (b) (4) lots made at the firm since 2015 was provided for the DS and DP as part of the pre-requests. A total of (b) (4) DS lots were reprocessed, including lot (b) (4) (deviation PR#779260) and lot (b) (4) (PR#1459175), and both were reprocessed at the DS (b) (4) (b) (4) step. I also reviewed the lot disposition status and noticed that one DS lot (b) (4) was shown as pending release, while the resulting DP lots (b) (4) had been manufactured on 4/21/2023. In addition, the manufacturing dates between several DS and DP lots were around 1 month or less which seemed short because the unprocessed bulk testing includes a (b) (4) in vitro (b) (4) assay, indicating additional DS lots may have been conditionally released.

On 6/7/2023, I discussed the firm's lot release procedure with Mr. (b) (6) QA Manager). Mr. (b) (6) provided an overview of lot release procedures covering standard and conditional release scenarios. Standard lot release is performed according to document 105-SOP-00048 "Manufacturer's Release Production of GMP Batches" version 14.0, which includes the review of full production record, QC test record, and QMS (deviations, events, OOX) records. In addition, the firm also performs conditional release of DS lots for DP production according to procedure described in document 105-SOP-001337 "Quarantine Shipment & Further Production under Quarantine Further Production under Quarantine" Version 4.0 **[EXHIBIT LB-01]**. Section 4.3.2 of the SOP lists prerequisites for further production under quarantine (FPQ) and specifies the minimum testing requirements which are endotoxin and bioburden for DS and visible particle for DP. The SOP does not require that unprocessed bulk testing results including mycoplasma and adventitious viruses be obtained and reviewed before further processing, and therefore the practice presents risks for introducing adventitious agents to the multi-product DP manufacturing area without obtaining the necessary safety testing results. I requested a list of (b) (4) lots that were conditionally released **[EXHIBIT LB-02]**, which showed a total of (b) (4) DS lots that were conditionally released (or FPQ) for producing (b) (4) DP lots without obtaining the safety testing results for unprocessed bulk, indicating a routine practice. The practice is against the requirement and principle outlined in 21 CFR 211.84(a), which requires that each lot of components shall be withheld from use until the lot has been tested and released for use by the quality control unit. The deficiency in firm's FPQ lot release procedure resulted in FDA **Observation 1**. *Refer to* ***section XV OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE*** *for more information.*

Cell Bank
(*This section was written by LB.*)

A two-tiered cell banking system including master cell bank (MCB) and working cell bank (WCB) has been established for (b) (4). (b) (4) cell banks are produced by (b) (4) and WCB vials are shipped to the firm and received by the warehouse team at Halei site. Cell banks at the firm are handled per SOP document BI-VQD-55240-S "Handling of cell banks / cell lines within BioPharma China" v17.0. Upon receiving, (b) (4) WCB vials are stored in "quarantine" liquid tanks until necessary testing are completed per document 105-T-002102 (b) (4) WCB in-coming testing requirement" v1.0. Released cell banks are moved to "released" (b) (4) tanks for long-term storage. The firm uses Halei site as the main cell bank storage site and Lishizhen (LSZ) site as the backup storage site for (b) (4) WCB.

On 5/29/2023, I inspected the cell bank storage area at Halei site accompanied by Ms. (b) (6) (b) (6) (Upstream Manager). The cell banks are stored in room (b) (4) located in the warehouse area on the (b) (4) floor of the (b) (4) building (b) (4) The room contains (b) (4) tanks, including (b) (4) The tank temperature is maintained at ≤(b) (4) °C. I discussed the WCB handover procedure with SMEs. The firm stated that internal transfer of the cell banks from warehouse to manufacturing suite is typically performed using (b) (4) Transporter that is validated for (b) (4) (b) (4) (b) (4) runs all showed at ≤(b) (4) °C) and the handover procedure is limited to (b) (4) or less. Internal transfer of the cell banks (e.g., between Halei and LSZ sites) may also use (b) (4) (b) (4) transporter (b) (4) #01-A-2003-TB) according to document BI-VQD-56381-S "Standard operation procedure for filling and shipping of (b) (4) transport containers" v5.0. On 5/31/2023, I discussed the validation of the (b) (4) transporter/shipper with Mr. (b) (6) (E&T Manager). Total 3 validation runs were performed to cover (b) (4) (b) (4) temperature logger showed the temperature remained at ≤(b) (4) °C. I requested and reviewed the cell bank shipping data and no concerning temperature excursions occurred.

Cell bank inventory is managed via paper records in form 105-SOP-000020_RA-03 "BioPharma China Cell Bank Login Record" v4.0. There was (b) (4) vial left for the WCB lot (b) (4) which was used for PPQ runs. The firm stated that a new WCB lot #(b) (4) has been manufactured by (b) (4) and used by the firm for routine production. The inventory showed (b) (4) vials of the new WCB in storage (b) (4) vials received initially). Lot (b) (4) was manufactured on 8/9/2023, released on 11/18/2022, and has been used in production since 2/2023. Although the (b) (4) time appeared to be comparable, the new WCB showed a lower initial (b) (4) as compared to the prior WCB lot.

On 6/5/2023, I inspected the WCB storage in room (b) (4) located in QC lab area at LSZ site, accompanied by Ms. (b) (6) (USP Manager) and Ms. (b) (6) (Senior USP Scientist). The room houses (b) (4) Temperature of (b) (4) tanks is monitored through the EMS alarm system. The firm stated that the warehouse in Halei site receives the (b) (4) cell banks from (b) (4) and

the cells are then moved to LSZ site for storage and backup. I reviewed the cell bank inventory of (b) (4) tanks which showed the last receiving date was 9/24/2021. End of Production Cells (EPCs) are stored in tank CN-2004. (b) (4) vials (# (b) (4) of the new WCB lot (b) (4) were used for the cell bank qualification runs at (b) (4) scale.

No objectionable conditions were noted.

DS Upstream Process
(*This section was written by LB.*)

On 5/29/2023 afternoon, I performed walk-through inspection of the upstream manufacturing area, accompanied by Mr. (b) (6) (Head of Upstream) and Mr. (b) (6) (Upstream Manager). The room (b) (4) houses (b) (4) equipment for in-process testing. Media raw materials are stored in room (b) (4) for weighing, which are then transferred (b) (4) room (b) (4) to the media preparation room (b) (4) Upon preparation, media is being conditioned at (b) (4) °C in production bioreactor. Mr. (b) (6) stated that the bioreactor temperature is monitored by SCADA alarm system. WCB vial thaw is performed using (b) (4) at (b) (4) °C for ≤ (b) (4) (according to the wall clock time). Cell culture is performed in rooms (b) (4) (has (b) (4) and (b) (4) (has (b) (4) The production of lot (b) (4) was ongoing in vessel 6 in room (b) (4)

On 5/30/2023, I observed the production bioreactor and harvest step for (b) (4) lot (b) (4) on day (b) (4) in Zone (b) (4) operated by Mr. (b) (6) (USP Scientist). Production cell culture was held in a (b) (4) bioreactor (b) (4). I discussed process controls for the production step with SMEs. Each (b) (4) ha (b) (4) pressure probe, and (b) (4) of (b) (4) probes. Probe alarms are monitored by SCADA and ll alarms are managed in GoTrack events. (b) (4) including (b) (4) are used during production stag (b) (4) are controlled. Unprocessed bulk at the end of the culture is tested for adventitious agents including sterility, mycoplasma, and in vitro virus assay to ensure product safety.

After (b) (4) of culture, (b) (4) controls are inactivated, and the bioreactor temperature was (b) (4) for about (b) (4) from (b) (4) °C to (b) (4) °C to prepare for harvest via (b) (4) Harvest filters consists of (b) (4) µm filters. (b) (4) pump (b) (4) (SIC-4035B) was used to pump cell culture to harvest filters at (b) (4) min (b) (4) % pump output) and then increased to (b) (4) min (b) (4) % output) as monitored by (b) (4) After the cell culture loading is complete, a (b) (4) is performed to maximize harvest yield. (b) (4) volumes are controlled.

No objectionable conditions were noted.

DS Downstream Process
(*This section was written by LB.*)

On 5/29/2023 afternoon, I performed a walk-through inspection of the downstream manufacturing area in Zone (b) (4) and Zone (b) (4) accompanied by Ms. Wenxiu Nie (Head of Downstream) and Ms. (b) (6) (Downstream Manager). Zone (b) (4) includes the DSP storage rooms (b) (4) (b) (4) area in (b) (4) purification area in

room (b) (4) Zone (b) (4) DSP area includes (b) (4) room (b) (4) for harvest and (b) (4) (b) (4) steps. IPC sample retains are stored in (b) (4) °C in room (b) (4) The firm provided an overview of the downstream process with corresponding equipment such as harvest tanks, (b) (4) and (b) (4) Filled DS bags may be stored in (b) (4) for up to (b) (4) before (b) (4) in room (b) (4) total).

The downstream process includes multiple open operations during preparation and processing steps as listed in Table 1 of 105-RA-000168 "Risk assessment for open operation during downstream production" Version 1.0 **[EXHIBIT LB-05]**. Open operations are performed at (b) (4) and (b) (4) processing steps with exposure of (b) (4) to the DSP suite environment. On 5/30/2023, I discussed open operations with Ms. Wenxiu Nie (Head of Downstream). Ms. Nie explained that at the (b) (4) step, the (b) (4) bag containing (b) (4) is connected to (b) (4) bag (b) (4) (b) (4) At (b) (4) step, the (b) (4) On 6/1/2023 morning, I observed the execution of (b) (4) step for the DS batch (b) (4) A (b) (4) is used to (b) (4) Although the tube was partially clamped off, a portion of the tubing was exposed, and the exposed section will have direct contact with the product. The duration of opening was not documented in the batch record. I expressed my concern that the open operations present risks for potentially introducing contaminants into (b) (4) from operators and the environment, and the firm's risk assessment document 105-RA-000094 "Virus risk assessment for (b) (4) Version 3.0 **[EXHIBIT LB-06]** does not justify or evaluate the worst-case conditions (e.g., maximum duration of open operations and maximum number of operators). There are no additional purification steps after (b) (4) has limited capability to remove (b) (4) based on the size of the (b) (4) In addition, the risk assessment claims that the duration of the (b) (4) connection is only (b) (4) and operators must wear face masks during open operation. However, face masks are not required for all other (non-open) manufacturing operations performed in the same suite or area as open operations per firm's gowning SOP. Deficiencies were also noted in documentation of open operations where the durations of each open operation were not documented in the corresponding batch records, as shown in the MBRs "105-MBR-000681 v13.0" for (b) (4) (b) (4) and "105-MBR-000685 v17.0" for (b) (4) **[EXHIBIT LB-07].** Therefore, there is a lack of traceability on how long each opening was for the open operation process. Additionally, deficiencies were noted in the firm's environmental control or gowning practice (see verbal discussion items **ZL-02** and **ZL-07**, respectively), leading to additional concerns of potential contamination risks from open operations. The deficiencies in the DS downstream manufacturing process control related to open operations resulted in FDA **Observation 5**. *Refer to **section XV OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE** for more information.*

Bioburden Reduction and Filling
(*This section was written by ZL.*)

Refer to Section VII. FACILITY INSPECTION WALK THROUGH

Bulk Container/Closure
(*This section was written by LB.*)

The DS is stored in (b) (4) bags, which are (b) (4) containers that are ready to use (pre-sterilized by (b) (4) The bag consists of (b) (4) layers; (b) (4) which minimizes the transmission of (b) (4)

No objectionable conditions were noted.

Hold Time Studies

(*The following was written by LB.*)

Hold time studies were performed as part of process validation to demonstrate biochemical stability of (b) (4) covering from harvest to (b) (4) DS filling. I reviewed the study report 106-P-029658-R09 "Hold stability of process intermediates (b) (4)) (commercial scale)" v3.0. Hold time study samples were stored in representative containers. The product quality attributes remained stable. The biochemical study results support the proposed commercial hold conditions.

No objectionable conditions were noted.

(*The following was written by ZL.*)
On June 5, 2023, Mr. (b) (6) , Process Validation Manager, and Ms. (b) (6) QC Manager, provided me (ZL) with an overview of the firm's hold-time (HT) studies for (b) (4) process intermediates, media preparation, and (b) (4) [**Exhibit ZL-24**] and microbial IPC sampling point selection strategy [**Exhibit ZL-25**].

During the inspection, I (ZL) requested and performed a cursory review of the following HT study summary reports with the firm's SMEs:

- **106-P-029658-R09** "Hold Stability of Process Intermediates ((b) (4) (b) (4) (commercial scale) (version 3.0, effective 09 Aug 2022)
- **106-P-029658-R10** "BDS Holding Performance ((b) (4) (commercial scale) (version 2.0, effective 06 Jul 2021)
- **106-STU-032899_R02** "(b) (4) Holding Time Study Report for (b) (4) (b) (4) Samples of Bacterial Endotoxin Test" (version 1.0, effective 09 Dec 2021)
- **106-STU-032899_R01** "(b) (4) Holding Time Study Report for Samples of Bacterial Endotoxin Test" (version 1.0, effective 11 Dec 2020)

My review of the 106-STU-032899_R01 revealed that a discrepancy had been encountered during the HT study for the bacterial endotoxin test samples. The recoveries of the sample test groups of (b) (4) and (b) (4) of (b) (4) failed at the time-0 (T_0) point. A deviation was not initiated to thoroughly investigate and identify the root causes, and to document the approval process for invalidating the original test results [refer to Section 4.1 in **Exhibit ZL-26**]. This concern was communicated to the firm's management as a **verbal discussion item** (ZL-05) during the closeout meeting on June 09,

2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

Supporting Areas (Media/(b) (4) *etc.*)
(*This section was written by ZL.*)

Refer to Section VII. FACILITY INSPECTION WALK THROUGH

B. DP PROCESSES

Manufacturing Process
(*The following was written by ZL.*)
A flow diagram of the manufacturing process for (b) (4) DP with sampling points, (b) (4) points, and hold points was provided as shown in [**Exhibit ZL-27**]. The process validation is described in the validation master plan (VMP) below:

- **106-P-041872-VMP** (b) (4): Manufacturing Process Validation Master Plan (ex-China" (version 1.0, effective 27 Feb 2023)

According to the VMP, a periodic review is performed (b) (4)

Batch Records
(*This section was written by YL.*)

Investigator Zhong Li and I reviewed DP PPQ manufacturing batch record, with (b) (6) (Senior QA Scientist) and appropriate firm SMEs, for (b) (4) During the review, Mr. (b) (6) demonstrated to me how he performed batch manufacturing data verification on the filling equipment and (b) (4) In addition, the firm provided a list of (b) (4) (b) (4) DP lots that have been manufactured since 2015 including PPQ batches for (b) (4) (b) (4) [**Exhibit YL-01**] as well as a list of process parameter out of acceptable range for DS and DP production [**Exhibit YL-02**]. For DS process related assessments refer to DS PROCESSES section.

The batch record instructions for DP manufacturing process appeared to be clear. QA audit appears to follow the established procedure, and no objectionable conditions were noted related to the batch record review.

Lots Made & Reprocessing
(*This section was written by YL.*)
A list of all (b) (4) lots reprocessed at the firm since 2015 was provided for the DS and DP as part of the pre-requests. One DP lot (b) (4) (MFG date April 30, 2021) was reported reprocessed [**Exhibit YL-03**]. Investigation of the reprocessed DP lot was documented in Deviation Report PR#914036 [**Exhibit YL-04**]. According to the same document, reprocessing was due to leakage of the (b) (4) bag. The root cause of the leakage, based on the firm's investigation, was due to a bag defect and insufficient check method prior to use. It should be noted that leakage related batch reprocessing events also were reported for DS batches, and deficiencies with regards to risk assessment and appropriate corrective actions were communicated to the firm's management pursuant to **FDA 483 Observation 6A**.

See section XV OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE for

more information.

BDS Thawing, Bioburden Reduction (b) (4) and (b) (4)
(*This section was written by ZL.*)

Refer to Section VII. FACILITY INSPECTION WALK THROUGH

(b) (4) Loading and Decontamination
(*This section was written by ZL.*)

Refer to Section VII. FACILITY INSPECTION WALK THROUGH

Filling-line Setup & Filling/Capping
(*This section was written by ZL.*)

Refer to Section VII. FACILITY INSPECTION WALK THROUGH

Visual Inspection
(*This section was written by YL.*)

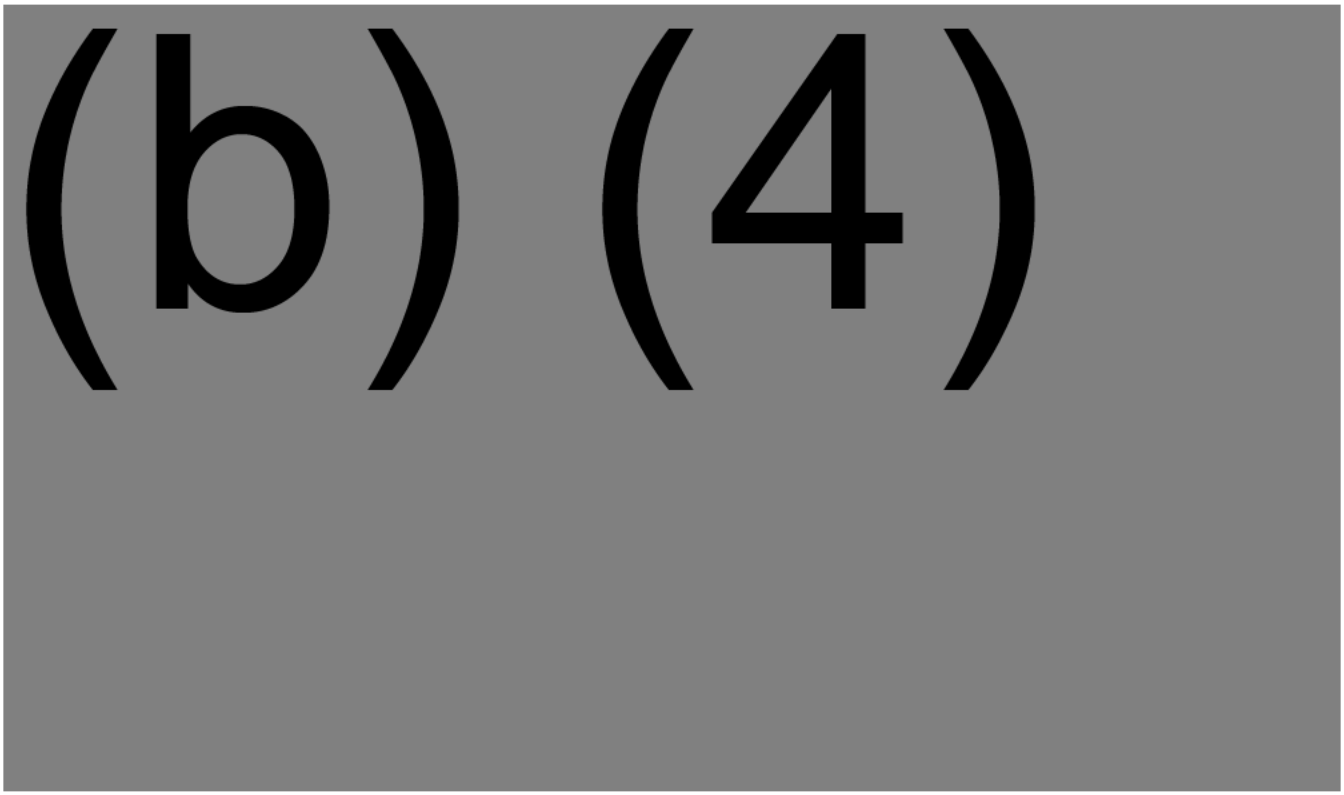
The firm's conducts 100% visual inspection (VI) of packaged (b) (4) drug product after filling operation by manual inspection. The 100% inspection was followed by AQL testing performed by QA personnel. In the afternoon of **May 30, 2023**, during the general walk-through inspection of the firm's DP manufacturing facility located on the (b) (4) floor of the (b) (4) building (b) (4) Investigator Zhong Li (ZL) and I discussed with Mr. (b) (6) (b) (6) (QA specialist) about the firm's visual inspection program. Mr (b) (6) explained that the firm's manual visual inspection training program includes eye test for visual acuity (b) (4) near vision) with no impairment in color perception followed by qualification test. The initial qualification test requires VI inspectors to successfully pass (b) (4) inspections using a test kit and for (b) (4) requalification pass (b) (4) inspection of the test kit. VI inspectors are required to achieve no less than 100% detection of critical defects, 95% detection of major defects, and 75% detection of minor defects in a test set containing less than 5% defect samples. The VI inspector qualification test are administered by QA. Mr. (b) (6) proceeded to show a few defect samples. The samples had comparable appearance to regulator samples and did not have obvious marks. No issues noted.

In the afternoon of **May 31, 2023**, I observed visual inspection of (b) (4) batch (b) (4) in room (b) (4) (visual inspection). Ms. (b) (6) (VI supervisor) and Mr. (b) (6) (b) (6) (QA specialist) provided an overview of the visual inspection process and accompanied me during observation. (b) (4) inspectors were manually inspecting drug product vials with oversight from (b) (4) supervisors. Stop and start times were recorded and breaks were implemented. In addition to 100% visual inspection performed by QC personnel, I noted that one QA inspector was also present to perform the QAL testing. I inquired how samples were selected for the AQL testing while the 100% visual inspection was still ongoing. Ms (b) (6) indicated that (b) (4) box (containing approximately (b) (4) samples) was to be selected from the boxes containing finished samples. I discussed with Ms. (b) (6) Mr. (b) (6) and Mr (b) (6) (QA Manager) and pointed out that such sampling practice might not provide a statistically valid sampling of the entire batch. A deficiency in visual inspection was noted.

*[see discussion for **FDA 483 Observation 2** in the Objectionable Conditions sections for details.]*

Aseptic Process Simulation (Media Fill)
(*This section was written by ZL.*)

On May 31, 2023, Mr. (b) (6) Process Validation Manager, and Mr. (b) (6) F&F Manager, provided me (ZL) with an overview of the firm's medial fill (MF) program, as depicted in the figure below:



The firm's Aseptic Process Simulation (MF) program is governed by the following procedures:

- **028-BIS-00502** "Aseptic Process Simulation (APS)" (version 1.0, effective 21 Apr 2021)
- **106-F-016581-VMP** "Aseptic Process Simulation (Media Fill) Validation Master Plan" (version 1.0, effective 17 Mar 2022)
- **BI-VQD-58310-S** "Intervention During Aseptic Filling for Fill and Finish" (version 14.0, effective 20 Jan 2023)

During the inspection, I (ZL) requested and reviewed the following MF records with the firm's SMEs:

- **106-F-016581-VMP** "Aseptic Process Simulation (Media Fill) Validation Master Plan" (version 1.0, effective 17 Mar 2022)
- **106-F-016581-VMP-A01** "APS History Summary and (b) (4) Plan" (version 3.0, effective 16 Feb 2023)

- **106-F-016581-P09** "Aseptic Process Simulation: (b) (4) Vial (Revalidation, 2022-05)" (version 1.0, effective 07 May 2022)
- **105-MBR-00971** "Media Fill (b) (4) Manufacturing Record" (version 8.0, approved 18 Jul 2022)
- **106-F-016581-VSR09** "Aseptic Process Simulation: Validation Summary Report of (b) (4) Vial (June 2022)" (version 1.0, effective 09 Aug 2022)

No objectionable conditions were noted.

Hold Time Studies
(*This section was written by ZL.*)

Refer to Section XI.A. Hold Time Studies

Support Areas (b) (4) *etc.*)
(*This section was written by ZL.*)

Refer to Section VII. FACILITY INSPECTION WALK THROUGH

Shipping Validation
(*This section was written by ZL.*)

According to the firm, "validation/qualification and shipping data, including temperature tracings and duration of monitoring for the Drug Product of (b) (4) shipment are under the responsibility of (b) (4) the (b) (4) holder."

C. CONTAMINATION/MIX-UP

Multi-product Manufacturing Controls
(*This section was written by ZL.*)

Throughout the inspection, I (ZL) discussed with the firm's SMEs about its new product introduction and multiproduct manufacturing control strategy governed by the following procedures:

- **BI-VQD-03324-S** "New Product Introduction in Clinical and Commercial Facilities" (version 4.0, effective 2022-10-05)
- **BI-VQD-55056** "Contamination Control Strategy in Biopharma China" (version 3.0, effective 30 Mar 2023)
- **099-BGS-00023** "Avoidance of Cross-contamination/mix-up and Change-over Concept in BioPharma" (version 2.0, effective 2016-08-01)
- **028-BIS-00474** "Risk Evaluation of Manufacturing of API or Drug Product in a Shared Facility" (version 1.0, effective 2020-05-08)
- **BI-VQD-58274-S** "Change-over Procedure of Drug Substance Production" (version 9.0, effective 2023-05-08)
- **BI-VQD-57835-S** "Cleaning and Line Clearance Management for Fill and Finish" (version 9.0, effective 2023-01-20)

The (b) (4) DS and DP manufacturing areas in the (b) (4) are designed and operated as a multiproduct facility, which performs contract manufacturing for various customers. The following product classes are manufactured in the facility: (b) (4) No antibiotics (*e.g.*, penicillin or penicillin-related compounds) or highly toxic, sensitizing, or hazardous active ingredients (*e.g.*, sex hormones, cytostatics, immunosuppressive drugs, beta lactams, live or attenuated viral products) are manufactured at the facility. The cell cultivation steps in the (b) (4) area, purification, and (b) (4) purification/formulation steps are conducted on a campaign basis. In case of open/temporarily open processes, only one product is processed at one time. In case of closed systems (*e.g.*, cell culture area for bioreactor cultivation), multiple products can be manufactured in a concurrent production mode. Aseptic processing is conducted on a campaign basis. Only one product is handled at one time in the DP filling area and product changeover procedures are conducted between each campaign.

During the inspection, I (ZL) requested and performed a cursory review of the following change-over records for the products processed in the facility with the firm's SMEs:

- 105-SOP-000425_Form-01 (3.0) "Documentation of product change-over within BioPharma China: from (b) (4) to (b) (4) DSP areas" 2021-05-18
- 105-SOP-000425_Form-01 (3.0) "Documentation of product change-over within BioPharma China: from (b) (4) to (b) (4) USP areas" 2022-01-20
- 105-SOP-000425_Form-01 (3.0) "Documentation of product change-over within BioPharma China: from (b) (4) to (b) (4), DSP areas" 2022-03-09

I (ZL) also requested and reviewed the following new product introduction (NPI) procedures and multi-product manufacturing risk assessments:

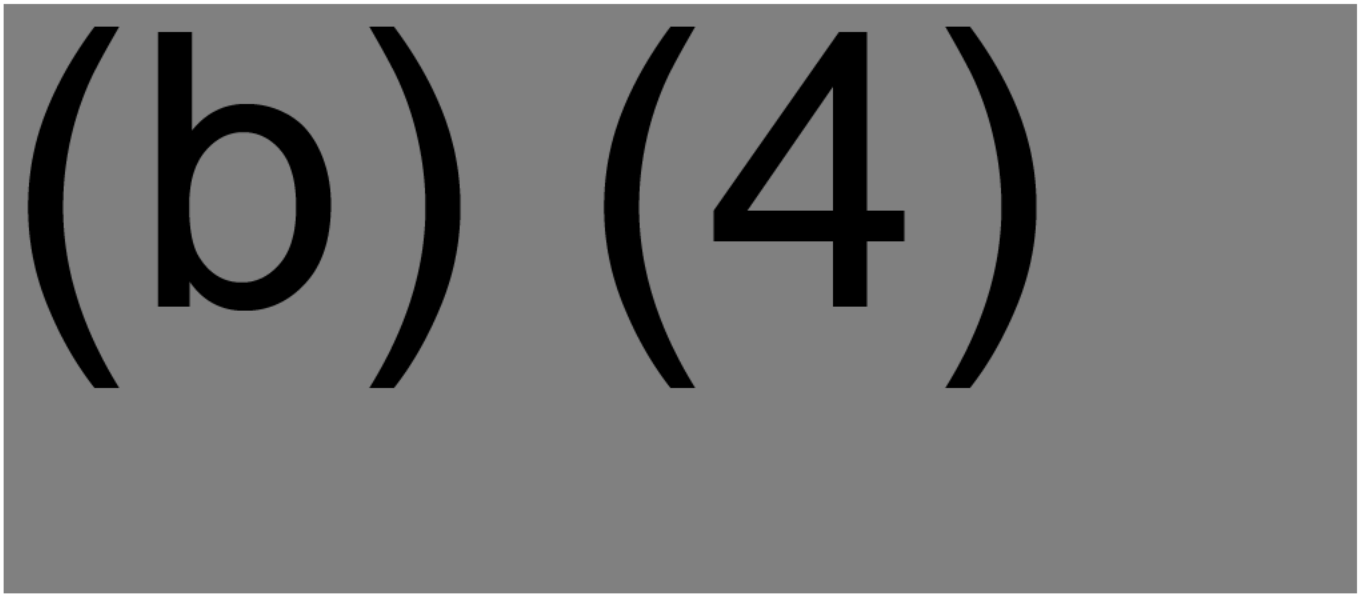
- **105-RA-000041** (b) (4) Product Specific Risk Assessment NPI" (version 2.0, effective 05 Nov 2021)
- **105-RA-000091** (b) (4): Product Specific Risk Assessment NPI" (version 2.0, effective 04 Mar 2023)
- **105-RA-000095** (b) (4): Product Specific Risk Assessment NPI" (version 1.0, effective 20 Mar 2020)
- **105-RA-000096_RA-03** (b) (4): Product Specific Risk Assessment NPI" (version 4.0, effective 13 Mar 2023)
- **105-RA-000096_RA-04** (b) (4) Product Specific Risk Assessment (b) (4) (version 1.0, effective 13 Jan 2022)
- **105-RA-000055** "Process Risk Assessment for Drug Substance Manufacturing Building Halei Rd. Site" (version 7.0, effective 07 Jul 2022)

My review of the above risk assessments revealed the following deficiencies: (1) The firm's (b) (4) process including multi-product manufacturing risk assessments does not appear to be based on health-based exposure limits (HBELs) such as Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE) values, determined by qualified toxicologists from available toxicological and pharmacological data. Specifically, ADE/PDE values were not obtained for

products coded (b) (4) which were introduced into the DP facility. I (ZL) expressed my concern to the firm that it lacks assurance each new, potentially potent or toxic product introduced into its DS and sterile DP commercial manufacturing facilities are adequately evaluated; (2) The firm's material, equipment, and people flows in the (b) (4) facility evidently display non-unidirectional, overlapping flows of workers, product, equipment, materials, and wastes within the facility, especially in the shared corridors and material/equipment transfer elevator shared by the DS (b) (4) and DP process areas. However, the firm's documented risk assessment,105-RA-000055, failed to evaluate potential cross-contamination risks from the unrestricted movement of personnel, equipment, and in-process materials. In addition, only qualitative assessments on cross-contamination were provided in the risk assessment, which failed to evaluate the appropriateness or adequacy of the cleaning and decontamination methods for removal of residues resulting from product spills and/or leakages from (b) (4) equipment, non-product contact equipment surfaces, and the surrounding and supporting manufacturing areas. I (ZL) expressed my concern to the firm that it lacks assurance that appropriate procedures and controls had been implemented in the facility to effectively maintain risk of cross-contamination at or below acceptable limits. These concerns were communicated the firm's management as a verbal discussion item (ZL-08) during a closeout meeting on June 09, 2023. Firm's management understood the concern and had no specific comments.

Microbial Controls (Bioburden)
(*This section was written by ZL.*)

On June 2, 2023, Ms. (b) (6) QC Microbiology Manager, provided me (ZL) with an overview of the microbial control strategy for the (b) (4) DS and DP manufacturing as shown in **[Exhibit ZL-28]**. A schematic process flow diagram for (b) (4) DS manufacturing with sampling points, (b) (4) points, and hold points is shown in the figure below.



The microbial controls implemented at the facility appear to be consistent with descriptions

contained in (b) (4) (b) (4) mg/(b) (4) mL.

No objectionable conditions were noted.

Pest Controls
(*This section was written by LB.*)

The firm's pest control is governed according to document 105-SOP-000945 "BioChina Site Pest Control Procedure" Version 5.0. The document describes the general principle and procedures of the firm's pest control program. Three types of pest control approaches are used, including access-blocking, non-pesticide, and pesticide approach. Routine pest control services are performed by contractor (b) (4) Regular maintenance is performed on pest control equipment including (b) (4) check for fly traps and (b) (4) test on all (b) (4) Maintenance records are documented using 105-SOP-000945_Form-01 Pest Control Maintenance Sheet (4.0). I requested and reviewed the most recent two maintenance reports dated 5/23/2023 and 5/30/2023.

No objectionable conditions were noted.

Gowning & Qualifications
(*This section was written by ZL.*)

The firm's gowning qualification for employees is governed by the following SOPs:

- **BI-VQD-03555-S** "Classification of GMP-relevant areas and gowning concept in BioPharma" (version 6.0, effective 10 May 2022)
- **BI-VQD-55239-S** "Gowning and Personnel Hygiene Requirements" (version 17.0, effective 12 Mar 2023)
- **BI-VQD-56690-S** "GMP Medical Examination in Biopharma China" (version 3.0, effective 10 Jan 2023)
- **BI-VQD-57274** "Guide to Disinfecting Hands/Gloves"
- **BI-VQD-56813** "Gowning Process for USP/DSP in HL RD Site"
- **BI-VQD-55367** "Gowning Process for Drug Product F&F Area in HL RD Site"
- **BI-VQD-54349** "Gowning Instructions for Room (b) (4) Visitor Change"

Throughout the inspection, the FDA inspection team entered the controlled manufacturing areas and performed the gowning procedures. We (LB and ZL) noted and pointed out to the firm's SMEs that the firm's current gowning practices in the DS manufacturing areas allow the reuse of Grade D gowns during the day, with the operators of both (b) (4) (b) (4) areas sharing the same gowning closet. We expressed our concern to the firm that there is a lack of adequate procedural controls in gowning to prevent potential cross contamination of the process areas (also refer to **FDA 483 Observation 5**). This was communicated to the firm's management as a verbal discussion item (ZL-07) during a closeout meeting on during the closeout meeting on June 09, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

XII. LABORATORY CONTROL

Data Control & Sample Tracking
(*This section was written by YL.*)

In the afternoon of **May 29, 2023**, during FDA general walk-through inspection of the upstream process (USP) areas and in DSP (b) (4) room (b) (4) grade D), Investigator Zhong Li (ZL) and I (YL) observed that the firm stored the keys to open the (b) (4) in a locked key box. The key box is protected by password which is changed (b) (4) The firm stated that personnel having access to the key box share the same password but only DSP floor manager can change the password and grant access to the key box. I requested the SOP describing key access and control policies. The following document was presented and reviewed:
106-E-013423 DMAP6: Equipment with Password with or User ID, SPS, HMI, and E-Records

In upstream process (USP) area and in Washing (b) (4) grade D): I performed a cursory review of the logbook entries and noted that the logbooks were reviewed by QA (b) (4)

No objectionable conditions were noted.

During the walk-through inspection of the IPC/Documentation Room (b) (4) grade D), I (YL) observed Mr. (b) (6) (Downstream Senior Technician) performing system suitability testing (SST) on the (b) (4) used for in-process checking (IPC). I noted that the testing results were printed out as paper copies and glued to the logbook as part of the record. When I inquired whether the electronic data generated by (b) (4) were kept or backed up, Ms (b) (6) Downstream manager indicated that the firm did not back up the electronic data by the (b) (4) used for in-process check (IPC). Ms. (b) (6) stated that the (b) (4) has a (b) (4) memory storing up to two hundred fifty (250) measurements. If not backed up, the previous stored data would be replaced by the new measurement and lost.

*[see **Observation 6B** in the Objectionable Conditions section for details].*

In the afternoon of **May 30, 2023**, Investigators Zhong Li (ZL), Leiyun Boone (LB), and I (YL) conducted a general walk-through inspection of the firm's QC laboratories located on the (b) (4) floor of the (b) (4) building. In the sample receiving room (b) (4) (b) (6) (QC manager) and Ms. (b) (6) (QC Scientist) provided an introduction on sample management procedures. Samples are received, labeled, and barcoded into the SAP system. The locations of the samples are tracked. I inspected sample storage refrigerators where (b) (4) samples are stored and observed that the samples are stored in bins in a refrigerator locked and regulated for temperature and humidity. The alarm system for the sample storage refrigerators were monitored by Engineering and Tech (E&T) central control system. An alarm panel was installed in the corridor where QC labs are located where alarm status could be monitored. Ms. (b) (6) explained how samples including reference standards are dispensed by the sampling team upon receiving sample request form. I also inspected stability chambers where (b) (4) DP stability samples are stored. I observed that the stability samples were stored in well-referenced bins in stability chambers regulated for temperature and humidity. I interviewed Ms. (b) (6) (Senior QC Analyst) and verified that the stability chambers were locked, keys controlled, and temperature/humidity monitored.

No objectionable conditions were noted.

In the afternoon of **May 30, 2023**, I (YL) conducted a general walk-through inspection of the firm's QC laboratories. Ms. (b) (6) QC Manager) and Mr. (b) (6) Senior QC Scientist) provide an overview of the analytical instruments housed by the QC lab. I requested and reviewed the following SOP:

BI-VQD-54343-S Data Management in QC Lab **[Exhibit YL-05]**

In Protein Analytics lab (b) (4), I confirmed with Ms. (b) (6) that the HPLC systems are controlled by central network servers. Raw electronic data is uploaded and stored via e-cloud and managed by BI headquarter IT teams. In addition, there are several stand-alone systems including pH meter, UV-Vis spectrophotometer, and ELISA plate reader. According to Ms. (b) (6) the pH meter and osmometer in the QC laboratories are used to perform (b) (4) DP batch release and stability testing. The testing results are to be printed out as paper copies and glued to the analysis report as part of the record. When I inquired whether the electronic data generated by pH meter were kept or backed up, Ms. (b) (6) explained that the electronic data were backed up (b) (4) by E&T personnel. The data electronically captured could be retrieved but they could not be edited, changed, or deleted. At my request, Ms. (b) (6) and Mr. (b) (6) demonstrated the retrieval of the pH meter data from a back-up storage disk.

No objectionable conditions were noted.

In the morning of **June 1, 2023**, I (YL) observed the in-process testing of (b) (4) drug substance (IPC) at QC Laboratories. The (b) (4) testing was performed by Ms. (b) (6) (QC Specialist, the analyst). After the samples were weighed in room (b) (4) (Balance Room), they were brought to Room (b) (4) for testing on (b) (4) (Instrument ID: O1-A-10701 (b) (4) The (b) (4) is a standalone instrument equipped with (b) (4) WinLab ES operating software. The testing raw data are generated and stored locally. I observed the analyst log into her unique account using her username and password. According to Ms. (b) (6) the account was not shared with other users. The analyst performed the test and printed out the test results. Before she moved to pick up the printout she logged off from the account. Following the IPC testing I observed data review conducted by Mr. (b) (6) (b) (6) (QC Specialist). The data review was performed according to SOP XXXX. Mr. (b) (6) compared reported data recorded in the lab notebook against raw data in the (b) (4) instrument, and verified sample information, pipet calibration, and weighing balance system suitability check.

Following IPC testing of (b) (4) drug substance, I observed the periodic review of analytical data by QC and QA, conducted by Ms. (b) (6) (QC Specialist) and Ms. (b) (6) (b) (6) (QA specialist). According to Ms. (b) (6) periodic review of analytical testing data for (b) (4) drug substance (DS) and drug product (DP) was conducted according to SOP BI-VQD-55525 QA oversight to QC (Effective 03/09/2023) and it included review of testing records, review of stored electronic data to verify no data alteration and deletion. The periodic review also verified whether testing runs were aborted and whether adequate documentation was achieved.

No objectionable conditions were noted.

In the afternoon of **June 1, 2023**, I (YL) continued the inspection in the QC laboratories. I

observed Osmolality measurement of (b) (4) drug product as part of the release testing. Ms. (b) (6) (QC Specialist) performed the test using one of (b) (4) Osmomats located in the Room (b) (4) and according to SOP 105-T-000070_5.0_(b) (4) (Effective 03/29/2023). The testing included the following: 1) sample preparation; 2) system suitability testing (SST); 3) calibration testing; and 4) sample testing. After the test was completed, the test results were printed on paper via a printer directly linked to the instrument, and the paper copies were signed and glued to the analytical report. I (YL) expressed my concern to the firm that the current procedure was deficient and was not able to assure that the data were attributable, complete, and accurate.

*[see **Observation 4C** in the Objectionable Conditions section for details].*

OOS Procedure
(*This section was written by LB.*)

Unexpected laboratory events including Out of Specification (OOS), out of expectation (OOE), out of trend (OOT) are handled according to SOP 099-BGS-00029 "Handling of OOX results" Version 5.0. On 5/30/2023, Mr. (b) (6) Senior QC Scientist, provided an overview of the firm's OOS (and OOE and OOT) management. General requirements for OOX investigation include root cause analysis, frequency and recurrence check, impact assessment, and identification of required immediate actions and CAPA plan if applicable. OOX investigations are required to be thoroughly executed, well documented, scientifically sound, and completed in a timely manner. The investigation process includes 2 phases. Phase 1 consists of laboratory investigation and phase 2 is the full-scale investigation. Phase 2 includes Phase 2a investigation and Phase 2b re-test as applicable. The final investigation outcomes require QA approval and closure. Additional requirements for OOX extension, closure, escalation, client notification, and QA support are defined in document BI-VQD-55589-WI "OOX Investigation additional requirements at Biopharmaceutical China" Version 3.0. Trending of OOX events is performed (b) (4) according to 099-BGS-00029-RD16.

No objectionable conditions were noted.

OOS Investigations

(*The following was written by LB.*)
I requested and reviewed a list of OOS/OOX associated with (b) (4) testing. Selected ones were further discussed with SMEs, including 2 OOS and several OOEs.

- **786480**: OOS: HL RD, QC, (b) (4) BDS Binding Activity test is out of specification.
- **1469414**: OOS: HL RD, QC, (b) (4) DP sample of Visible Particle (b) (4) DP
- **701327**: OOE: HL RD,QC, (b) (4) ,IPC,CGE_Non-reduced results and HPSEC
- **1558670**: OOE: LSZ RD,QC, (b) (4) (b) (4) result of (b) (4) exceed expectation
- **1583216**: OOE: (b) (4) exceed expectation

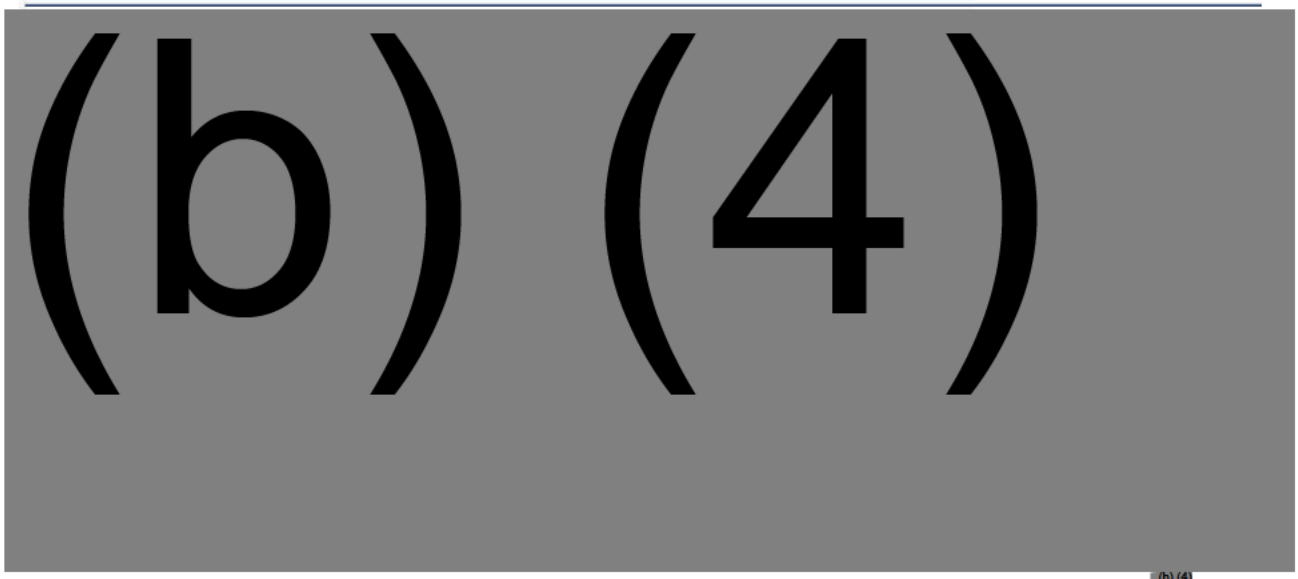
- **1558670**: OOE: LSZ RD,QC,(b) (4) (b) (4) result of (b) (4) exceed expectation

OOS PR# 786480 was reported for binding activity ELISA release testing of (b) (4) DS batch (b) (4) I discussed the OOS investigation with Ms. (b) (6) on 6/2/2023. The initial release testing result using sample ID (b) (4) was (b) (4) %. The result was out of specification of (b) (4) - (b) (4) % for this assay, resulting in OOS PR#786480 **[EXHIBIT LB-10]**. A repeat testing was performed based on preliminary investigation that concluded an error in the sample pre-dilution step, and the repeat result of (b) (4) % was reported as the final release data for the DS batch. However, the OOS investigation did not include thorough root-cause analysis and justification prior to performing retesting. The deficiency in OOS investigation for PR# 786480 led to FDA **Observation 6b**. Refer to section XV OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE for more information.

Biochemical/Physical Testing Lab & Instruments
(*This section was written by LB.*)

On 5/31/2023, I discussed the firm's sample management with Ms. (b) (6) (QC Scientist) who provided an overview of sample management process as shown below. QC samples from DS and DP manufacturing are taken according to pre-defined sampling plans and then handed over to the QC Sample Administration Group. Inventory of QC samples is managed in LIMS per BI-VQD-56413-S "Handling of QC samples in GBS LIMS" Version 8.0.

Sample Management



On 5/31/2023, I performed a walk-through inspection of the biochemical labs located on (b) (4) floor of the QC area within the same (b) (4) building (b) (4) Room (b) (4) is used for sample receiving and storing stability chambers of 5°C and (b) (4) °C. Paper logbooks with restricted key access are used for documenting sample aliquots. Reserve samples (and reference standards) are stored at (b) (4)

I requested a list of QC equipment with corresponding methods. HPLC and CE system used for peptide mapping, (b) (4) testing, in-process (b) (4) testing, and (b) (4) size and charge variant

analysis is located in lab (b) (4) Binding ELISA for potency and identity testing, residual HCP, pH, protein content by UV, and osmolality are tested using instruments located in Protein Analytics lab in room (b) (4) Other appearance and general tested are performed using equipment such as inspection box, particle counter, and turbidimeter located in room (b) (4) and (b) (4) The equipment appeared to be adequately maintained for the intended use.

No objectionable conditions were noted.

Biochemical/Physical Testing Methods & Validation
(*This section was written by LB.*)

On 6/5/2023 morning, I observed the execution of CZE performed by Mr. (b) (6) Testing is performed according to document 105-T-000070 "(b) (4): CZE (Capillary zone electrophoresis)" version 5.0. Capillary was installed to PA (b) (4) (ID #O1-A-10601-CG) to start conditioning first. BDS and DP samples together with reference standard #(b) (4) (RS01) were diluted and used in the testing. System suitability requirements are defined. Testing procedures are documented in paper records and need to be reviewed by a qualified reviewer before final release of the testing results in LIMS.

On 6/6/2023, I observed the execution of (b) (4) binding ELISA potency testing performed by Ms. (b) (6) (QC Scientist). The assay was performed according to the document 105-T-000069 "(b) (4): Binding ELISA" Version 10.0 **[Exhibit LB-11]**. The procedure includes (b) (4) and plate reading. QC sample (b) (4) along with reference standard (#(b) (4) and quality control were used in the testing. Samples are pre-diluted to (b) (4) (x dilution in (b) (4) steps) followed by a serial dilution step. Serial dilution of the samples is performed within (b) (4) plates. The firm stated that the in-dilution is performed according to corporate practice for ELISA assays, which include (b) (4) HCP ELISA performed according to 105-T-001484 (b) (4) HCP ELISA (process-specific)" Version 3.0 **[Exhibit LB-12]**. I expressed my concern that performing serial dilution within assay plates may disturb the (b) (4) and thus lead to high assay variability. Trending of binding ELISA assay control show approximately 30% variability, and serval invalid assays show high variability related to sample dilution **[Exhibit LB-13]**. The deficiency in the ELISA assay procedure related to in-plate dilution led to FDA **Observation 7A**. *Refer to* ***section XV OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE*** *for more information.*

On 6/6/2023, I also discussed the ELISA data acquisition, processing, and storage with Ms. (b) (6) (QC Scientist). SoftMax Pro 7.0 is used to acquire and automatically calculate the testing results. Compatibility testing was performed between the older software version 6.4 and the current version. HCP ELISA protocol was changed to process-specific method in 9/2021 under a change control. I also observed CZE data analysis by Mr. (b) (6) Automatic integration was applied first with manual integration used as necessary. Manual integration requires review by secondary and is traceable in audit trail.

Analytical method validation is performed according to the requirements and principles outlined in the SOP document BI-VQD-04074-S "Validation of Analytical Procedures" Version 3.0. Specific method protocols are used to guide each method validation, and

validation reports are used to summarize the study results. General compendial methods such as pH, osmolality, subvisible particles, and extractable volume tests are verified. Validation of non-compendial methods were completed prior to PPQ. No major changes to the methods were made post validation. I requested and reviewed the following method validation reports. No objectionable conditions were noted.

- **106-M-015342_R01**: Method validation report: (b) (4) Protein content by UV, version 1.0
- **106-M-015344_R01**: Method validation report: (b) (4) HPSEC, version 2.0
- **106-M-015346_R01**: Method validation report: (b) (4) peptide map, version 2.0
- **106-M-015347_R01**: Method validation report: (b) (4), CGE reduced, version 2.0
- **106-M-015348_R01**: Method validation report: (b) (4) CGE non reduced, version 2.0
- **106-M-015349_R01**: Method validation report: (b) (4) CZE (Capillary Zone Electrophoresis), version 1.0.
- **106-M-015350_R01**: Method validation report: (b) (4) Binding ELISA , version 3.0
- **106-M-035083_R01**: Method validation report: (b) (4) HCP ELISA (process-specific), version 2.0

Microbiological Testing Lab & Instruments
(*This section was written by ZL.*)

See FACILITY INSPECTION WALK THROUGH for the general walk-through inspection of the microbiology laboratory. During the inspection, I (ZL) requested and reviewed the following qualification reports or calibration records for the instruments in the firm's microbiology lab:

- Gel-clot Endotoxin Testing Block Heater, Asset ID: HB-10751
- Absorbance Microplate Reader, Asset ID: O1-A-10400-RD
- Biotek HTX Multi Mode Microplate Reader, Asset ID: O1-A-10401-RD
- Vacuum Integrity Test Instrument, Asset ID: PT-10151

No objectionable conditions were noted.

Microbiological Testing Methods & Validation
(*This section was written by ZL.*)

Bacterial Endotoxin Test

During the inspection, I (ZL) requested and reviewed the following documentation related to bacterial endotoxin test (BET) of the (b) (4) DS and DP with the firm's SMEs:

- **BI-VQD-55823** "Determination of Bacterial Endotoxin – Kinetic Chromogenic Assay" (version 14.0, effective 26 May 2023)
- **105-T-000315** "(b) (4): Determination of Bacterial Endotoxin – Chromogenic LAL Assay" (version 12.0, effective 05 May 2023)
- **105-T-001671** "(b) (4) Rabbit Pyrogen Testing – DP release" (version 2.0, effective

2020-08-21)

- **106-M-031274_R01** "(b) (4): Verification Report for Determining BET Interfering Factor of In Process Control (IPC) samples & (b) (4) (version 2.0)
- **106-M-015740_R01** "(b) (4): Verification Testing Report for Determining B ET Interfering Factor of BDS" (version 1.0, effective 30 Mar 2018)
- **106-M-015979_R01** "(b) (4): Verification Testing Report for Determining BET Interfering Factor of DP" (version 1.0, effective 24 Jul 2018)

A low endotoxin recovery (LER) study conducted by the firm demonstrated that the undiluted (b) (4) DP samples exhibit the LER phenomenon. To circumvent LER, the firm implemented the pyrogen test in accordance with USP <151>, Method 105-T-001671, in addition to the LAL (limulus amebocyte lysate) assay to verify that the DP is not pyrogenic. According to the firm, a LER mitigating method proposed for quantitative determination of bacterial endotoxin in the formulated DS and finished DP using Endo-RS Kit and Endo-LISA is still under development. On May 30, 2023, in Lab (b) (4) I (ZL) observed a QC microbiologist performing BET on IPC samples for (b) (4) DS Batch #s (b) (4) and (b) (4) in accordance with Method 105-T-000315. Deficiencies in the firm's BET documentation and data review process were noted and verbally communicated to the firm's management (ZL-09 and ZL-04, respectively), during the closeout meeting on June 9, 2023.

Bioburden and EM Test

During the inspection, I (ZL) requested and reviewed the following documentation related to bioburden test (Microbial Enumeration Test - MET) of (b) (4) DS and DP with the firm's SMEs:

- **105-T-000434** "(b) (4): Microbial Enumeration Test (Bioburden)" (version 7.0, effective 2021-06-28)
- **BI-VQD-58823** "Media Quality Control" (version 11.0, effective 10 May 2023)
- **106-M-031278_R01** "(b) (4): Method Suitability Verification Summary Report of Microbial Enumeration Test - IPC Samples" (version 2.0, effective 14 Sep 2020)
- **106-M-031279_R01** "(b) (4): Method Suitability Verification Summary Report of Microbial Enumeration Test - Drug Substance" (version 1.0, effective 17 Jul 2019)
- **106-M-032798_R01** "(b) (4): Method Suitability Verification Summary Report of Sterility Test (b) (4) Harvest" (version 1.0, effective 25 Oct 2019)
- **106-M-033656_R01** (b) (4): Method Suitability Verification Summary Report of Sterility Test - DP" (version 1.0, effective 25 Oct 2019)

On June 1, 2023, I (ZL) observed (2) QC microbiologists performed plate reading of EM samples in Incubation Room (b) (4), in accordance with BI-VQD-55310-S "Test Methods of Microbiology and Particle for Environment Control" (version 13.0, effective 25 May 2023). I (ZL) noted and pointed out to the firm that the blank "EM Sampling and Test Record" forms used by the QC analysts were not adequately controlled [**Exhibit ZL-29**]. Specifically, the blank forms printed were not reconciled by the firm's quality unit to evaluate any discrepancies between the forms printed and the forms that were actually used and reported. I (ZL) expressed my concern to the firm that it failed to establish adequate document control of the

blank forms to ensure the accuracy and completeness of the GMP records. This was communicated to the firm's management as a verbal discussion item (ZL-09) during the closeout meeting on June 9, 2023. Firm's management understood the concern and had no specific comments during the closeout discussion.

Sterility Test

During the inspection, I (ZL) requested and reviewed the following documentation related to sterility test of (b) (4) DS and DP samples with the firm's SMEs:

- **105-T-001380** "(b) (4) Sterility Test for (b) (4) Harvest" (version 2.0, effective 2021-01-04)
- **105-T-001380** "(b) (4): Sterility Test for Drug Product" (version 2.0, effective 2021-01-04"
- **105-T-001614** "(b) (4): Container Closure Integrity Test (CCIT) – DP Stability Samples" (version 1.0, effective 2020-07-2)
- **106-M-032798_R01** (b) (4): Method Suitability Verification Summary Report of Sterility Test (b) (4) Harvest" (version 1.0, effective 25 Oct 2019)
- **106-M-033656_R01** (b) (4): Method Suitability Verification Summary Report of Sterility Test - DP" (version 1.0, effective 25 Oct 2019)
- **106-M-035134_R01** "(b) (4): Validation Report for CCIT via (b) (4) Dye Ingress" (version 1.0, effective 13 Jul 2020)

A Container Closure Integrity Test (CCIT) in accordance with Method # 105-T-001614, is performed on the (b) (4) DP stability samples. On June 7, 2023, I (ZL) observed a QC microbiologist performing a sterility test (by (b) (4) method) of a (b) (4) harvest sample (Batch (b) (4) in Sterility Testing Room (b) (4) in accordance with Method 105-T-001380.

No objectionable conditions were noted.

Reference Standards
(*This section was written by LB.*)

Reference standards are managed according to document 105-SOP-001237 "Management of reference standard in Boehringer Ingelheim Biopharma China" Version 3.0. On 5/31/2023, I inspected the reference standard storage area located in QC lab (b) (4). (b) (4) working reference standards (lot # (b) (4)) are stored at (b) (4) °C freezer O1-A-10052-FR. Inventory is managed in paper logbook #105-RL0093. Each vial contains (b) (4) mL material and is (b) (4) only. The LSZ site is used to store primary and working reference standards for (b) (4)

No objectionable conditions were noted.

Sample Shipping & Validation
(*This section was written by LB.*)

Sample shipment is managed according to document BI-VQD-56949-S "Shipping of samples" Version 2.0. Unprocessed bulk from the DS production cell culture step is shipped at ≤ (b) (4) °C to

(b) (4) for mycoplasma and adventitious viruses testing. The DS and DP QC samples are shipped to the client site in (b) (4) for cell-based potency testing under respective storage conditions (e.g., 2-8°C for the DP release and long-term stability samples). Majority of the (b) (4) in-process and QC testing are performed at the firm and do not require shipping. I did not cover sample shipping validation during this inspection.

No objectionable conditions were noted.

XIII. PACKAGING AND LABELING

Packaging/Labeling Materials & Operations
(*This section was written by LB.*)

Document BI-VQD-54998-S "Shipping packaging general practice" version 6.0 defines the principles and procedures regarding the firm's packaging and labeling. Packaging materials are stored in ambient storage area of the warehouse. Packaging and labeling are performed by trained operators and require verification from a second operator. Package labels are printed according to templates provided in document BI-VQD-54998-S-TPL02 "Package Label Print Template" version 1.0. Labeling of materials is described in document BI-VQD-54202-S "Labeling and status assignment in BioPharma" with examples for different status (e.g., Shipping in Quarantine) described in document BI-VQD-54202-S-AD07 "General Identifications" version 9.0.

No objectionable conditions were noted.

XIV. CORRECTIONS FROM PREVIOUS INSPECTION/FDA 483

[The current inspection is the initial inspection of the facility.]

XV. OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE:

OBSERVATION 1

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

Specifically,

Not all lots of (b) (4) drug substance (DS) are withheld from use until the lots have been full released by the quality control unit. Between December of 2017 and May of 2023 (b) (4) (b) (4) lots of (b) (4) DS were further processed and manufactured into (b) (4) drug product (DP) lots, without obtaining unprocessed bulk testing results and full DS release testing results; and completing all associated document and data reviews by your quality unit.

Supporting Evidence and Relevance:
(*This section was written by LB.*)

Document 105-SOP-001337 Quarantine Shipment & Further Production under Quarantine Version 4.0 **[EXHIBIT LB-01]** describes the firm's procedures for further processing the DS into DP, prior to obtaining the full release testing results for the DS lots (i.e., conditional release). Section 4.3.2 of the SOP lists prerequisites for further production under quarantine and specifies the minimum testing requirements which are endotoxin and bioburden for DS and

visible particle for DP. The SOP does not require that unprocessed bulk testing results, including mycoplasma and adventitious viruses, be obtained and reviewed before further processing. I requested a list of (b) (4) lots that were conditionally released **[EXHIBIT LB-02]**. The list shows a total of (b) (4) DS lots were further processed under quarantine for producing (b) (4) DP lots without obtaining the safety testing results for unprocessed bulk, indicating that this is a routine practice. The practice is against the requirement and principle outlined in 21 CFR 211.84(a), which requires that each lot of components shall be withheld from use until the lot has been tested and released for use by the quality control unit. I explained that further processing without obtaining the full DS testing results presents potential risks for introducing adventitious agents and contaminants into the multi-product DP manufacturing area.

Management's Response:

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

OBSERVATION 2

Your firm has not established and followed appropriate visual inspection procedures designed to assure batches of (b) (4) products meet appropriate specifications and statistical quality control criteria as a condition for their approval and release.

Specifically, while observing the 100% visual inspection of (b) (4) drug product, Batch # (b) (4) on 31 May 2023, the following deficiencies were noted:

A. Instead of performing AQL visual inspection after the 100% visual inspection, you initiated and performed AQL inspection while the 100% visual inspection of the same batch is still on-going. You did not provide scientifically sound justification that such approach would ensure a statistically valid sampling for the inspection process.

B. Your Quality Assurance (QA) analyst did not follow your Standard Operating Procedure (SOP), Document # BI-VQD-54842 (version 12.0, effective date 16 Jan 2023), to perform AQL inspection. Per the SOP section 4.9 AQL Visual Inspection, "a sampling process that represents the whole lot is required, (e.g., at fixed time intervals or a fixed number per tray)." The QA analyst did not randomly select samples at fixed time intervals or a fixed number of vials per tray. Instead, an entire tray (or a box) was used for AQL inspection. Your current practice may introduce statistically biased AQL results, potentially misrepresent the whole lot for all defect categories during batch approval and release.

Supporting Evidence and Relevance:
(*This section was written by YL.*)

The firm maintains SOP, Document # BI-VQD-54842 (version 12.0, effective date 01/16/2023) **[Exhibit YL-06]**. This procedure describes the process for manual visual inspection in the Visual Inspection (VI). According to the scope of the SOP, the document "is applied to all products and media fill for visual inspection and AQL visual inspection in the Visual Inspection area". In the following sections, the SOP provides a detailed description of the requisite visual inspections. Under section 4.3 Product Transfer and Storage and paragraph 4.3..4, the SOP specifies that the visual inspection is conducted with drug product stored and transferred in boxes or trays (box and tray appears to be used interchangeably), and under paragraph 4.3.6, the quantity of drug

product in a full tray is specified as (b) (4) vials fo (b) (4) vial size in a tray size of (b) (4) mm long, (b) (4) wide, and (b) (4) mm high. Under section 4.7 Manual Visual Inspection Operation, the inspector is instructed to pick up one (1) tray (step B), perform visual inspection (step C to I), repeat the steps "until the maximum number of vials is reached", and "place inspected vials in the inspected tray" (step R). Under section 4.9 AQL Visual Inspection and paragraph 4.9.1.2, AQL inspector is instructed to "take required number of AQL samples to check the quality of inspection refer to 4.9.2. The sample may be a random or a representative sample. Defects may not be distributed equally over the lot, and therefore a sampling process that represents the whole lot is required, (e. g. (e.g., at fixed time intervals or a fixed number per tray)". Under section 4.9.2 Sampling size and paragraph 4.9.2.1, the AQL inspection is to "collect the required numbers of AQL samples randomly, and visually inspect the samples in real time during inspection or upon completion of the inspection".

In addition, under section 6.1, the SOP references Document# BI-VQD-09207 Pharmaceutical Defect Evaluation List (PDEL) (version 2.0, effective date 11/15/2022) **[Exhibit YL-07]** and USP <1790> (effective date 08/01/2017). USP <1790> recommends that Acceptance Sampling and Testing (i.e., AQL testing) is performed "after 100% inspection". According to BI SOP BI-VQD-09207 Pharmaceutical Defect Evaluation List (PDEL) and under section 6.1.1 Risk Assessment By Acceptance Sampling, "In the specific case of the application of USP <(1)790> or equivalent pharmaceutical requirements (additional AQL testing after 100% visual inspection of parentals, cf. 028-BIP-00545 Visual inspection of Parenteral Products/Vaccines)….The principles of the pharmacopeial requirements regarding sampling should be followed and accordingly, an AQL acceptance sampling plan should be executed post 100% inspection process."

Based on my discussions with Ms. (b) (6) (Visual Inspection Manager) and Mr. (b) (6) (QA manager) during the May 31, 2023 inspection, it appeared that the observed practices, i. e., performing AQL testing while the 100% visual inspection is still on-going and taking an entire tray to conduct AQL testing, were the standard operation practices for visual inspection at the firm. Such practices appeared to have been used for previous (b) (4) drug product batch testing and releases.

A discussion was held with (b) (6) QP & Project Quality Manager), (b) (6) (Head of Quality), and BI China Management. I communicated the observed discrepancies between the actual operation practices and the SOPs. As of the current inspection, the firm's visual inspection procedures are not adequate and may introduce statistically biased AQL results, potentially misrepresenting the whole lot for all defect categories during batch approval and release.

Management's Response:

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

OBSERVATION 3

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

Specifically,

A. While observing the Fill & Finish (b) (4) loading for the filling of (b) (4) DP (batch # (b) (4) on 31 May 2023, the following deficiencies were noted:

1. Sterilized indirect product-contact parts including stopper chute, stopper bowl and (b) (4) and stoppering system ((b) (4)) were removed from the (b) (4) and exposed to the Grade C/ISO8 (in operation) environment (b) (4) prior to the loading and installation of the parts (b) (4)
2. While transporting and installing the above stopper feeding and stoppering parts (b) (4) (b) (4) the operator's gloved hands made direct contact with the indirect product-contact surfaces of the sterile parts. In addition, the operator was observed leaning his/her head and upper body (b) (4) during the setup.
3. The operator performing the above setup operations was observed with his/her face not fully covered by facemask and safety goggle. In addition, the operator was observed performing the setup activities with rapid movement.
4. There are no smoke studies to demonstrate unidirectional airflow and sweeping action over and away from the exposed sterile parts of the stopper feeding and stoppering systems (b) (4) throughout the (b) (4) loading operations.

B. While observing the aseptic setup for the filling of (b) (4) DP (batch # (b) (4) on 01 June 2023, and reviewing the dynamic smoke study videos (106-E-015574-VSR02) for the aseptic vial-filling line, the following deficiencies were noted:

1. While installing the (b) (4) the operator was observed holding the (b) (4) of the (b) (4) and (b) (4) the non-sterile (b) (4) with the (b) (4) exposed.
2. While performing stopper addition, the operators blocked first air to the stoppers within the stopper bowl with non-sterile (b) (4) The (b) (4) (b) (4) remained situated above the stopper bowl throughout the filling operations.
3. While connecting the filling (b) (4) bag to the (b) (4) the operator was observed blocking first air over the exposed tubing connector openings with the non-sterile (b) (4) (b) (4) gloves.
4. There is no assurance of the integrity of the (b) (4) bags used for the Fill & Finish (b) (4) manipulations. No physical evaluation is performed to assure that the (b) (4) bags are integral and not compromised prior to or after use.

C. Environmental monitoring of aseptic processing areas following aseptic assembly of filling components and aseptic filling operations are deficient. For example,

1. During the aseptic assembly and filling operations, (b) (4) gloves were used ambidextrously (i.e., the same glove used with both the left and right hands of the operators). These gloves are not required to be monitored (finger dab) ambidextrously during environmental monitoring following filling activities. Monitoring of the gloves should be performed according to their use.
2. Environmental monitoring in the aseptic filling line is not appropriately positioned in

locations to optimize detection of environmental contaminants. For example,

i. There is no non-viable particles (NVP) monitoring in the (b) (4) chamber.

ii. Microbiological surface samples are not taken from the (b) (4) (b) (4) gloves.

D. Your firm lacks adequate assurance that the capper (ID # O1-A-6805-FF) used to manufacture the (b) (4) DP is maintained in a validated state. Specifically, periodic revalidation is not required for the critical equipment in accordance with SOP 106-O-016908-VMP-RD01 (version 6.0, effective 28 Dec 2022). An initial validation study for the capper (b) (4) was performed in April of 2018, and no revalidation has been performed since then. In addition, the capper has been calibrated for the range of (b) (4) – (b) (4) bar while the actual operating range is (b) (4) – (b) (4) bar for the past (5) years (refer to PR# 1550874).

E. Your firm lacks an established cleaning and sanitization program to prevent the introduction of microbial contamination into controlled manufacturing environments. For example, your disinfectant efficacy studies, 599-D-015623-R01-A01 (version 1.0, effective 06 Jul 2018) and 106-STU-038514_P01_RA-01 (version 1.0, effective 29 Jun 2021), do not adequately support the sanitization procedures for the antimicrobial and sporicidal effectiveness of the sporicidal agent (b) (4) for all representative manufacturing surfaces in the facility. Materials used for the (b) (4) gloves, and LAF (b) (4) were not included in the studies.

Supporting Evidence and Relevance:
(*This section was written by ZL.*)

A. On May 31, 2023, the FDA investigators (ZL, LB, and YL) observed the filling-line (b) (4) loading for (b) (4) DP Batch # (b) (4) in the DP filling room (b) (4) on the (b) (4) floor of the (b) (4) building. During the observation of the manufacturing process, I (ZL) noted and pointed out to Mr. Jerry Yu, Head of DP Production, the following deficiencies in the firm's (b) (4) loading operations: (1) The operators were observed removing the sterilized indirect product-contact parts including stopper chute, stopper bowl and (b) (4) and stoppering system (b) (4)) from the (b) (4) and exposing the sterile parts to the Grade C (ISO8 in-operation) environment (b) (4) prior to the loading and installation of the parts (b) (4) (2) While transporting and installing the stopper feeding and stoppering parts (b) (4) the primary operator was observed touching the indirect product-contact surfaces of the sterile parts with his/her gloved hands. In addition, the operator was observed leaning his/her head and upper body (b) (4) during the setup process; (3) The primary operator performing the intrusive setup operations (b) (4) was observed with his/her face not fully covered by facemask and safety goggle. In addition, the operator was observed performing the setup activities with rapid movements; (4) The firm failed to conduct dynamic smoke studies to demonstrate unidirectional airflow and sweeping action over and away from the exposed sterile parts of the stopper feeding and stoppering systems (b) (4) throughout the loading operations.

Additional deficiencies observed by the FDA investigators were communicated to the firm's management as verbal discussion items (ZL-01) during the closeout meeting on June 9, 2023.

B. On June 1, 2023, the FDA investigators (ZL and YL) observed the filling-line aseptic setup and subsequent filling/capping operations for (b) (4) DP Batch #(b) (4) in the DP filling room (b) (4) on the (b) (4) floor of the (b) (4) building. During the observation of the manufacturing process, I (ZL) noted and pointed out to Mr. Jerry Yu, Head of DP Production, the following deficiencies in the firm's filling-line aseptic setup operations: (1) During the installation of the (b) (4) the operator was observed holding the (b) (4) of the (b) (4) and (b) (4) the non-sterile (b) (4) with the (b) (4) exposed; (2) During the stopper addition, the operators were observed blocking first air to the stoppers within the stopper bowl with non-sterile (b) (4) (b) (4) The (b) (4) remained situated above the stopper bowl throughout the filling operations; (3) During the connection of the filling (b) (4) bag to the (b) (4) the operator was observed blocking first air over the exposed tubing connector openings with the non-sterile (b) (4) gloves. These poor aseptic techniques were also captured in the dynamic smoke study videos for the aseptic vial filling line **[Exhibit ZL-30]**; (4 (b) (4) (b) (4) bags are used for the handling of materials entering and leaving the (b) (4) ports to provide for the (b) (4) from the (b) (4) environment during the aseptic setup and filling operations. Only a visual inspection was performed on the integrity of the (b) (4) bags. The firm's SMEs confirmed that the (b) (4) Bags had not been subject to any physical evaluation (for example a pressure decay test). I (ZL) expressed my concern to the firm that there is lack of assurance of the integrity of the (b) (4) bags used for the filling line (b) (4) manipulations.

Additional deficiencies observed by the FDA investigators were communicated to the firm's management as verbal discussion items (ZL-01) during the closeout meeting on June 9, 2023.

C. My review of the firm's environmental and personnel monitoring of aseptic processing areas following aseptic assembly of filling components and aseptic filling operations revealed the following deficiencies:

(1) During the observation of the aseptic assembly of filling components and aseptic filling operations on May 31, 2023, and June 1, 2023, I (ZL) noted and pointed out to the firm's SMEs that (b) (4) gloves were used ambidextrously, *i.e.*, the same glove port was used with both the left and right hands of the operators. However, according to BI-VQD-56735-S-AD02 "Halei Road Site Routine Environmental Monitoring Sampling Plan and Layout" (version 22, effective 30 Mar 2023) **[Exhibit ZL-31]**, these (b) (4) gloves are not required to be monitored (finger dab) ambidextrously during environmental monitoring following filling activities (refer to Section 2.3). I (ZL) stated to the firm that monitoring of the (b) (4) gloves should be performed the same as the gloves are used.

(2) My review of the firm's environmental sampling plan for the aseptic filling line during routine production described in BI-VQD-56735-S-AD02 **[Exhibit ZL-31]** revealed the following deficiencies:

(i) The designated Grade A (ISO 5) area inside the (b) (4) (b) (4) chamber, where the open vials are transported from the (b) (4) (b) (4) to the filling (b) (4) is not subject to performing Non-Viable-Particle (NVP)

monitoring during "in operation" conditions. I (ZL) expressed my concern to the firm that there is no data to demonstrated that this Grade A area is maintained to acceptable particle levels and/or that the production operations do not exceed the established alert and action levels. I (ZL) stated to the firm that NVP monitoring would be needed to be performed in order to demonstrate that the Grade A (ISO 5) classification is maintained during the aseptic filling process.

(ii) According to BI-VQD-56735-S-AD02, microbiological surface samples are not taken from the (b) (4) gloves (refer to Section 2.3 of **Exhibit ZL-31**), while surface monitoring is only performed on the (b) (4) during the media fills (refer to Section 2.2 of **Exhibit ZL-31**). I (ZL) stated to the firm that the unique compact configuration of the filling (b) (4) on the firm's aseptic filing-line presents high risk of contamination associated with the manipulations using the (b) (4) (b) (4) gloves in the apparently narrow/tight space (b) (4) The surface viable samples should be taken from the (b) (4) in addition to the fingers, to ensure and verify that a state of environmental control is maintained (b) (4) (b) (4) during aseptic setup and filling operations.

Additional EM deficiencies observed by the FDA investigators were communicated to the firm's management as verbal discussion items (ZL-02) during the closeout meeting on June 9, 2023.

D. According to the firm's SOP 106-O-016908-VMP-RD01 (version 6.0, effective 28 Dec 2022) [**Exhibit ZL-32**], periodic revalidation/requalification is not required for certain process equipment including the capping machine (capper) (ID # O1-A-6805-FF) used to manufacture the (b) (4) DP, when there have been no significant changes for these systems. The capper was initially qualified for the (b) (4) DP components (containers, stoppers and caps etc.) in 2018 [**Exhibit ZL-33**]. The capper was requalified for new (b) (4) components in 2023 [**Exhibit ZL-34**], but no revalidation has been performed for the (b) (4) components since 2018. Only a periodic documentation review was performed [**Exhibit ZL-35**]. In addition, a deviation investigation, PR# 1550874 [**Exhibit ZL-36**], found that the capper had been calibrated for the range of (b) (4) – (b) (4) bar while the actual operating range is (b) (4) – (b) (4) bar for the past (5) years. I (ZL) stated to the firm that periodic revalidation/requalification should be performed on the capper, to ensure and verify that this critical equipment essential to the DP sterility assurance is maintained in a validated state.

E. During the inspection, I (ZL) requested and reviewed the firm's disinfectant efficacy studies, 599-D-015623-R01-A01 (version 1.0, effective 06 Jul 2018) [**Exhibit ZL-37**] and 106-STU-038514_P01_RA-01 (version 1.0, effective 29 Jun 2021) [**Exhibit ZL-38**]. I (ZL) noted and pointed out the firm that not all representative manufacturing surfaces in the (b) (4) DP manufacturing facility had been included in the studies to support the sanitization procedures for the antimicrobial and sporicidal effectiveness of the sporicidal agent (b) (4) For example, materials used for (b) (4) gloves, and LAF (laminar airflow) (b) (4) were excluded from the studies. I (ZL) expressed my concern to the firm that it lacks an established cleaning and sanitization program to prevent the introduction of microbial contamination into controlled manufacturing environments used for the manufacture of sterile drug products in the (b) (4) manufacturing facility.

I (ZL) stated to the firm that, with the above observations, it lacks adequate aseptic controls, environmental control, equipment qualification, and disinfection program to prevent microbiological contamination of sterile drug products manufactured at the facility. Ms. Anji Shen, Head of Quality System, acknowledged my concerns.

Management's Response:

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

OBSERVATION 4

Your firm failed to exercise appropriate controls to protect the electronic data acquisition and/or manufacturing control systems used for (b) (4) drug substance and drug product manufacturing.

Specifically,

A. Management of access controls is inadequate for computerized systems. For example,

   1. Multiple personnel share a "Default" Administrator user account to manage the Unicorn system that is used to control and collect process data for DS manufacturing equipment. Furthermore, each "Default" Administrator user has an additional user account.

   2. A QC analyst has multiple levels of user privileges for Empower (BIChrom) system, including Coordinator, Sign2, User_AH1, and User_Data_Import.

B. Your firm maintains (b) (4) which are used to perform in-process checks during drug substance manufacturing. You do not back up the raw data generated and stored on the equipment. Per your drug substance manufacturing department head, the data capacity storage for the (b) (4) is up to 250 tests, after which the oldest data are overwritten and lost if not backed up. Additionally, the current equipment SOP permits users not in administrator role to modify and delete test results. The above practices are not in-line with your corporate SOPs including BI-VQD-04122-S-AD02, section 3.1.5.

C. Your firm maintains (b) (4) Osmomats which are used to perform drug product batch release testing. Your firm's current equipment set up and testing practices, including analytical method procedure, do not provide adequate assurance that the basic principles of data integrity especially regarding data completeness, consistency, and accuracy are adhered at all times.

D. It appears that your firm has not established adequate and consistent controls to store and backup all computerized systems that may generate, transmit, process, and protect data. Multiple deviation investigations (including PR #1580781, 1302594, 1003302, and 1302571) reported by your firm showed manufacturing equipment operation and audit trail data lost. The lack of adequate back-up programs to ensure completeness, consistency, and accuracy of the electronic data is a gap in your Data Integrity Program.

E. Audit trails enabled in the Kaye ValProbe data acquisition systems are not reviewed for each data set during the equipment validation review process. The systems are used to collect data from dataloggers during the temperature mapping and thermal validation of critical (b) (4) DP process equipment, including the (b) (4) O1-A-6504-AV) and the (b) (4)

(b) (4)(O1-A-6802-SZ). In addition, your firm failed to evaluate and determine the adequacy of the computerized system validation for a TESTO 174/Comsoft data acquisition system utilized by your firm's service contractor,(b) (4) to collect and process data for the environment mapping studies of the (b) (4) (b) (4)

Supporting Evidence and Relevance:

(*The following was written by LB.*)

A. Unicorn and Empower computerized systems are used in data collection, processing, and storage for (b) (4)manufacturing and QC testing, respectively. The firm's document "BI-VQD-04122-S-AD02 Points to consider for computerized systems version 4.0" requires that individual login credentials be used with no shared accounts, and that the number of user accounts should fit the intended use of the system. However, the firm's Unicorn has a "Default" Administrator account without a specific user ID that is shared by (b) (4)employees **[Exhibit LB- 03]**. In addition, each of these (b) (4)employees has an additional account under their specific user IDs, including Administrator, Power user, and user. For Empower user list **[Exhibit LB-04]**, one QC analyst involved in routine QC testing was shown to have multiple levels of user privileges, including Coordinator, Sign2, User_AH1, and User_Data_Import. According to the empower SOP document 028-BIS-00498 Operating the Chromatography Data System BIChrom (Empower 3) Version 1.0, the Coordinator role has privileges beyond routine testing needs such as setting up projects. I stated that a shared account does not provide personnel traceability in audit trail and that analysts involved in routine QC testing should be limited to basic user privileges.

(*The following was written by YL.*)

B. **Exhibit YL-08** is SOP# BI-VQD-10816 "Data Integrity Governance within Boehringer Ingelheim" Version 4.0, effective date 04/22/2022. BI-VQD-10816 is a Corporate Directive that "is to describe the baseline requirements and practices necessary…to ensure Data Integrity (DI)." Under section 6.1 Data Integrity Compliance and sub-section 6.1.1 Basic Principles, "All data must be included in the Quality System," and sub-section 6.1.2 Raw data, "Raw data are retained in the form in which they were originally recorded, or as a 'true copy', throughout the Retention Period." **Exhibit YL-09** is a typical User Manual for a (b) (4) that is used in the QC lab. Under section 5 Setup and sub-section 5.5 Data Transfer Setup, the user manual stated that the (b) (4) can store up to 1000 (b) (4) tests and after which the oldest data are overwritten and lost if not backed up. **Exhibit YL-10** is SOP# BI-VQD-57429-S "Operation Procedure for(b) (4) (b) (4) Under section 4.3.8 Reprint Procedure, the SOP latest 250 data can be stored" version 4.0, effective date 01/20/2023. **Exhibit YL-11** is a copy of (b) (4) logbook recording (b) (4) esting results. The (b) (4) were used to perform in-process check (IPC) testing during (b) (4) DS manufacturing.

During the inspection, I also noted multiple discrepancies and conflictions between BI corporate directive SOPs and the firm's SOP and procedure for specific analytical equipment. For example, under sub-section 6.1.4 Hybrid Systems in SOP# BI-VQD-10816 "Data Integrity Governance within Boehringer Ingelheim" **[Exhibit YL-08]** states clearly that "For Hybrid Systems it must be ensured that the original data generated is retained

and/or that the record archived represents a try copy of the data….For a hybrid system, **a printout of the electronic data is not equal to raw data**." However, under section 4.3 Operation Procedure in SOP# BI-VQD-57429-S "Operation Procedure for (b) (4) (b) (4) **[Exhibit YL-10]**, the firm states that "the printouts should be checked by one operator and will regard as the raw data." In addition, under section 3.1.5 Data Recording and Storage Requirements in SOP# BI-VQD-04122-S-AD02 "Points to consider for Computerized Systems" **[Exhibit YL-12]** states that "The system shall prevent unauthorized deletion, modification and damages to the records. Similarly, the system shall protect backup and archived data from unauthorized deletion and modifications. The system shall not automatically delete data for any reason." Under sub-section 3.2.1.1.1 User account management, the above SOP states that the access control concept must be established to ensure that only trained and authorized personnel with segregation of duties (SoD) can perform "deletion of, change to or input of data/metadata into records." However, under section 4.1.4 User management and system setting in SOP# BI-VQD-57429-S "Operation Procedure for (b) (4) **[Exhibit YL-10]**, the firm allows an "expert" to delete analysis results of the analytical system.

A discussion was held with (b) (6) (QP & Project Quality Manager), (b) (6) (Head of Quality), and BI China Management. I communicated the observed conflictions and discrepancies existing in the SOPs and the concerns about the firm's understanding of data integrity governance and compliance. As of 06/09/2023, BI China initiated Deviation PR#1655647 to address the observations and committed to investigate and ensure the electronic data generated by all hybrid systems are backed up.

C. During my observation of the Osmolality testing of (b) (4) DP on June 1, 2023, I noted that only one analyst performed the testing, and the testing involved a calibration test (b) (4) measurements) prior to the sample testing. The calibration test was conducted using a calibration standard solution and the calibration standard solution is supplied by (b) (4) in a (b) (4) mL vial. The standard solution has an osmolality of (b) (4) mOsmo/kg while the osmolality specification for (b) (4) drug product is between (b) (4) and (b) (4) mOsmo/kg. I also noted that there was a "Quit" function button on the instrument. Ms. (b) (6) (QC Specialist) indicated that analyst was instructed to "not to press the Quit function" during the experiment. I inquired what would happen if Quit function button was pressed and was told that an "aborted run" message would be printed out and the testing would be considered aborted. **Exhibit YL-13** and **Exhibit YL-14** provide the test records for determination of osmolality for (b) (4) DP or DS release testing.

I confirmed with Ms. (b) (6) QC Manager) and Mr. (b) (6) Senior QC Scientist) that it was QC laboratory's standard practice that osmolality testing was performed by a single analyst. The same analyst was also responsible for preparing the analytical testing report. Data review was performed by a second analyst. However, such review was not performed in real time and only the analytical report would be reviewed. For example, in **Exhibit YL-14** page 8, the analyst performed the test on 05/06/2023 while data review was done on 05/12/2023.

A discussion was held with (b) (6) (QP & Project Quality Manager), (b) (6) (Head of Quality), and BI China Management. The following data integrity concerns were

communicated regarding the osmolality testing: 1) raw data are not protected against modification by a user. Specifically, the test is performed by a single analyst and the raw data are the printout sheets. The current testing procedure did not implement control strategies to eliminate the opportunity to quit/abort/discard the test results; 2) the standard solution is of the same osmolality of the testing samples. The current testing procedure did not implement measures to prevent misuse of calibration solution for the actual sample testing; 3) data review is not performed in real time. All printouts were signed and dated by a single analyst which provided opportunities for data manipulation and alteration. As of 06/09/2023, BICN initiated Change Control PR#1606527 to address the observation regarding the calibration solution. The firm's current procedures lack adequate assurance that the basic principles of data integrity such as being attributable, legible, contemporaneous, original, and accurate, are always adhered.

D. **Exhibit YL-15** provides BI corporate level SOP for system backup and restore/recovery. BI SOP# BI-VQD-10816 "Data Integrity Governance within Boehringer Ingelheim" Version 4.0, effective date 04/22/2022 **[Exhibit YL-13]**, the corporate directive that governs BI data integrity practices, states that "Backup and Restore processes must be in place to allow recovery in case of system failure, data corruption, or loss. Those processes must prevent unauthorized access, modification, or deletion of data." SOP 028-BIS-00522 "Operational Use of Computer Systems" Version 5.0, effective date 11/02/2020 **[Exhibit YL-16]** and under section 6.4.5.2 Backup and Restore/Recovery states that "Backup and restore/recovery ensures that computer systems are regularly backed up in order that restore of user data and recovery of the entire system without loss of data integrity."

Exhibit ZL-12 listed process, facility, and equipment deviations associated with the manufacture of (b) (4) DS and DP in the (b) (4) Building (b) (4) manufacturing facility since the initiation of the process performance qualification (PPQ) for US market. Multiple data losses were reported on multiple computer systems. For MFCs/win system, a series of data loss was reported in Deviation# 1580781 (initiated 03/13/2023), 1577789 (initiated 03/09/2023), 1302594 (initiated 06/03/2022), and 1003302 (07/31/2020). For SCADA system, another series of data losses were reported via Deviation #1422557 (initiated 10/09/2022), #1132398 (initiated 12/09/2021), #1089063 (initiated 10/28/2021), and #758755 (initiated 11/02/2020). In addition, **Exhibit YL-17** reported (b) (4) electronic data loss due to a hard drive capacity breach. Based on my discussions with the firm's SMEs, the firm did not have data backup and restore processes in place to allow data recovery in the case of MFCs/win system and (b) (4) data losses, and the acquired raw batch data were lost and could not be retrieved.

A discussion was held with (b) (6) (QP & Project Quality Manager), (b) (6) (Head of Quality), and BI China Management. As of the current inspection, the firm has not been able to assure that the computer systems are regularly backed up to ensure the completeness, consistency, and accuracy of the electronic data.

(*The following was written by ZL.*)

E. The firm uses the Kaye ValProbe systems to collect temperature measurement data from data loggers for the environment mapping and thermal validation of process equipment, including (b) (4) (O1-A-6504-AV) [**Exhibit ZL-39**] and the (b) (4) (O1-A-6802-

SZ) [**Exhibit ZL-40**]. According to the installation and operational qualifications report, 106-E-027846-VAPR02-R-A01-3 (version 1.0, effective 30 Jul 2020), audit trails were enabled in the Kaye ValProbe data acquisition systems [**Exhibit ZL-41**]. However, it was confirmed by the firm's SMEs that the audit trails in the systems had not been reviewed for each data set during the firm's equipment qualification review process. In addition, the firm failed to evaluate and determine the adequacy of the computerized system validation for a TESTO 174/Comsoft data acquisition system, which is utilized by the firm's service contractor, (b) (4) to collect and process data for the environment mapping studies of the (b) (4) [**Exhibit ZL-42**]. I (ZL) expressed my concern to the firm that it had failed to have adequate procedural controls to ensure that its electronic data records are fully protected from potential unauthorized manipulations. I (ZL) stated to the firm that FDA expects that all data be reliable and accurate. During the inspection, Ms. Anji Shen, Head of Quality System, acknowledged my concern.

Management's Response:

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

OBSERVATION 5

Multiple open unit operations are performed in (b) (4) DS manufacturing process, such as (b) (4) (b) (4) steps, in a grade D environment without adequate environmental control and gowning practices.

Supporting Evidence and Relevance:
(*This section was written by LB.*)

Table 1 of 105-RA-000168 "Risk assessment for open operation during downstream production" Version 1.0 **[EXHIBIT LB-05]** lists all open operations performed during (b) (4) DS manufacturing, including opening of tubing ends connected to (b) (4) bags during (b) (4) and (b) (4) steps. During these open operations, tubing end plugs from the (b) (4) bags are (b) (4) are used to secure the tubing ends between (b) (4) bag and (b) (4) bag or (b) (4) Although the tube was partially clamped off, a portion of the tubing was exposed, and the exposed section will have direct contact with the product. The durations of openings are not documented in the respective batch records. These open operations present risks for potentially introducing viruses, mycoplasma, or other contaminants into the (b) (4) from operators and the environment. Moreover, there are no additional purification steps for (b) (4) and/or remove potential contaminants after the (b) (4) (b) (4) step, which itself has limited capability to remove (b) (4) based on the size of the (b) (4) On May 31, 2023, Ms. Wenxiu Nie (Head of DSP) provided an overview of the firm's risk assessment for open operations, as documented in 105-RA-000168 (Risk assessment for open operation during downstream production Version 1.0) and 105-RA-000094 (b) (4) risk assessment for (b) (4) Version 3.0) **[EXHIBIT LB-06]**. The risk assessment does not justify or evaluate the worst-case conditions (e.g., maximum duration of open operations and maximum number of operators). The risk assessment claims that the duration of the (b) (4) lasts

(b) (4) and operators must wear face masks during open operation. However, there is a lack of traceability for how long each open operation took because the firm does not track the opening duration, according to master batch record 105-MBR-000681 (b) (4) Drug Substance: (b) (4) and neutralization" Version 13.0 [EXHIBIT LB-07] and 105-MBR-000685 (b) (4) Drug Substance:(b) (4) " Version 17.0 [EXHIBIT LB-08]. Additionally, face masks are not required for all other (non-open) manufacturing operations performed in the same suite or area as open operations per firm's gowning SOP, and deficiencies were noted in the firm's environmental control and gowning practice (see verbal discussion items ZL-02 and ZL-07, respectively, in *section XVI. General Discussion with Management), which adds additional layer of risks to firm's open operation practice*.

Management's Response:

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

OBSERVATION 6

Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications, do not always include appropriate conclusions and follow-ups.

Specifically,

A. Multiple deviations and events were raised due to leakage in (b) (4) DS cell culture, downstream purification, and filling processes, such as deviations PR# 707682, 804025, 1038242, 1274193, and 1308704, and events PR# 754985, 1095204, and 1100190. The impacted materials were further processed without adequate risk assessment and appropriate corrective actions to mitigate potential risks of product contamination.

B. Out of Specification (OOS) PR#786480 was reported for binding activity ELISA release testing of (b) (4) DS batch (b) (4) . However, the OOS investigation did not include thorough root-cause analysis and justification prior to performing retesting.

Supporting Evidence and Relevance:
(*This section was written by LB.*)

A. Deviations PR# 707682, 804025, 1038242, 1274193, and 1308704, and events PR# 754985, 1095204, and 1100190 **[EXHIBIT LB-09]** were raised due to leaks during (b) (4) DS cell culture, downstream purification, and filling processes between 2020 and 2022. The impacted materials were continuing to be used for manufacturing without adequate risk assessment and corrective actions. In PR# 707682, 1038242, and 1274193, obvious leaks were observed from (b) (4) assembly during (b) (4) stage. The cell culture continued after (b) (4) ports were tightened with limited process monitoring based on bioburden and visual check under microscope, which does not cover all possible contaminants. In events PR# 754985, 1095204 and 1100190, leaks occurred to (b) (4) bags and the products were transferred to a new bag and held till next unit operation, without implementing any sterile (b) (4) during the transfer. In PR# 804025 and 1308704, transfer tubing leakages occurred during DS filling and the tubing from the same side of transfer

pump upstream of the leakage point were used to (b) (4) a new bag for subsequent filling. The corrective actions are not sufficient to prevent potential product contamination, and all these leakage events were classified as minor deviations or events based on limited risk assessment.

B. The binding ELISA potency result of the DS batch (b) (4) from the initial release testing (sample ID (b) (4) was (b) (4) %. The result was out of specification of (b) (4) - (b) (4) % for this assay, resulting in OOS PR#786480 **[EXHIBIT LB-10]**. The DS release sample was tested together with (b) (4) stability samples and the stability samples all had passing results. Based on that the release and stability samples were handled in the same way through serial in-plate dilution except for the pre-dilution step, the phase 1 OOS investigation concluded that the most likely root was handling error during the sample pre-dilution step. Based on this conclusion, a repeat testing was performed, and the repeat result of (b) (4) % was reported as the final release data for the DS batch. The firm stated that no retains of any pre-diluted samples were kept at that time; therefore, no additional lab testing was performed to confirm the root cause was indeed due to sample handling of pre-dilution step, before performing the repeat testing. I (LB) stated that repeat testing in this case should not be performed until additional investigation and testing are performed to identify and confirm the assignable root cause(s).

OBSERVATION 7

Laboratory controls do not include the establishment of scientifically sound and appropriate standards designed to assure that components and in-process materials conform to appropriate standards of identity, strength, quality, and purity.

Specifically,

A. The testing procedures are not adequate for the HCP ELISA assay used for (b) (4) DS release testing, and for binding ELISA, an identity and potency assay used for release (and stability) testing of (b) (4) drug substance and drug product. The sample preparation procedures include a predilution followed by serial dilution steps. The serial dilution of reference standards, assay control, and QC samples are performed directly inside the (b) (4) assay plates. The in-plate dilution practice is not appropriate and may cause high assay variability.

B. During the analysis of (b) (4) DS and DP by capillary gel electrophoresis, your QC analysts integrate closely eluting peaks or poorly resolved peaks using valley-to-valley integration mode, which does not reflect the true area under the peaks. Peak integration in this manner disproportionately reduces the area for the smaller peaks and consequently underestimates the relative amount of the smaller peaks, *i.e.*, the impurity peaks. Your SOP BI-VQD-58294 "Integration Guidelines of Chromatographic Data Analysis" (version 5.0, effective 11 Apr 2023) prohibits the use of the valley-to-valley manual integration for multicomponent analyses.

Supporting Evidence and Relevance:

(*The following was written by LB.*)

A. (b) (4) binding ELISA assay is performed according to the SOP document 105-T-000069 (b) (4) Binding ELISA Version 10.0 **[Exhibit LB-11]** and HCP ELISA is performed

according to 105-T-001484 (b) (4) HCP ELISA (process-specific) Version 3.0 **[Exhibit LB-12]**. Both assays include a sample pre-dilution step for reference standards, assay controls, and QC samples. (b) (4) assay plates are (b) (4) for binding ELISA and anti-HCP antibodies for HCP ELISA, and then the pre-diluted samples are further serial diluted within the (b) (4) assay plates. Performing serial dilution within assay plates may disturb the (b) (4) and thus lead to high assay variability. Trending of binding ELISA assay control show approximately 30% variability, and serval invalid assays show high variability related to sample dilution **[Exhibit LB-13]**. For example, invalid assay PR# (b) (4) showed (b) (4) % coefficient variation for a duplicate sample dilution and PR# (b) (4) for HCP ELISA showed (b) (4) % RSD for a reference standard duplicate dilution, which are much higher than the required criteria of ≤ (b) (4) %. The firm stated that the in-plate dilutions are performed according to cooperate practice for ELISA assays.

(*The following was written by ZL.*)

B. During a walk-through inspection of the firm's QC Instrument Lab (b) (4) on June 7, 2023, I (ZL) requested and examined the chromatograms on a PA 800 Plus Pharmaceutical Analysis system, for analysis of (b) (4) DS and DP samples in accordance with Method 105-T-000072 "Determination of the Purity of (b) (4) Samples using reduced - Capillary Gel Electrophoresis (CGE)" (version 6.0, effective 2023-03-29). I (ZL) noted and pointed out the firm's SMEs that the peaks for the analytes of interest had not been properly integrated in the CGE data analysis. Specifically, a valley-to-valley peak integration mode, which does not reflect the true area under the peaks, was utilized during the data analysis [**Exhibit ZL-43**]. I (ZL) expressed my concern that integration performed in this manner disproportionately reduces the area for the smaller peaks and consequently underestimates the relative amount of the smaller peaks, *i.e.*, the impurity peaks, which can potentially lead to a failure to detect out-of-specification (OOS) results for degradation and impurity analysis by chromatography. In addition, the firm's SOP BI-VQD-58294 "Integration Guidelines of Chromatographic Data Analysis" (version 5.0, effective 11 Apr 2023) prohibits the use of the valley-to-valley manual integration for multicomponent analyses [refer to Page 7 of 10 of **Exhibit ZL-44**]. During the inspection, Ms. Anji Shen, Head of Quality System, acknowledged my concern.

Management's Response:

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

XVI. GENERAL DISCUSSION WITH MANAGEMENT

The following were communicated verbally to the firm's management during the close-out meeting on June 9, 2023:

Discussion Items Written by ZL:

ZL-01: I (ZL) reiterated my concern to the firm about the poor aseptic process techniques observed during the aseptic filing-line setup and subsequent DP filling operations. There were no further comments by the firm's management.

ZL-02: I (ZL) reiterated my concern with the deficiencies in the firm's environmental monitoring program. There were no further comments by the firm's management.

ZL-03: I (ZL) reiterated my concern with the deficiencies in the HEPA filter leak test limit, inadequate requalification of the DP(b) (4) and inadequate qualification of (b) (4) There were no further comments by the firm's management.

ZL-04: I (ZL) reiterated my concern with the deficiencies in the segregation of duties in its management of the computerized systems' user privileges, data backup/retrievals, and the determination for repeated or aborted analyses/runs during the audit trail reviews. There were no further comments by the firm's management.

ZL-05: I (ZL) reiterated my concern with the deficiencies in the firm's deviation investigations. There were no further comments by the firm's management.

ZL-06: I (ZL) reiterated my concern with the deficiencies in the firm's qualification and audit of HVAC service providers. There were no further comments by the firm's management.

ZL-07: I (ZL) reiterated my concern with the deficiencies in the firm's clean room gowning procedures. There were no further comments by the firm's management.

ZL-08: I (ZL) reiterated my concern that the firm had not performed an adequate contamination control risk assessment for its DS and DP manufacturing operations in (b) (4) as well as the deficiency in the (b) (4) There were no further comments by the firm's management.

ZL-09: I (ZL) reiterated my concern with the deficiencies in the firm's documentation controls. There were no further comments by the firm's management.

ZL-10: I (ZL) reiterated my concern with the deficiencies in the firm's facility cleaning and DES. There were no further comments by the firm's management.

ZL-11: I (ZL) reiterated my concern with the deficiencies in the firm's facility maintenance program. There were no further comments by the firm's management.

XVII. ATTACHMENTS

1. FDA 483, Inspectional Observations, issued on May 29, 2023

XVIII. EXHIBITS

Exhibit LB-01 105-SOP-001337_BI-VQD-58400-S_4.0 Quarantine Shipment & Further Production under Quarantine 10 pages

Exhibit LB-02 Batch list of Further Production under Quarantine 2 pages

Exhibit LB-03 Unicorn user list and Default Administrator account 2 pages

Exhibit LB-04 QC Empower user account list 1 page

Exhibit LB-05 105-RA-000168 Risk assessment for open operation during downstream production Version 1.0 23 pages

Exhibit LB-06	105-RA-000094 (b) (4) risk assessment for (b) (4) Version 3.0 12 pages
Exhibit LB-07	105-MBR-000681 "(b) (4) and Neutralization version 13.0" 48 pages
Exhibit LB-08	105-MBR-000685 (b) (4) Drug Substance (b) (4) v17.0 47 pages
Exhibit LB-09	Reports for leakage deviations and events 79 pages
Exhibit LB-10	OOS PR# 786480 Report 6 pages
Exhibit LB-11	105-T-000069 (b) (4) Binding ELISA Version 10.0 20 pages
Exhibit LB-12	105-T-001484 (b) (4) HCP ELISA Version 3.0 23 pages
Exhibit LB-13	Trending of Binding ELISA assay controls and list of invalid assays 23 pages
Exhibit YL-01	List of (b) (4) DP Lots Manufactured, 4 pages
Exhibit YL-02	List of process parameter out-of-acceptable range for DS and DP, 2 pages
Exhibit YL-03	BI DP Reprocessed Lot (b) (4) 1 page
Exhibit YL-04	PR#914036-HL RD, FF, (b) (4) bag leakage, 31 pages
Exhibit YL-05	BI-VQD-54343-S Data management in QC Lab, 25 pages
Exhibit YL-06	BI-VQD-54842-S Visual Inspection and AQL of Vials V12, 31 pages
Exhibit YL-07	BIS-00501 Pharmaceutical Defect Evaluation List (PDEL), 44 pages
Exhibit YL-08	029-BIP-00004 Data Integrity Governance within Boehringer Ingelheim, 20 pages
Exhibit YL-09	QC (b) (4) user manual, 48 pages
Exhibit YL-10	BI-VQD-57429-S Operation Procedure for (b) (4) (b) (4) 38 pages
Exhibit YL-11	BI-VQD-57429-S-FO02 (b) (4) Logbook Scan, 3 pages
Exhibit YL-12	BI-VQD-04122-S-AD02 Computerized Systems, 12 pages
Exhibit YL-13	Osmometer Test Record Jan 6th, 8 pages
Exhibit YL-14	Osmometer Test Record May 6th, 8 pages
Exhibit YL-15	027-BIS-00061 System Backup and Restore Recovery, 14 pages
Exhibit YL-16	SOP BIS-00522 Operational Use of Computer Systems, 21 pages
Exhibit YL-17	PR#1302571 Deviation Complete Report, 8 pages
Exhibit ZL-01	BICN Opening Presentations 51 pages
Exhibit ZL-02	Opening Meeting Attendees 1 page
Exhibit ZL-03	Closeout Meeting Attendees 1 page
Exhibit ZL-04	Organizational charts 6 pages
Exhibit ZL-05	Persons interviewed by the FDA inspection team 15 pages
Exhibit ZL-06	Warehouse Exit Door 1 page
Exhibit ZL-07	(b) (4) Caulk Bead Damages 1 page
Exhibit ZL-08	(b) (4) Kinetic-QCL Bulk Kit Certificate 3 pages
Exhibit ZL-09	BET Data Review Record 4 pages

Exhibit ZL-10 Photos of Lishizhen Warehouse Doors 1 page
Exhibit ZL-11 Photos of Process Equipment in (b) (4) 3 pages
Exhibit ZL-12 Lists of deviations associated with the manufacture of (b) (4) 8 pages
Exhibit ZL-13 Deviations on Facility Ceiling Water Leaks 3 pages
Exhibit ZL-14 Deviations associated with the filter integrity test failures 16 pages
Exhibit ZL-15 List of Change Controls associated with the manufacture of (b) (4) 10 pages
Exhibit ZL-16 Extended Workbench Assessment for (b) (4) (b) (4) 2 pages
Exhibit ZL-17 List of Computerized Systems 6 pages
Exhibit ZL-18 Overview of HVAC Systems 8 pages
Exhibit ZL-19 Overview of Alarm Management Systems 9 pages
Exhibit ZL-20 List of major processing equipment for (b) (4) DS 8 pages
Exhibit ZL-21 List of major processing equipment for DP 3 pages
Exhibit ZL-22 Cleaning Validation Presentation 10 pages
Exhibit ZL-23 Process flow diagrams for (b) (4) DS 4 pages
Exhibit ZL-24 (b) (4) DS Hold Time Studies 11 pages
Exhibit ZL-25 (b) (4) DS IPC sampling point selection 12 pages
Exhibit ZL-26 106-STU-032899_R01_(b) (4) Holding Time Study Report for Samples of Bacterial Endotoxin Test 24 pages
Exhibit ZL-27 Process flow diagrams for (b) (4) DP 2 pages
Exhibit ZL-28 Microbial control strategy and hold time study and lifetime study 14 pages
Exhibit ZL-29 EM Sampling and Test Record forms 10 pages
Exhibit ZL-30 Smoke study report of DP filling line_106-E-015574-VSR02 17 pages
Exhibit ZL-31 BI-VQD-54238-S-AD02 Halei Road Site Routine Environmental Monitoring Sampling Plan and Layout 21 pages
Exhibit ZL-32 SOP 106-O-016908-VMP-RD01 11 pages
Exhibit ZL-33 106-E-015022-VSR 49 pages
Exhibit ZL-34 106-E-015022-VSR 13 pages
Exhibit ZL-35 106-E-015022-PR03 26 pages
Exhibit ZL-36 Deviation PR1550874 57 pages
Exhibit ZL-37 599-D-015623-R01-A01 21 pages
Exhibit ZL-38 106-STU-038514-R-RA01 Evaluation of microbicidal efficacy of (b) (4) 22 pages
Exhibit ZL-39 (b) (4) Requalification Data 106-E-011702-VAP06-TC04-R01-A09 313 pages
Exhibit ZL-40 (b) (4) Requalification Data 106-E-015021-VAP08-TC04-R01_1.0 264 pages

Exhibit ZL-41 Kaye ValProbe Systems IOQ 106-E-027846-VAPR02-R-A01-3 131 pages
Exhibit ZL-42 106-E-012809-VAPR03-TC12-R_1.0 Periodic Requalification Testing of (b) (4) (b) (4) 81 pages
Exhibit ZL-43 CGE Peak Integration Chromatograms 3 pages
Exhibit ZL-44 BI-VQD-58294-S Integration guidelines of chromatographic data analysis 11 pages

XIX. SIGNATURES

Zhong Li -S
Digitally signed by Zhong Li -S
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Zhong Li, Ph.D., Senior Pharmaceutical Quality Assessor
CDER/OPQ/OPMA/DBM

Leiyun W. Boone -S
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Yiwei Li, Ph.D., Supervisory Chemist
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