DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Office of Biological Products Operations/Office of Regulatory Affairs U.S. Food and Drug Administration 12420 Parklawn Drive, ELEM-2142, Rockville, MD 20857 Tel: 301-796-2720 Email: orabioinspectionalcorrespondence@fda.hhs.gov Industry Information: www.fda.gov/oc/industry	April 3, 2018 to April 12, 2018
	FEI NUMBER 1000525461

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Adam S. Grossman, President and CEO

FIRM NAME	STREET ADDRESS
ADMA Biologics Inc.	5800 Park of Commerce Blvd. NW
CITY, STATE AND ZIP CODE Boca Raton, FL 33487	TYPE OF ESTABLISHMENT INSPECTED Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1

Failure to prevent unauthorized access of changes to data and to provide adequate controls to prevent omissions of data.

Controls for electronic data acquisition systems have not been established:

A. The (b) (4) System used for (b) (4) and the (b) (4) used for (b) (4) determination lack username/passwords and audit trails.

B. The (b) (4) Analyzer used for determination of (b) (4) and the (b) (4) System used for (b) (4) (b) (4) determination have a "delete" results functionality available to the analyst.

C. The (b) (4) used for identity testing of raw materials does not capture creation or deletion of data files in an audit trail. The software permits an analyst to generate and view an (b) (4). If the analyst does not manually save the file, it is deleted.

D. Data can be deleted from the hard drive of computers associated with analytical equipment, for example, the (b) (4). Additionally, there are no procedures for electronic data back-up and back-up of the data had not been performed.

E. (b) (4) workbooks F-SAF-3049-a and F-SAF-3049-c used for determination of accuracy, linearity, and calibration curves are not protected from alteration.

F. Procedures that describe how to perform review of audit trails have not been established.

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	Justin A Boyd Michelle L. Forster	Michele L. Forster, PhD, Investigator Justin A. Boyd, Investigator	04/12/2018

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G. Personnel granted administrator rights in the (b) (4) (b) (4) software and (b) (4) software are the same personnel responsible for reviewing and approving data generated by the software.

H. There is no periodic review of assigned user roles and permissions in (b) (4) to assure only appropriately authorized individuals can enter data and make modifications.

OBSERVATION 2

Issuance and use of documents is not controlled.

Controls have not been established to ensure submitted paper documents are original. Personnel responsible for recording GMP data can print GMP records used to record raw data from the Master Control document system or the (b) (4) system. The number of documents printed is not tracked, allowing personnel to reprint forms without oversight. Personnel were observed to print more documents than needed and discard extras.

A. On April 3, 2018 discarded GMP documents were observed in shred bins.

i. Examples of documents that had data recorded, discarded, and re-written include:

a. F-QA2225-a, Quality Assurance Raw Material Checklist for (b) (4) (b) (4) inspection lot (b) (4)
b. F-QC2256-a, QC Product Labels Reconciliation Form for (b) (4), lot (b) (4)
c. Form F-QC2161-a, (b) (4) Assay Reporting Sheet, was used to record sample information for (b) (4) study (b) (4) for Bivigam drug substance that was later recorded in a table in Notebook No. (b) (4)

ii. Examples from the shred bins of blank GMP documents that were printed, not used, and discarded include:

a. F-SAF3058-a, ADMA Biologics Interim Control Plan for Quality Control Laboratories Review of QC Laboratory Audit Trail
b. F-QC3126-f, Qualification Exam for (b) (4)
c. F-QC3242-a, Data Sheet for Determination of (b) (4) in IGIV Products by a (b) (4) Method

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Using (b) (4) Kit
d. F-QC3174, b and c, maintenance forms for the (b) (4) (b) (4)

B. On April 5, 2018, uncontrolled instructions for completing (b) (4) workbooks used to perform calculations during method validation and reference standard qualification studies (Forms F-SAF3049-a through f) that were not reviewed and approved by the Quality Unit were found on a shared network. Furthermore, a printed copy of F-SAF-3049-b containing instructions for completion of the validation precision workbook was observed posted on the wall at a workstation in the laboratory office area.

OBSERVATION 3

Discrepancies were not thoroughly investigated.

A. (b) (4) lot (b) (4), was tested for (b) (4) by (b) (4) on September 5, 2017. Review of the audit trails showed the analyst started the analysis on instrument on (b) (4). The analysis was performed twice. Undesirable results were obtained due to an apparent equipment problem. The analyst switched the analysis to instrument (b) (4) and performed the analysis a third time. Only the third analysis was reported in the data packet. The analyst retroactively changed the name of the first (b) (4) sample sets from (b) (4) the official name for the sequence required by procedure, to "test."

Deviation DEV17529 was opened on October 16, 2017 for separate data integrity issues that included not reporting all analyses associated with the same analyst. The investigation reported a retrospective review of the work this analyst had performed was completed to detect any similar instances. This review specifically included testing of lot (b) (4) However, the investigation did not detect the modifications and failure to report all data.

B. An investigation has not been opened to address recurring invalid assays generated using procedure SOP QC3014 "(b) (4)." During 2017, there were seven invalid assay reports generated when the (b) (4) of the (b) (4)(b) (4) did not meet acceptance criteria. Each report identifies the likely root cause as isolated instrument (b) (4) variation. Results from individual samples are invalidated and retested, while other samples tested as part of the (b) (4) and subject to the same possible

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instrument variations are accepted. Additionally, instruments errors resulting in invalidation of partial data sets do not require invalid assay reports and are not trended to evaluate the performance of the equipment.

C. An investigation has not been opened to address recurring invalid assays generated using procedure QC 2100 "(b) (4) ." No less than eight invalid assay reports were generated for failure to meet the assay (b) (4) criteria for sample (b) (4) between September 28, 2016 and September 22, 2017 during in process testing of Bivigam for (b) (4)

D. Out-of-specification (OOS) (b) (4) results obtained on October 10, 2016 for Bivigam in process samples (batch (b) (4)) were invalidated during laboratory investigations documented in OOS 16054 and 16055 due to malfunction of the (b) (4) (b) (4) System. The test performed on October 10, 2016, which included in process testing of Bivigam lot (b) (4) , after the last passing instrument calibration was not invalidated and repeated.

E. Investigations into environmental deviations do not always include justified conclusions. Environmental Deviation Report (EDR) #17001 was opened when six WFI samples exceeded action levels for total microbial counts for samples collected February 7, 2017. The investigation identified the probable root cause as contaminated hoses and/or other equipment without thoroughly describing the rationale to support this root cause.

OBSERVATION 4

Responsibilities of the quality unit are not in writing.

Written procedures for evaluation and reporting of adverse events have not been established by your firm. Per the client specified guidelines signed December 20, 2017, your contractor is responsible for receipt, handling, initial evaluation, and reporting of adverse events; your firm is responsible for the final review and approval of individual case safety reports, periodic reports, and trending reports.

OBSERVATION 5

Studies have not demonstrated equipment does not alter the quality of drug substances.

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Extractable and leachable data has not been collected for contact surfaces in the manufacturing processes of Bivigam drug substance, Nabi-HB drug substance, and (b) (4) product. For example, surfaces for which there is no extractable or leachable data include, but are not limited to, (b) (4)(b) (4) used during (b) (4) (b) (4) (b) (4) used during (b) (4) (b) (4) or (b) (4) tubing used during (b) (4)

This is a repeat observation from the March 2016 FDA 483.

OBSERVATION 6

Scientifically sound test procedures have not been established and followed.

A. The (b) (4) reference standard used for determination of (b) (4) during in process, release, and stability testing of Nabi-HB performed per SOP QC2100 was qualified using the same method (SOP QC3182) that was found to be inadequate in Observation 8 on the March 2016 FDA 483. For example, the reference standard used for testing of Nabi-HB filled, unlabeled vial lot 170125 (released as packaged vial lot 170124 on February 2, 2018) was qualified using SOP QC3182.

B. System suitability criteria for the (b) (4) system have not been established for method QC3207 "(b) (4)."

C. (b) (4) of (b) (4) is permitted. Procedures describing when (b) (4) can be performed and how to do (b) (4) have not been established.

D. The microbiology laboratory lacks data to support the minimum time (b) (4)) and incubation conditions of (b) (4)°C for recovery of yeast and mold organisms during routine environmental monitoring.

E. Damage to (b) (4) and air bubbles between the (b) (4) and the (b) (4) were observed for 5 of (b) (4) WFI samples read on April 9, 2018.

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F. Qualification of (b) (4) workbooks F-SAF-3049a through f used to perform calculations during method validation and reference standard qualification is inadequate as follows:

i. The mathematical equations (i.e., calculations) used to develop the (b) (4) formulas were not documented, reviewed, or approved.
ii. The outputs of the (b) (4) formulas have not been checked for accuracy against user-specified calculations.

OBSERVATION 7

Procedures for monitoring and maintenance of facilities and equipment are not adequately followed or established.

A. Procedure FAC3085 "Recovery from Power Disruption," approved April 21, 2016 and generated in response to the March 2016 FDA 483, has not been followed:

i. Trending is required to be performed and reviewed (b) (4) . Trending reports for (b) (4) (b) (4) were still in a draft status on April 10, 2018.

ii. The procedure requires form F-FAC3085-a to be filled out by the utilities department any time there is a power disruption. On October 29, 2017, there were three power disruptions, but no form F-FAC3085-a was generated.

iii. No form has been implemented to assess the impact of power disruptions on the laboratory in building (b) (4) On July 12, 2017, a power disruption causing shutdowns of building (b) (4) systems occurred. No assessment of the impact to laboratory systems was made.

iv. Following a power disruption on April 7, 2017, no form F-FAC3085-b was initiated to assess the impact of the failure of the power to (b) (4) and the impact on any activities in buildings (b) (4) .

B. SOP FAC2035, "Operation of the (b) (4))" used for handling of alarms monitored by the (b) (4) is inadequate or not followed in that:

i. The following critical alarms occurred and were not further investigated:

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a. Numerous alarms beginning on or before April 5, 2018 associated with pressure differential transmitter (b) (4) , which measures pressure differentials in the (b) (4) area
b. Numerous alarms beginning on or before October 2, 2017 associated with temperature sensor (b) (4) which measures the temperature in the cleaning area used for (b) (4)

ii. The procedure indicates that facilities management is responsible for ensuring that all alarm acknowledgements for critical alarms are performed and documented in the system and on a work order. There is no process in place to provide this assurance.

iii. The procedure is unclear regarding steps to take following alert and alarm excursions. For example, on April 12, 2018, facilities personnel indicated that only critical alarms that are "persistent" are investigated; however, criteria for "persistent" have not been defined.

iv. There is no trending of critical alarms to evaluate whether additional actions are needed.

v. There is no requirement to explain the reason for acknowledging alarms.

C. There is no requirement to evaluate corrective work orders for the need for a deviation investigation to determine potential impact.

OBSERVATION 8

Procedures describing sanitizers and sanitizing schedules have not been shown to be effective.

A. The '(b) (4) Manufacturing Areas Environmental Monitoring Data Annual Trending Report 2017" identified Bacillus species, spore forming organisms, as the most common isolates from the manufacturing environment. The schedule for routine sanitization does not include periodic use of a sanitizer shown to be effective against spore forming organisms.

B. Study FR-2009-10 "Testing Disinfectant Agents for Antimicrobial Action on Hard Surface" did not

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demonstrate effectiveness of the sanitizer composition and concentration required in procedures for cleaning and sanitizing the production environment.

C (b) (4) of the manufacturing environment with (b) (4) is performed after shutdown activities. The effectiveness of the (b) (4) process has not been validated.

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