**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| Director, Division of Inspections and Surveillance<br>FDA / CBER / Office of Compliance and Biologics Quality<br>10903 New Hampshire Avenue (W071-5128) TEL: 240-402-9159<br>Silver Spring, MD 20993-0002 CBERFDA483responses@fda.hhs.gov<br>Industry Information: www.fda.gov/oc/industry | March 2-9, 2023<br>FEI NUMBER<br>3011033616 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Takahiko Nonogaki, Chairman and President

| FIRM NAME | STREET ADDRESS |
|---|---|
| Unigen Inc. | 11 Miyaji, Ikeda-Cho |
| CITY, STATE AND ZIP CODE | TYPE OF ESTABLISHMENT INSPECTED |
| Ibi District, Gifu, Japan 503-2406 | Licensed Biological 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 (I) (WE) OBSERVED:

OBSERVATION 1

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

a) Column re-use studies for the (b) (4) columns for influenza B strains with high (b) (4) (at the worst-case scenario of NMT (b) (4) have not been performed.

b) A failure in revising the (b) (4) limit of (b) (4) for rHA B antigen from NMT (b) (4) (b) (4) in a timely manner. The firm committed to revise the (b) (4) limit of (b) (4) in 2017, but change control for this revision occurred in February 2021.

c) (b) (4) DS batches of FluBlok (b) (4) (b) (4) had been manufactured with an (b) (4) process that deviates from the approved manufacturing process from May 23 to July 21, 2021. These DS batches had not been put on stability nor evaluated with additional characterization tests.

d) There is a lack of data to support the quality performance of the (b) (4) (b) (4) for a maximum of (b) (4)

e) There is a lack of data on the (b) (4) control of the (b) (4) measurement by the (b) (4) machines used in the manufacturing facility.

f) Cracked (b) (4) resin column was used for the downstream processing of (b) (4) batches of rHA antigen DS. Deviations F2022D022 and F2022D028 were opened due to the observation of Cracked (b) (4) column during sample loading of DS batches (b) (4) and (b) (4) respectively. The same (b) (4) column was continuously used for

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processing of additional DS batches (b) (4) and (b) (4) without performing the (b) (4) (b) (4) of the column. These affected batches had not been evaluated with additional characterization tests nor stability studies.

g) Deviation 2021D043, dated 11/29/2021, reported calibration by an external company was conducted on Nov 29, 2021 but failed due to exceedance of the allowable range (b) (4) at the (b) (4) reference value. It was concluded that this event was caused by a failure due to aged deterioration associated with long-term use of the calibrated instrument, (b) (4) A preventive action was to identify similar instruments, take the same corrective action, and change to non-calibration instruments. This preventive action was not reported to the authorized Market Approval Holder (MAH) (i.e. license holder).

h) The quality agreement with license holder requires Unigen to report change controls that could affect product quality. Change control 2020C182 involved a change in the raw material used by the vendor to make the (b) (4) (b) (4) which is (b) (4) during the purification process of rHA. Unigen never reported the change to the license holder.

i) Change Control Procedure, UGG-MF02-AL-ZZ-01 requires the change applicant to consult with managers of different functional areas that might be affected by a requested change. Change control 2020C182 was initiated by the Quality unit (change applicant) as a result of a vendor notification of a change in the raw material making up the (b) (4) The Quality unit never consulted with the manufacturing or product process groups before accepting the change by the vendor. Nor did they notify any group in advance of using the new material. Additionally, the SOP requires testing (b) (4) lots of the new material before relying on the COA or COR prior to releasing the material for use in manufacturing. Manufacturer Lots (b) (4) and (b) (4) of material code (b) (4) have been received and released by the Quality unit relying solely on the COA since the change was implemented.

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy, the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has been already distributed. Specifically,

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a) Approximately 16 Material Abnormality Reports from 2/1/2021 – 3/1/2023 reported foreign matter for 20 lots of (b) (4) (b) (4) A Deviation Report has not been initiated for this trend and the only corrective actions have been to return the (b) (4) to the vendor. The 15 Raw Material Abnormality Reports opened in 2022 remain open, and no response has been received for supplier complaints submitted. The current Deviation Control Procedure, Doc No: UGG-MF05-AL-ZZ-01, dated 12/13/2022, does not have criteria for when raw material abnormalities would trigger initiating a Deviation Report.

b) Written procedures are lacking for the quality oversight of vendors who supply raw materials and components for use in the manufacturing of rHA BDS. There are no quality agreements in place with any vendor to specify the terms of the supplier relationship. Nor is there a procedure in place for Unigen to address and manage complaints against vendors who deliver lots which are damaged or do not otherwise meet specifications.

OBSERVATION 3

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

a) Thirteen deviations exceeding the (b) (4) acceptance criteria of NMT (b) (4) for the (b) (4) of the influenza B rHA were identified from 2017 to 2022. A total of 17 batches of influenza B rHA DS were affected and they were proceeded to production. In the investigation report, there was no indication that the firm had performed thorough investigation to identify the root cause for an (b) (4) for the influenza B rHA since their initial PPQ runs. These affected batches had not been evaluated with additional characterization tests nor stability studies. Until now, no corrective actions have been implemented to resolve this recurring issue.

b) Seven deviations that failed the lower range of acceptance criterion for the (b) (4) of (b) (4) column was identified from 2021-2022 and affecting 7 batches of B/Phuket rHA antigen. Only one out of the 7 deviations had (b) (4) criterion was compiled. For the rest of the deviations, (b) (4) (b) (4) even with a failed (b) (4) No comprehensive investigation on the quality performance of the (b) (4) column nor optimized buffer usage had been considered in the

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investigation; however, an incorrect range of the (b) (4) was concluded but with no supporting data. Two years since the initiation of the first deviation, no corrective actions have been implemented to address this recurring issue.

c) Deviation F2021D048, dated 9/30/2021, reported a deviation of sample shipping temperature for Flublok batches in 2021. As an improvement response it was to change arrangements with transporters, reviewing transporters, and introducing a temperature monitoring system. A CAPA was not implemented and the action was to be considered through the Annual Product Review (APR).

d) Deviation 2021D040, dated 5/31/2021, reported contact surface microbes of gloves exceeding the action limit were detected. The root cause was thought to be that the operator forgot to disinfect his hand with (b) (4) after touching around the goggles, which has a high risk of contamination. The justification on why a CAPA was not required was not documented.

e) Deviation 2021D031, dated 10/11/2021, reported the blank form of management of pre-treatment and water facility of water for production was lost on 10/11/2021. Corrective actions to include changing the record ledger, and preventive actions to include education on the procedures for issuing the forms were conducted, but a CAPA effectiveness check not implemented.

OBSERVATION 4

Backup data is not assured as exact, complete, secure from alteration, erasure or loss through keeping hard copy or alternate systems. Specifically,

Review of the backup of (b) (4) Lot on 3/7/2023 to the Hard Drive Disk (HDD) revealed that scanned image (Image Report: (b) (4) could not be retrieved from the backup QC-HDD-03, and the file is not secure from deletion. Additionally,

a) Deviation 2022D063, dated 9/21/2022, reported a loss of storage date due to failure of the (b) (4) (b) (4) Instrument No. (b) (4) Data from the period of June 13, 2022 to September 02, 2022 have not been backed up.

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b) Deviation F2021D027, dated 4/12/2021, reported loss of stored data due to failure of PC hard disk constituting the digital imaging system (device number: (b) (4) The main cause of this event was accidental physical damage to the HDD. Around April 12, 2021, when an attempt was made to perform a (b) (4) inspection of the digital imaging system, in (b) (4) Room (b) (4) errors were displayed on the PC monitors constituting the device. The failure of the Hard Disk Drive (HDD) in the PC was confirmed and the data backup was not carried out during the period from March 22, 2020 (the last backup date) to Apr 12, 2021.

c) Deviation 2021D044, dated 12/9/2021, reported on 12/7/2021 that the data of the (b) (4) card used in the electronic recorder on the (b) (4) equipment control panel in the (b) (4) Room (b) (4) was partially missing. The range of missing data was 961 files from October 15, 2021 to November 24, 2021.

d) Deviation 2021D052, dated Jan 5, 2022 reported a (b) (4) inspection was conducted on December 20, 2021, and the temperature data was missing for the QC (b) (4) Test Lab temperature incubators (Equipment numbers: (b) (4)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."