DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/OPQ/OPMA/DBM, Attn: Zhihao Peter Qiu, Ph.D., Acting Director 10903 New Hampshire Avenue; White Oak Building 22 Silver Spring, MD 20993 E-mail: OPFBLAInspection483Responses@fda.hhs.gov	01/27/2020-01/31/2020
	FEI NUMBER 1937990

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kelly L. Foster, Head of Operations for Cherokee – St. Louis, Madison/Verona, Schaffhausen

FIRM NAME	STREET ADDRESS
Sigma-Aldrich Manufacturing LLC	3300 South Second St.
CITY, STATE, ZIP CODE, COUNTRY Saint Louis, MO 63118-3306	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

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

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Your firm failed to thoroughly investigate manufacturing deviations. Specifically, the (b) (4) (b) (4) skid, (b) (4) has failed at least (b) (4) times during the (b) (4) commercial manufacturing process. This critical process equipment is the only TFF skid that is used in the manufacturing process.

The (b) (4) skid failed 24 August 2018 (NCR 200445824) during batch (b) (4) due to a failure of the programming of the (b) (4) NCR 200445824 states "This is not the first time the operators have observed a (b) (4) malfunction; however, it is the first time it was documented." The associated NCR to abandon the batch, NCR 200445859 states, "This is the (b) (4) time out of the last (b) (4) batches (not all of (b) (4)) that this has occurred."

The (b) (4) TFF skid failed 8 October 2019 (NCR 2187160) during batch (b) (4) . During equilibration, the tank was fully drained, and the recipe did not reach the expected "(b) (4) " weight criteria during buffer discharge. The cause of the NCR was determined to be a cap screw of (b) (4) (b) (4) coming out of alignment. Repairs were made 10 October 2019 and the equipment was put back into service prior to closing the deviation.

The (b) (4) TFF skid failed on the next batch, 15 October 2019 (NCR 2194911), during batch (b) (4) During equilibration, the tank was fully drained, and the recipe did not reach the expected "(b) (4) " weight criteria during buffer discharge. The investigation determined that the failure was the cap screw on (b) (4) coming out of alignment. The investigation identified five potential root causes and performed associated corrective actions for all 5 and identified 4 additional best practices to improve the performance of the (b) (4) TFF skid.

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	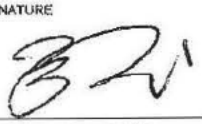	Zhong Li, Ph.D., Chemist William Hallett, Ph.D., Lead Chemist Chih-Jung Hsu, Ph.D., Staff Fellow	1/31/2020

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The (b) (4) TFF skid failed 21 January 2020 (NCR 2297329) during batch (b) (4) This deviation is still open, but preliminary findings indicate a problem with a pressure control valve and the tank fully draining instead of leaving (b) (4) of equilibration buffer in the system.

On two of these occasions, batches (b) (4) and (b) (4) drug substance intermediate was thawed and then refrozen so that the TFF skid unit could be repaired. The freeze-thaw process for the (b) (4) was not part of the validated (b) (4) manufacturing process.

OBSERVATION 2

The bulk-fill process for (b) (4) is deficient regarding the system for monitoring environmental conditions. Specifically, (b) (4) settling plate was placed approximately (b) (4) inches away from the working area during open filling operation in the biological safety cabinet. The settling plate receives unidirectional airflow and may not capture potential contaminants in the critical working area during the filling. In addition, no viable surface sampling is performed immediately after the filling operations.

OBSERVATION 3

Your firm lacks an established cleaning and sanitization program to prevent the introduction of contamination into controlled manufacturing environments used for the manufacture of (b) (4) (b) (4) Specifically,

(a) Your firm's disinfectant efficacy studies ((b) (4)) do not adequately support the sanitization procedures for the antimicrobial and sporicidal effectiveness of the disinfectants and sporicidal agents for all representative manufacturing surfaces in your (b) (4) commercial facility.

(b) Your cleaning and sanitization for the (b) (4) Facility (Doc# 3290782-LS, version 17.0, effective 28-Aug-2019) lacks sufficient detail to ensure that the treated surface remains wet for a (b) (4) contact time. In addition, OP-050928 (Doc# 1015838-LS, version 6.0, effective 14-Aug-2019) does not require the documenting of the contact time in the cleaning logbook during the cleaning.

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	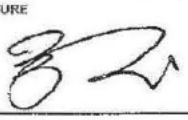	Zhong Li, Ph.D., Chemist William Hallett, Ph.D., Lead Chemist Chih-Jung Hsu, Ph.D., Staff Fellow	1/31/2020

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OBSERVATION 4

Your firm has not established adequate procedural controls to protect the stand-alone electronic data acquisition systems. Specifically,

(a) The (b) (4) system installed on the (b) (4)) has not been validated. The system is used to collect data for the environment mapping studies of environmentally controlled product storage equipment and testing equipment. In addition, the date and time settings in the Microsoft Windows operating system are not protected.

(b) Audit trail review is not performed for testing data that are generated by the (b) (4) system (3DS-0001), (b) (4) (3AIA-0307), (b) (4) (3AISP-0128), and (b) (4) TOC Analyzer (3AIA-0252).

(c) There is a lack of documented evidence that the above data acquisition systems have been validated for data backup/transfer and retrieval.

OBSERVATION 5

Your firm lacks adequate assurance that critical equipment is maintained in a validated state. Specifically, periodic revalidation is not performed for the production freezers used for (b) (4) (b) (4) manufacturing and storage, and QC incubators used for (b) (4) (b) (4) testing.

OBSERVATION 6

Testing of a critical raw material is not adequate. Specifically, process gas, (b) (4) (b) (4) used for (b) (4) commercial manufacturing, is not tested for identity upon receipt from the supplier, nor is an analysis conducted to verify the reliability of the supplier's certificates of analysis.

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OBSERVATION 7

Your equipment cleaning validation swab study, (b) (4) Surface Sampling Validation Report (Doc ID: 1053367421-LS, version 1.0, effective 24-May-2018), does not adequately support the cleaning procedure for reactor (b) (4) Specifically, swab recoveries of the residual protein (b) (4) intermediate have not been demonstrated from all representative product contact surfaces.

OBSERVATION 8

Your (b) (4) buffer stability study, Doc ID 121219397-LS (version 1.0, effective 13-Sep-2019), fails to provide reliable endotoxin testing data to support the expiration dates for the (b) (4) buffer ((b) (4)) and (b) (4) buffer ((b) (4)) that are used in the manufacture of (b) (4) bulk drug substance (b) (4)

OBSERVATION 9

The (b) (4) test method, used for (b) (4) in-process samples and buffers, was not verified prior to the process performance qualification of (b) (4)

1/31/2020

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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 judgment, 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."