DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing 10903 New Hampshire Avenue; White Oak Building 51 Room 2269, Silver Spring, MD 20993 E-mail: OPMA(b) (4)nspection483Responses@fda.hhs.gov	11/30/2023-12/14/2023
	FEI NUMBER 3015786877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Hongwei Wang, General Manager

FIRM NAME	STREET ADDRESS
Suzhou Suncadia Biopharmaceuticals Co., Ltd.	No. 350 Fengli Street, Industrial Park
CITY, STATE, ZIP CODE, COUNTRY Suzhou, Jiangsu,215028, China	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product Manufacturer

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

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

The (b) (4) drug product manufacturing process and procedures do not support frequent high-risk interventions to aseptic processing (HRIAP) in the vial fill line. Specifically,

HRIAP during Fill Line Operations

A) The (b) (4) fill line is (b) (4) (b) (4)

B) After gowning, operators in Grade B are required to walk through the Grade A laminar flow at two locations crossing B (observation window side), and/or crossing A (operation bench side) in order to conduct drug product manufacturing operations. Crossing site B and crossing site A are located within the grade A laminar flow fill line. Personnel crossings at site B and A occur during both fill line setup and filling operations.

C) Sterilized equipment and container closure stoppers are moved from Grade B through crossing site B and crossing site A in a cart (dimensions 143 cm X 198 cm X 65.5 cm) to the operation bench side during both setup and filling operations.

D) Crossings at sites B and A require manual dismantling and reassembly of vial guard rails and the vial conveyor belt with gloved hands within the fill line in order to allow personnel and cart crossings.

E) During (b) (4) of filling operations, filled vials for in-process testing are placed on (b) (4) in grade B that is (b) (4) across the laminar flow underneath the conveyor belt during operations.

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Inadequate decontamination of the Fill Line after HRIAP

A) After personnel crossings at sites A and B, the laminar flow area is not decontaminated with a sporicidal agent.

B) The manually disassembled and reassembled guard rails and conveyor belt that guide the (b) (4) vials to the (b) (4) are not decontaminated with a sporicidal agent prior to resuming filling operations.

Inadequate documentation regarding HRIAP

A) Crossings at site A and site B during filling operations are limited to (b) (4) crossings (b) (4) (b) (4) without raising a deviation, however, not each operator crossing is counted as a unique crossing. Two or more operators crossing the laminar flow during (b) (4) are documented as a single crossing event. The batch record does not note the number of operators crossing sites A and B during drug product manufacturing

B) The number of crossings at B and A during fill line setup are not documented or limited.

Inadequate complementary data to support HRIAP

A) No smoke study was performed with the operator pushing the cart (143 cm X 198 cm X 65.5 cm) at crossing sites B and A to show that unidirectional air flow was not impacted at other critical locations within the fill line.

B) Smoke studies during personnel movement across the laminar flow were often filmed near the operator impeding the ability to conclude that operator crossings did not impact unidirectional air flow at other critical locations within the fill line.

C) Before HRIAP, vials but not stoppers undergo line clearance. No smoke study was provided to evaluate the impact on unidirectional flow at the stopper bowl area to support vial clearance but not stopper line clearance.

D) There are no non-viable particle probes within the laminar flow including the crossing sites.

E) Personnel monitoring for operators working within the Grade A do not test shoe caps for the presence of microorganisms, a likely source of operator contamination.

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OBSERVATION 2

Your firm has not established adequate procedural controls over equipment systems to ensure data integrity and system access. Specifically,

A) SOP M-00 009 for (b)(4) purity analysis by IEC-HPLC describes the assay procedure and chromatogram data integration analysis. Peak areas are initially reported automatically according to the pre-set parameters using the software OpenLab CDS 2.6 from Agilent. The data integration method with automatic analysis and reporting has been installed since February 5, 2021. (b)(4) the program performs an automated integration. However, it is noted that essentially all IEC-HPLC peak integrations, are performed manually because the operator determined that the automated integration is not accurate. There are significant differences (≥ 5% main peak area) in the same chromatogram when integrated automatically or manually. The current SOP does not have adequate instructions to perform the manual integration to ensure reproducibility and peak area accuracy.

B) Appropriate controls are not exercised over QC testing system to assure that testing and control records are only instituted by authorized personnel. A pH meter ID E-002281 located in QC chemistry lab (b)(4) appeared to be in a ready-to-use screen and was not user and password protected during the 11/30/2023 QC lab inspection. According to your QC manager, user account and password function of the pH meter were disabled even though the same is used for QC release and stability testing. Unprotected usage and/or shared user account renders critical quality data used to inform batch release and stability decisions not attributable. The absence of the required data control measures contradicts your Data Integrity policy GR-007, Version 3, Effective date 01/15/2019, section 7.1.1.

C) Your firm maintains (b)(4) pH meter (b)(4) (b)(4) which are used to perform QC batch release and stability testing during drug substance and drug product manufacturing. These instruments are "stand-alone" units and each unit stores electronic testing data on the unit. You do not capture, and back up raw electronic data generated and stored on these units. The absence of the required data

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control measures contradicts your Data Integrity policy GR-007 "Management Procedure of Data Integrity", Version 3, Effective date 01/15/2019, section 7.3.6.2.

D) System administrator account, i. e., "admin" account controlled by IT department, for critical manufacturing computer system was used by manufacturing operation unit to perform batch manufacturing production. According to Deviation # DR 211211M, during the manufacturing of (b)(4) PPQ batch (b)(4) a malfunction of the capping equipment led to a PDA computer communication error. After restart, only system administrator "admin" account was accessible. Upon approval from QA, the manufacturing operation unit performed manufacturing operations using the administrator account. Subsequently, instead of reinstalling the user account and conducting normal operations, the "admin" account was used to manufacture three additional drug product batches. (b)(4) Sharing and using administrator account or any other account for non-designated purposes or actions is against the data integrity, i. e., ALCOA+ principles and contradicted your Data Integrity policy document GR-007 "Management Procedure of Data Integrity".

E) Comprehensive reviews of all electronic data including audit trails are not performed by the Quality Assurance (QA) unit for standalone and network systems of all production records and QC testing results prior to the final approval of manufacturing batch records (MBR). According to your QA supervisor, comprehensive batch record review by QA – prior to final approval of such record – is limited to paper review of the manufacturing record and verification of QC study reports. You do not review and verify critical raw data including audit trails to ensure completeness and accuracy of the testing results and critical process parameters.

F) Document controls are not in place to assure product quality. The official blank forms such as master production and control records and QC release testing reports are not bound, numbered, and time-stamped when they are issued by quality unit. There is no assurance that issuance of multiple sets of the same document or replacement of a certain page in the document can be easily detected.

G) According to IT department personnel, periodic review of system login and user account to ensure appropriate user role assignment for manufacturing floor and QC computer systems is not preformed. Upon request, IT department is not able to generate access control list (ACL) for the

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PDA computer system used for DP manufacture operations. Standard operating procedures (SOP) for such periodic review and access control have not been created and followed.

OBSERVATION 3

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

A) Critical operations are not always performed with sterile tools. For instance, the aseptic connection with (b) (4) to product contact sterile tubing was performed by the operator using (b) (4) gloves. The installation of the (b) (4) into its (b) (4) required (b) (4) the (b) (4) part of the (b) (4) gloves. In addition, the (b) (4) were removed prior to the aseptic connection and (b) (4) installation.

B) Media fills are performed with dedicated (b) (4) that are not used in routine production.

C) The manufacturing process includes (b) (4) (b) (4) The material (b) (4) is not incubated for growth in media fills.

D) Non-product contact equipment within the RABS is not cleaned with a sporicidal agent before every batch.

E) Sanitization of the RABS (b) (4) do not always use a new side of the wipe at new wiping locations. Sanitization of the RABS (b) (4) were not always performed from (b) (4)

F) Guard rails that are dissembled for personnel crossing are placed underneath the conveyor belt on a shelf near the floor before reassembly and restart of filling.

G) Introduction of stoppers blocked first air on the stopper (b) (4)

H) The installation of the stopper (b) (4) was performed without a cover on the stopper bowl.

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OBSERVATION 4

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

Not all lots of drug substances (DS) are withheld from use for further manufacturing until the DS lots have been fully released with all associated document and data review by the quality control unit. From January 2021 to current, (b) (4) of (b) (4) lots were further processed and manufactured into drug product before final release of the DS.

OBSERVATION 5

Your firm did not establish appropriate visual inspection (VI) procedures designed to assure batches of (b) (4) products meet the specifications and quality control criteria as a condition for their approval and release. Specifically,

A) Observed during the 100% visual inspection of (b) (4) drug product, Batch # (b) (4) on 12/07/2023, VI inspectors held (b) (4) units and examined the (b) (4) units against a (b) (4) background for (b) (4) (b) (4) The amount of time used to inspect each unit is not sufficient to meet the "approximately (b) (4) the backgrounds" requirement stipulated by (b) (4) It should be noted that the subject drug product is in (b) (4) form which is considered a (b) (4) product (b) (4) pre (b) (4)

B) Observed during inspection of the VI qualification kit, the qualification test sample units do not represent the real drug unit in which the qualification unit has a numbered label on top of the vial while the real drug unit does not have such label.

C) You have not established a clear procedure – supported by scientifically sound rationale – to handle multiple and sequential 100% visual inspection or AQL testing failures and how you conduct reinspection of the drug units under such situations.

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OBSERVATION 6

Capping (b) (4) validation data to ensure container closure integrity is inadequate. Specifically,

A) As per Process Validation Protocol for (b) (4) Injection only (b) (4) vials per PPQ batch were selected from a batch size of approximately (b) (4) vials to evaluate container closure integrity. Capping (b) (4) parameters ranges are not validated as there is a single setting on the capping (b) (4) station.

B) Two additional studies (VO-P 801 008 05 and VO-P 801 008 08) were performed after PPQ that tested (b) (4) vials and (b) (4) vials respectively for container closure integrity using the commercial production capping (b) (4) parameters. The justification for the sampling size to support container closure integrity for commercial batch sizes of approximately (b) (4) vials was not provided.

OBSERVATION 7

Scientifically sound and appropriate controls are not implemented for (b) (4) manufacturing operation to ensure that drug products conform to appropriate standards of identity, strength, quality and purity. Specifically,

A) Deviation No. 230101M, dated 01/01/2023 was initiated by your firm to document "abnormal air pressure" in the (b) (4) during the manufacturing of (b) (4) injection batch (b) (4) Subsequently, (b) (4) post-personnel found the (b) (4) value of the (b) (4) of the (b) (4) decreased and approached to the limit of (b) (4) (b) (4) fluctuation lasted for 41 minutes. According to the firm's SME, such (b) (4) fluctuation was outside of the parameter range for the (b) (4) operation. No additional assessment of potential impacts to drug product quality was performed by the firm.

B) Deviation No. 230803M, dated 08/08/2023 was initiated by your firm to document (b) (4) generator failure of the filling machine" during the manufacturing of (b) (4) injection batch (b) (4) As a result of the equipment failure, (b) (4) of the same

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drug product was performed on (b) (4) drug units. According to the firm's SME, no drug product development data are available to support the above loading number and loading pattern in the (b) (4) The normal loading for the product is up to (b) (4) units. The firm does not have adequate data to provide assurance that the quality, purity, and the physical properties of the (b) (4) product are maintained.

C) Deviation No. 230607M, dated 06/21/2023 was initiated by your firm to document "unacceptable leakage rate" during the manufacturing of (b) (4) injection batch (b) (4) Root cause analysis identified that "the approximate leak point" was "the (b) (4) in the (b) (4) of the (b) (4) According to discussions with the firm's SME, such leak may allow ingress of air from an uncontrolled and nonsterile environment into the sterilized (b) (4) containing drug units. The firm did not perform retrospective risk analysis of the above leak and the potential impacts on the sterility control of the previously manufactured batches.

OBSERVATION 8

SOP's do not provide adequate information to ensure the consistency of assay performance. Specifically,

A) SOP M-00 236 01 particulate contamination visible particles (USP) for (b) (4) drug product release and stability testing is not sufficient to ensure the effective control for visible particles as there are no acceptance criteria for inherent visible particles size, color, shape, and content. In addition, the training program for operators to identify the variation in visible particle characteristics is inadequate because the training materials do not contain suitable samples with different types of inherent visible particles.

B) No positive controls with defects ≤ (b) (4) µm are used during routine container closure integrity testing.

C) A small amount of (b) (4) dye, in the dye immersion method to assess container closure integrity, is spiked into a control to make a limit of detection vial which is used as the comparison against test vials to determine if the assay complies/non-complies. There is no

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system suitability criteria around the absorbance value for the limit of detection vial thus the more spike added to the limit of detection vial the easier for the assay to comply.

OBSERVATION 9

Raw material management is inadequate. Specifically,

(b) (4) for (b) (4) DS manufacturing is dedicated for either the US market or the China market. According to the information in the raw material management system, GS ERP, the (b) (4) (raw material ID # (b) (4) was released for China commercial manufacturing only, however, it was used in the current batch for intended US manufacturing. The GS ERP data management system is not designed to detect mix-ups of raw materials that are dedicated to either US or foreign markets.

OBSERVATION 10

Appropriate designs to ensure that complete data derived from all tests necessary to assure compliance with established specifications and standards are not included in the laboratory records. Specifically,

A total of (b) (4) Microsoft (MS) excel spreadsheet templates are used to perform calculations for your QC release testing, stability testing, and biological potency testing. Observed are the following:

A) All templates are kept in one document folder.
B) No system security is defined. QC personnel can open all templates.
C) Username and password protection and restriction to the templates are not established.
D) After data entry and calculation, an electronic copy containing original data entries was deleted. Only paper printout copy is kept and included as part of the laboratory reports.
E) No audit trail functions are enabled for the spreadsheet templates.

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F) Second person review of the original electronic record cannot be verified.

G) Standard operating procedure (SOP) for individual spreadsheet template is not available.

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