DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	
DISTRICT ADDRESS AND PHONE NUMBER Division of Biotechnology Manufacturing; WO 51 / Room 2269 10903 New Hampshire Avenue Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	DATE(S) OF INSPECTION 02/02/2023-02/10/2023 FEI NUMBER 3000209996
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED Mr. Kevin Ingham, Site Head & General Manager	
FIRM NAME AGC Biologics Inc.	STREET ADDRESS 21511 23rd Dr SE
CITY, STATE, ZIP CODE, COUNTRY Bothell, WA 98021	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

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 appropriate conclusions and follow-up.

Specifically,

A. Your firm failed to conduct prompt and thorough deviation investigations to identify appropriate root causes and to implement sustainable corrective action and preventive action (CAPA). With respect to deviations related to (b) (4) drug substance that were due to close in 2022 and in 2023 prior to the initiation of the inspection (up to February 2, 2023), approximately 60% of closed deviations closed late and there are over 80 open deviations that are past due.

   1. Batch disposition of commercial supply drug substance lots is not performed in a timely manner due to open deviations. For example, at the initiation of inspection, non-dispositioned commercial supply lot (b) (4) (filled on 25Aug2022), lot (b) (4) (filled on 10Sept2022), lot (b) (4) (filled on 15Sept2022), lot (b) (4) (filled on 29Sept2022), and lot (b) (4) (filled on 16Dec2022) all have open deviations that are past due.

   2. Several deviations were not created in a timely manner from the date of occurrence. For example, DEV-07184, DEV-09348, DEV-12519, DEV-11932, DEV-10641, DEV-06466, DEV-04038, and DEV-04533 were created after significant time had elapsed from the date of occurrence. As noted in Observation 4.I., significant delays were also observed from the date of detection to the date of deviation creation.

   3. The following routine environmental monitoring trend investigations are still pending at the initiation of inspection: DEV-03431 (created on 07Mar2021); DEV-05228 (created on

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
		Zhong Li, Ph.D., SPQA Charles Yuan-Chia Kuo, Ph.D., Staff Fellow Brian Janelsins, Ph.D., Lead Microbiologist Teegan Dellibovi-Ragheb Ph.D., Interdisciplinary Scientist Michael Araneta, MPH, Supervisory Consumer Safety Officer Andrew "Drew" Haack, Ph.D., Consumer Safety Officer	02/10/2023

25Jun2021); DEV-05835 (created on 12Aug2021); DEV-05855 (created on 16Aug2021); DEV-10004 (created on 01May2022); DEV-11361 (created on 27Jul2022); DEV-11710 (created on 20Aug2022); and DEV-12499 (created on 08Oct2022).

4. The following process specific monitoring excursions are still under investigation at the initiation of inspection:

   a. DEV-11939 was created on 03Sep2022 for viable air excursion in Room (b) (4)
   b. DEV-13177 was created on 27Nov2022 for viable air excursion in Room (b) (4)
   c. DEV-13220 was created on 29Nov2022 for personnel monitoring in (b) (4) Fill Room (b) (4)

5. The following deviation investigations related to process equipment leaks are still pending at the initiation of inspection: DEV-13275 (created on 04Dec2022); DEV-13306 (created on 06Dec2022); DEV-13616 (created on 03Jan2023), and DEV-13692 (created on 10Jan2023). DEV-11954 was created on 05Sep2022 and the investigation was closed on 24Jan2023 with no CAPA implemented.

6. The following deviation investigations related to improper documentation are still pending at the initiation of inspection: DEV-05510 (created on 18Jul2021), DEV-09169 (created on 07Mar2022), and DEV-12035 (created on 25Aug2022).

7. DEV-11938 was initiated on 03Sep2022 for a primary operator personnel monitoring excursion. An investigation was not completed until 23Jan2023 with a due date of (b) (4) The post-operation personnel monitoring of the (b) (4) operator who performed (b) (4) and filling resulted in the growth of EM plates which exceeded alert and action limits for multiple sites of the body. The (b) (4) operator also had EM results which exceeded alert limits. No CAPA was implemented to address this excursion at the (b) (4) filling process, a highly critical step which could impact the product quality and contaminate the ISO 5 environment. The investigation was performed four months later on 27Dec2022, which concluded that the plates could be contaminated during the handling or transfer process of plates. The late investigation could raise a potential risk of microbial control in the filling room and related process. The environmental monitoring of filling room and batch results cannot be used to justify not having a CAPA to correct and prevent similar events. In addition, based on the filling process we observed on

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February 6, 2023, the personnel monitoring plates were closed and wrapped with (b) (4) in filling room by microbiologist before transferred to QC lab, thus the contamination risk during transfer is relatively low. The investigation is inadequate.

8. DEV-12128 was initiated on 15Sep2022 for a bioburden excursion result of (b) (4) CFU/10 mL TAMC (alert limit > (b) (4) CFU/10 mL) for (b) (4) An investigation was not completed until 27Jan2023. The investigation conclusion indicated that all other factors from (b) (4) were ruled out except manpower, which implied the potential contamination source from operators or QC associates. However, no CAPA was implemented to address this excursion after investigation, which is inadequate.

9. Several deviations (e.g., DEV-08865, DEV-08893, DEV-08895, DEV-04647, and DEV-06879) involve duplicate or missed testing of QC samples across multiple methods (e.g., protein concentration (b) (4) and pH). Most deviation investigations identified issues with the tracking of the test status of QC samples, which occurs via QC Chemistry Assay logs (non-electronic) and Trello (electronic). However, appropriate CAPAs (e.g., training of analysts, further improving the procedure, etc.) have not been implemented in response to these investigations to ensure that this issue does not persist.

B. Your investigation into an out-of-specification for commercial product failed to extend to all relevant lots. On 22Dec2022, you created investigation DEV-13526 (Out-of-Specification for (b) (4) Drug Product), when your customer informed you that drug product made from AGC drug substance lot (b) (4) was out of specification for pH. In this investigation, you and your customer identified a potential root cause originating from drug product manufacturing at your facility. The deviation investigation attempts to identify affected lots by analytical testing for (b) (4) concentration. This investigation was inadequate in that your testing failed to extend to all distributed lots within expiry to determine the scope of the issue. For example, AGC drug substance lot (b) (4) for product (b) (4) was not tested for (b) (4) concentration.

C. A leak was found on a terminal HEPA filter (ID 165-5) located in Solution Preparation Suite (Room (b) (4) during a routine HEPA certification conducted by a service contractor's technician on 03Aug2022. A small puncture in the filter was identified and patched using (b) (4) sealant. No deviation was initiated to investigate the potential impact of the HEPA failure on the process

solutions prepared in the suite.

D. A "critical" deviation, DEV-00641, was opened on 22Jul2022, for a discrepancy in which the (b) (4) (b) (4) of the (b) (4) (b) (4) used in the DS manufacturing, (b) (4) differed from the nominal (b) (4) Your firm's proposed CAPA for the deviation failed to tighten the acceptance criteria range for the (b) (4) installation test so that a variation in the (b) (4) in the supplied (b) (4) which may have a significant adverse impact to the product, can be detected during the (b) (4) installation.

OBSERVATION 2

Your firm has not established adequate procedural controls to protect the electronic data acquisition and manufacturing control systems used for DS manufacturing in Building (b) (4) at the AGC Biologics Bothell facility.

Specifically,

A. The computerized system used to control and collect process data from a (b) (4) (b) (4) (asset ID (b) (4) 0309) in Building (b) (4) has not been validated to protect original electronic records and relevant meta*data (e.g., a*udit trails). During data review, only final printouts of the test results are reviewed, and they are not verified against the original electronic records.

B. The data acquisition systems (Kaye ValProbe software, version 1.64) installed on the validation laptops # 010129 (Asset ID unknown) and # 010968 (Asset ID ANA0637) have not been validated. The Kaye ValProbe systems are used to collect process data from wireless data loggers for the environment mapping and thermal validation of process equipment. In addition, audit trail review is not performed for the data that are generated by these systems. During data review, only final printouts of the process results are reviewed, and they are not verified against the original electronic records.

C. The computerized system used to control and collect process data from a (b) (4) (b) (4) system (asset ID ANA0613) located in Purification (b) (4) Room (b) (4) of Building (b) (4) has not been validated.

D. Audit trails enabled in the computerized systems (SoloVPE Software, version 3.1.289.0, and Cary WinUV Software Suite, version 5.1.0.1019) used to control and collect in-process (b) (4) (b) (4) testing data from a SoloVPE Spectrophotometer (asset ID ANA0612) in the (b) (4) (b) (4) (Room (b) (4) of Building (b) (4) are not reviewed for each data set during the lot review process. In addition, the date and time settings in the Microsoft Windows operating system are not protected.

E. The computerized system (EndoScan V, version 6.02) used to control and collect endotoxin testing data from a (b) (4) Plate Reader (asset ID ANA0720) in the QC microbiology laboratory has not been fully validated to protect original electronic records and relevant metadata (e.g., audit trail, data backup/transfer and retrieval). Audit trails enabled in the data acquisition system are not reviewed for each data set during the lot review process.

OBSERVATION 3

There is a lack of assurance that your drug substance manufacturing operations in Building (b) (4) at the AGC Biologics Bothell facility are appropriately designed to ensure the prevention of contamination of equipment or product by environmental and processing conditions that would be expected to have an adverse effect on product quality.

Specifically,

A. Your documented risk assessment, SEA-RIA-000091 "SEA Site Adventitious Agent Control Risk Assessment Report" (version 2, effective 02Feb2023), does not provide adequate justification for your current multi-product manufacturing strategy and controls to prevent potential cross-contamination. For example:

1. The risk assessment failed to evaluate potential cross-contamination risks from the unrestricted movement of personnel, equipment, and in-process materials in the clean corridors of Building (b) (4)

2. The risk assessment 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.

3. The risk assessment failed to evaluate the potential cross-contamination risks associated with process solution compounding process, which utilizes a (b) (4) process performed in the Concurrent Manufacturing Suite, Bioreactor Suite (Room (b) (4)

4. The risk assessment failed to evaluate the potential cross-contamination risks associated with the manual cleaning operations that can occur in the Concurrent Manufacturing Suites, Bioreactor Suite (Room (b) (4), and (b) (4) Suite (b) (4) (Room (b) (4)

5. The risk assessment failed to evaluate the potential cross-contamination risks associated with the staging of the dirty parts (including (b) (4) parts) and cleaned parts in the same Room (b) (4) of Building (b) (4)

B. Your SOP and Master Production Record for (b) (4) (SEA-SOP-000160 and SEA-MPR-000260) specify transferring the product storage container with processed (b) (4) intermediate material into (b) (4) suite Room (b) (4) (Step (b) (4) in the SOP, Step (b) (4) in the MPR) prior to completing the (b) (4) for (b) (4) integrity (Step (b) (4) in the SOP, Step (b) (4) in the MPR). This procedure creates potential risk for maintaining (b) (4) (b) (4) Furthermore, during the (b) (4) unit operation for two batches of (b) (4) drug substance (batches (b) (4) the (b) (4) failed or gave abnormal results during the (b) (4) (DEV-11982 and DEV-01928). According to the executed batch records for (b) (4) the material was moved from Room (b) (4) to Room (b) (4) on 6Sept2022, then was transferred back to Room (b) (4) on 8Sept2022 for reprocessing of the (b) (4) unit operation. Therefore, product which had not demonstrated sufficient assurance of (b) (4) clearance was held in a (b) (4) suite for a period of two days.

C. There is a lack of assurance that your cleaning and sanitization/sterilization procedures for product-contact process equipment in your Building (b) (4) DS manufacturing facility are effective in preventing cross-contamination and microbial contamination. Specifically,

1. Your determination of the product residue limit, Maximum Allowable Carry Over (MACO), is not 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.

2. You have not validated the (b) (4) dirty hold time (DHT) for process equipment and parts, which is specified in SEA-SOP-000108 "General Equipment Cleaning Procedures" (version 25, effective 25Jun2021).

3. You have not validated the (b) (4) sterile hold time (SHT) for the (b) (4) Fill Tubing Assembly, (b) (4) and (b) (4) pH Probe Assemblies, as specified in SEA-SOP-000112 "Operation of the (b) (4) in Manufacturing" (version 14, effective 02Nov2022).

4. Your TOC swabbing recovery studies, SEA-VSR-000135 (version 1, effective 11Oct2017) and SEA-VSR-00071 (version 1, effective 20Jun2019), failed to access all representative product contact surfaces. For example, gaskets (b) (4) were excluded from the studies.

5. Your manual cleaning procedure described in SEA-SOP-000108 (refer to Section 11.7) does not specify the (b) (4) rinse (b) (4) rinse) volume that is required for the cleaning verification.

D. Your firm lacks an established cleaning and sanitization program to prevent the introduction of microbial contamination into controlled manufacturing environments in your Building (b) (4) DS manufacturing facility. Specifically,

1. Your firm's disinfectant efficacy study (DES), SEA-QR-000255 (version 2, effective 12Jul2022) 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 facility. For example, materials used for (b) (4) (b) (4) walls, window glass, (b) (4) floor mat, and chairs were not included in the study. In addition, the DES has not established the disinfectant expiration limits.

2. Your cleaning and sanitization procedure for the classified DS manufacturing areas in the facility, SEA-SOP-000087 (version 46, effective 18Oct2022) and SEA-SOP-000154 "Building (b) (4) Personnel and Material Flow" (version 31, effective 10Oct2022), do not require documentation and verification that the treated surfaces are wetted and remain wetted for the contact time(s) validated in the DES.

E. There is a lack of adequate justification for the environmental monitoring (EM) locations specified in SEA-SOP-000098 "Routine Environmental Monitoring Program for Manufacturing Facility" (version 33, effective 30Aug2022). For example,

- A total of (b) (4) surface sampling locations is selected for Solution Prep Suite (Room (b) (4) and,
- A total of (b) (4) surface sampling locations is selected for Bioreactor Suite (Room (b) (4)

Only (b) (4) sample locations are selected for the above process suites. According to your firm's risk assessment, SEA-RIA-000092 "Building (b) (4) Environmental Monitoring Program Risk Assessment Summary Report" (version 2, effective 22Aug2022), Risk Mitigation Recommendations for Surface Sample Locations include to develop EM sample location maps for SEA-SOP-000098 that include the locations of (b) (4) (b) (4)

F. The trap placement identified in your pest control procedure, specifically traps mapped in building (b) (4) is not current. You perform a (b) (4) trending for pest sightings in these traps that are in placed in your GMP area.

G. Your procedure does not require personnel monitoring by the operator performing cell (b) (4) steps. On 3Feb2023, we (AKH, MA, ZL, CK, TDR, and BJ) observed operator (b) (6) performing cell (b) (4) of product (b) (4) of lot (b) (4) During this cell (b) (4) step, I observed that he did not touch his fingers to the plate media. Your procedure, SEA-SOP-000143 "Process Specific Environmental Monitoring Program" (version 32, effective 19Aug2021), does not require that operators perform personnel monitoring during cell (b) (4)

OBSERVATION 4

Standard Operating procedures or work instructions are not followed or are inadequate.

Specifically,

A. Your endotoxin procedure, SEA-ANM-000013 v32, "Endotoxin Determination Using the LAL Kinetic Chromogenic Method", did not state the sample storage hold time of endotoxin, which is

inadequate. According to your normal practice, the primary samples are allowed to be stored at 2-8°C for (b) (4) before being tested, and that is based on the sample storage condition memo, SEA-RCD-007685, 12Aug2022. However, the memo only referred to scientific publications with study conditions using a storage temperature of (b) (4) °C, however no enough data have been shown using the same temperature and duration as stated above. In addition, the endotoxin may have adsorbed to the container surface over a period of time. The justification for long-term storage of endotoxin samples at 2-8°C is insufficient.

B. On February 6, 2023, we (ZL, CK, TDR and BJ) observed the demonstration of (b) (4) drug substance (b) (4) simulation) bulk filling process in Rm (b) (4) at the ISO5 Laminar Air Flow Workstation (LAFW). During the filling process, the (b) (4) operator was observed to adjust the (b) (4) (b) (4) on top of the (b) (4) with her gloved right hand holding an (b) (4) wipe. According to the procedure of aseptic practice, SEA-SOP-000375 "Cleanroom Behavior & Aseptic Practices" (version 8), "moving hands, gowns, sleeves, or any other components over open product are prohibited". The (b) (4) operator failed to follow SOP during the drug substance bulk fill unit operation.

C. On February 6, 2023, we (ZL, CK, TDR and BJ) observed the post-use environmental monitoring process after the completion of drug substance bulk filling operation in Room (b) (4) During the personnel hand sampling (finger dab), the (b) (4) operators failed to follow the procedure, SEA-SOP-000346 version 18, "Environmental Surface Monitoring", to roll their fingers with sufficient contact time on the sampling plates. In addition, during the surface monitoring of (b) (4) with contact plates, the (b) (4) operator was observed to open the lid of contact plate with her gloved right hand holding an (b) (4) wipe, and the process is not documented in the SOP.

D. On February 3, 2023, in the QC microbiology laboratory (Room (b) (4) we (ZL and CK) observed a QC analyst performing Colony Counting of environmental monitoring (EM) plates with no contemporaneous verification. We were informed that the contemporaneous verification check of the bioburden test is not necessary. It was determined to be low risk after post-mitigation based on the risk assessment report SEA-RIA-000117, "Microbial Colony Counting Contemporaneous Verification Risk Assessment" (version 1). However, the assessment underestimated the risk after post-mitigation and did not consider the criticality of direct product impact processes (IPC, release, PSM). A second analyst verification of the critical manufacturing steps for EM and bioburden plate

reading should be implemented from a microbial control perspective to detect any microbial contamination of (b) (4)

E. SEA-SOP-000281 (Stability Study Initiation, Execution, and Termination) and stability protocol SPN-1342-02 are not being followed. The SOP requires that stability testing must be initiated within the test window indicated on the Stability Data Summary Sheet (Section 9.2.4.1), and in the event that testing must be performed outside the test window, the firm must confirm with the client that samples can be returned to the long-term storage condition until testing is able to be performed (Section 9.2.4.1.1). However, stability testing of lot (b) (4) (protocol SPN-1342-02) at the initial test time-point (0 months) for SE-UPLC analysis was performed (October 13, 2021) outside the test window (b) (4) by a significant number of days, and sample was (b) (4) before testing, which is not the long-term storage condition (2-8°C) of (b) (4) drug substance. Furthermore, SE-UPLC testing at 3 months occurred on February 14, 2022, which is (b) (4) outside the test window (b) (4) (b) (4) testing at 3 months occurred on November 16, 2021, which is (b) (4) outside the test window, (b) (4) testing at 3 months occurred on October 04, 2021, which is (b) (4) outside the test window, and (b) (4) (b) (4) testing at 3 months occurred on October 04, 2021, which is (b) (4) outside the test window. SE-UPLC testing at 6 months occurred on January 3, 2022, which is (b) (4) outside the test window (b) (4) , and (b) (4) testing at 6 months occurred on February 11, 2022, which is (b) (4) outside the test window. Furthermore, SE-UPLC (b) (4) (b) (4) testing at 12 months occurred on June 29, 2022, which is (b) (4) (b) (4) outside the test window (b) (4)

G. SEA-SOP-000540 (Reprocessing of Active Pharmaceutical Ingredients and Intermediates) is inadequate. This SOP states that APIs and intermediates that do not meet their established specifications may be reprocessed using a procedure that has been demonstrated or judged to be effective in producing materials that meet the established specifications (Section 1). Decisions on reprocessing are based on whether material would be acceptable as is (Section 6.2) and whether reprocessing is technically feasible (Section 6.3). This procedure doesn't clearly describe the scenarios that would lead to reprocessing and the scenarios that would not lead to reprocessing. Section 6.1 of the SOP describes that if an API or intermediate fails to meet established quality attributes or is found to be unsuitable due to other factors (e.g., a newly defined test is failed, a

contamination is observed that may not be apparent through normal testing, or testing produces unacceptable results in a downstream process or product), an investigation is initiated and reprocessing is considered. There is concern that reprocessing according to this SOP may occur due to contamination events. The reprocessing protocol should explicitly state that reprocessing is not allowed in the event that contamination is detected or due to other product quality issues.

H. SEA-SOP-000071 (b) (4) Fill) and SEA-MPR-000262 (b) (4) – Bulk (b) (4) and Filing) are inadequate. There are insufficient instructions to document the time (b) (4) intermediate material is kept at ambient conditions in the suite prior to (b) (4) and fill, and the procedures in place do not ensure that the (b) (4) and filled drug substance is moved to final storage at 2-8°C in a timely manner. Therefore, there are inadequate procedures and instructions to ensure (b) (4) is not exposed to ambient conditions in an uncontrolled and unacceptable manner.

I. GLB-SOP-000027 (Global Event and Deviation Management) is not being followed. Section 8.3.1 of the SOP states that the event/deviation record must be initiated within (b) (4) from the date of detection. However, DEV-01872, DEV-04533, DEV-06466, DEV-09348, DEV-08895, DEV-04647, and DEV-05924 were initiated beyond (b) (4) (e.g., DEV-04533 was created 80 days beyond the requirement).

J. SEA-CON-000011 (b) (4) Quality Agreement) is not being followed. Section 15.4 states that "AGC shall target batch disposition (b) (4) after the day of final bulk fill date." However, (b) (4) commercial supply lot (b) (4) was filled on June 01, 2022 and missed the target disposition date of 8/3/2022 by ~(b) (4) and other (b) (4) commercial supply lots that have not been dispositioned (lot (b) (4) lot (b) (4) lot (b) (4) and lot (b) (4) are significantly past their respective (b) (4) target date for batch disposition (up to (b) (4) past target).

K. Your procedure for monitoring line pressure of process (b) (4) is inadequate in that it does not specify actions if the (b) (4) ine pressure exceeds your specification. For example, on 1/30/2023 and 2/1/2023, the line pressure of (b) (4) was recorded to be (b) (4) psi, respectively, with a specification of (b) (4) psi ± (b) (4) psi. Your procedure, SEA-SOP-000380, "Use and Maintenance of (b) (4) (b) (4) Systems for Manufacturing" (version 16, 02Sep2021), does not indicate what corrective action is required if the pressure exceeds your specification.

L. According to the procedure of operating water baths, SEA-SOP-000511 version 6, "Operation of Water Baths in Manufacturing", the cleaning procedure is to wipe out residual water from (b) (4) (b) (4) with another wiping after (b) (4) wipes or (b) (4) are applied. In order to prevent microbial ingress in water baths, a sanitization procedure should be included in the cleaning procedure for decontamination. A documented worklog should also be enforced.

M. SEA-ANM-000140 (b) (4) – Size Exclusion by UPLC) and SEA-ANM-000210 (b) (4) – Analysis by (b) (4) are inadequate. These written procedures include instructions for performing peak integration via (b) (4) and SE-UPLC analyses of (b) (4) drug substance and drug product samples. Certain areas on the (b) (4) and chromatogram (SE-UPLC) are excluded from peak integration without adequate justification. This increases the risk of not reporting product-related variants, which may have an impact on potency. Furthermore, the peak integration scheme used for (b) (4) analysis is subject to variability and may not be consistently applied between sequence runs and across analysts.

N. On February 3, 2023, after cell inoculation demonstration of (b) (4) we (ZL, CK, TDR, and BJ) walked through the (b) (4) and a couple pools of liquid were observed on the floor at the center of (b) (4) room (Room (b) (4) close to the floor drain.

OBSERVATION 5

Your firm's quality unit's oversight of your GMP manufacturing operations is inadequate.

Specifically,

A. Your firm lacks security control to prevent the access of GMP utility and equipment by the unauthorized persons outside your facility. For example, the outdoor storage area of (b) (4) and (b) (4) tanks are not protected, rendering the process (b) (4) control panels susceptible to manipulation by unauthorized personnel.

B. The facility cleanliness and maintenance are inadequate for GMP grade manufacturing. Specifically,

1. According to facility cleaning procedure, SEA-SOP-000087 version 46, "Facility Cleaning & Sanitization", the facility cleaning is scheduled routinely from (b) (4) for various sections of cGMP areas. The performance of facility cleaning in your firm is inadequate. For

example, the (b) (4) stuck with dust was observed throughout the Clean Corridor (ISO 8).

2. On February 6, 2023, we (ZL and CK) observed tape covered on mesh covers of multiple HEPA filters due to the missing bolts throughout the Clean Corridor and manufacturing suite.
3. On February 2, 2023, during the general walk through, multiple leaks underneath the (b) (4) tank and pump were observed including an oil leak from CCA filter in the Clean Utilities room (Room (b) (4)
4. On February 2, 2023, a chemical corrosion stain was observed around the top cover of the (b) (4) tank for Line (b) (4) (Room (b) (4) and a rusty spot was observed around the pipe cover of the (b) (4) generator in the same room.
5. On February 10, 2023, during the general walk through in Building (b) (4) we (ZL and CK) observed a white substance spilled on the floor inside (b) (4) room, (Room (b) (4)

C. Your quality unit does not fully exercise its responsibilities regarding the critical service contractor qualification. Specifically, your quality unit has not conducted any on-site audit of (b) (4) (b) (4) who is responsible for HEPA certification in your Building (b) (4) drug substance manufacturing facilities.

D. Your firm lacks timely quality review of batch records. For example, it took up to (b) (4) from QA receipt to final sign-off of the MBR for commercial supply lot (b) (4) (manufactured 15Sept2022). Similar trends were observed during review of the MBR for lot (b) (4) (manufactured 1Jun2022). The process of QA batch record review is not clearly described in SEA-SOP-000130 (Master Production Record and Laboratory Record Review). Delays is QA review and sign-off of batch records were routinely observed beyond the (b) (4) target date for batch disposition. In addition, delays in QA review of batch records show inadequate quality oversight that can prevent appropriate actions from taking place to address issues during manufacturing operations. As an example, DEV-6918 (Exceeded mixing time (b) (4) MBR-3064 step (b) (4) (b) (4) was initiated after MBR review by QA. Because review and approval of the MBR by QA took place 4 months after date of occurrence, no immediate action was taken in response to this issue.

E. DEV-14022 (b) (4) Lot (b) (4) SEA-MPR-000262, Product labels printed with incorrect lot number) was initiated after FDA investigators toured the Building (b) (4) room and, upon review of

the (b) (4) drug substance lots located in a locked cage in the quarantine area of 2-8°C storage, noted that there was a discrepancy between the product label and the status tag (toe tag). The product label indicated lot (b) (4) and the status tag indicated lot (b) (4) both initialed and dated 1Feb2023. For such a critical deviation to occur, quality oversight failed at multiple steps in the processes defined by SEA-SOP-000105 (Assigning Lot Numbers and Issuing Manufacturing Batch Records), SEA-SOP-000071 (b) (4) Fill), SEA-SOP-000248 (Line Clearance) and SEA-SOP-000437 (Materials Control Procedure – Intermediates and API), all of which includes steps for verification of product labels. In addition, the discrepancy was not identified during either batch record verification or out-of-plant manufacturing review of MBR-3069 (b) (4) Deviation report DEV-14022 states that there have been other instances of incorrectly issued labels in the last 12 months. For example, DEV-10499 (b) (4) lot# (b) (4) SEA-MPR-000629, solution (b) (4) lot number in record and on labels not matching) and DEV-10839 (Incorrect printed lot number on (b) (4) (b) (4) sample labels).

F. The (b) (4) manufacturing process and controls as described in the (b) (4) application are not being followed. Change control CR-06479 was implemented to support the introduction of reprocessing at the (b) (4) unit operation, and change control CR-05482 was implemented to support a (b) (4) cycle of (b) (4) and (b) (4) (b) (4) purification unit operations) for commercial supply lot (b) (4) Furthermore, a new primary reference standard was implemented to the (b) (4) process and control strategy during the (b) (4) review period; this primary reference standard is intended to test commercial supply lot (b) (4) (b) (4) (released by firm, but not by client) on stability and test other commercial supply lots at release and on stability (not yet released by firm and client). These changes are not part of the process and controls described in the (b) (4) application, and (b) (4) (b) (4) there are no written procedures in the change control reports or quality agreement or other provided documents that specifically state that these impacted lots cannot be released to the US market (b) (4)

G. Final product dispositions have been on hold due to pending investigations that were detected in 2021 and 2022. These deviations have not been closed nor have been completed.

H. Your quality control unit failed to open a complaint and perform a risk assessment when notified by your customer of quality concern for product released by your firm. On 22Dec2022, your customer

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Division of Biotechnology Manufacturing; WO 51 / Room 2269 10903 New Hampshire Avenue Silver Spring, MD 20993 E-mail: OPMABLAInspection483Responses@fda.hhs.gov	02/02/2023-02/10/2023
	FEI NUMBER 3000209996

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Mr. Kevin Ingham, Site Head & General Manager	
FIRM NAME AGC Biologics Inc.	STREET ADDRESS 21511 23rd Dr SE
CITY, STATE, ZIP CODE, COUNTRY Bothell, WA 98021	TYPE ESTABLISHMENT INSPECTED Drug Substance Manufacturer

notified you that drug product manufactured at your facility, AGC lot (b) (4) for product (b) (4) was found to be out of specification for pH and identified that the root cause may be due to residual (b) (4) carryover in bulk drug substance. While a deviation investigation was opened, no complaint or associated risk assessment, as detailed in SEA-SOP-000351 "Contract Manufacturing Client Product Complaints and Recalls" was performed.

I. Your quality control unit has not ensured that all equipment used in drug substance testing has been qualified and is adequate for its intended use. On 3Feb2023, we (AKH, ZL and CK) observed microbial testing of (b) (4) in laminar flow hood, BSC0324. This equipment had not undergone qualification to demonstrate that it suitable for its intended use.

10FEB2023

	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
SEE REVERSE OF THIS PAGE	ZL CK AKH TDR AG P	Zhong Li, Ph.D., SPQA Charles Yuan-Chia Kuo, Ph.D., Staff Fellow Brian Janelsins, Ph.D., Lead Microbiologist Teegan Dellibovi-Ragheb Ph.D., Interdisciplinary Scientist Michael Araneta, MPH, Supervisory Consumer Safety Officer Andrew "Drew" Haack, Ph.D., Consumer Safety Officer	02/10/2023