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 60 Eighth Street, Atlanta, Georgia 30309 404 - 253 - 1169 Industry Information: www.fda.gov/oc/industry	28 APR - 06 MAY 2022
	FEI NUMBER 1050373

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Douglas B. Burns, Ph.D., President

FIRM NAME	STREET ADDRESS
Grifols Therapeutics LLC	8368 U.S. 70 Business Hwy West
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Clayton, North Carolina 27520	Biologic Drug 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

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

A. The media fill batch production record does not document receipt (b) (4), and reconciliation of the "Integrity Rejects" vials with the total number of vials filled. DOC#:CS-000-AR-082 Media Fill Requirement for Aseptic Filling effective 03 January-2022 details your firm's procedure for media fill vials accountability and handling. Your procedure identifies that media fill vials with "integrity defects" must be segregated as "Integrity Rejects" and (b) (4) for NLT (b) (4). Your firm's batch production records categorize the "Integrity Rejects" as over seal vials, out of tolerance vials, excessive foam vials, calibration vials, (b) (4) reject vials, and out of tolerance vials. For example:

i. Media Fill Batch # (b) (4) date filled 04/14/2021 documents the total integrity rejects as 26 vials and the total vials filled as (b) (4). After (b) (4) media filled vials reconciliation total was (b) (4) There is no documentation that the 26 integrity reject vials were (b) (4).

ii. Media Fill Batch # (b) (4) date filled 11/10/2021 documents the total integrity rejects as 9 vials and the total filled (b) (4). After (b) (4) the media filled vials reconciliation total was (b) (4). There is no documented evidence that the 9 vials were (b) (4).

B. Your firm's Quality Unit does not perform a periodic review of all intrusions in the filling line to determine if the intrusion is repeated and if that intrusion should be incorporated into an aseptic process simulation (media fill). Operational and Mechanical Intrusions that occurred during filling of the sterile drug products Alpha 1 MP, batch # B3CBF00143, and Albumin, batch # K08G012753, were documented in the batch records. However, there is no

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Laurel A. Beer Susan Jackson	Gene Arcy, CSO Susan Jackson, CSO Laurel Beer, CSO	05/06/2022

process whereby the Quality Unit performs a periodic evaluation of all intrusions to determine if the activity has significant impact on the manufacturing process.

C. Your Quality Unit failed to initiate a deviation for a discrepancy in the media fill batch record (b) (4) a media fill that was used to requalify the aseptic process on Line (b) (4) where US marketed products, including Albumin, are filled. The times documented in the batch record for when the operator performed the intrusion "fill line adjustment", when the operator exited the filling room, and when the operator's personnel monitoring sample was taken, do not align with contemporaneous documentation. Specifically, the operator's documented exit time indicates the operator was already out of the Line (b) (4) filling room when the personnel monitoring sampling was performed.

OBSERVATION 2

Bioburden monitoring of manufacturing processes leading to the production of pre-sterile bulks are inadequate or inconsistent.

A. Your firm produces clarified bulk material (b) (4)) that is shipped to a sister site for formulation and filling in the production of Alphanate. Currently, the derivation of action limits is pending the collection of enough bioburden data. In addition, the SOP, Identification of Incoming Microbial Cultures, CS-000-BB-153, requires the speciation of ALL bioburden samples. However, (b) (4) samples collected from different process steps were not speciated. Per your firm's director of quality control, this was not done because bioburden values (CFU/mL) did not exceed the temporary action levels that were established, even though all samples were to be speciated regardless of action level.

B. Your firm's bioburden monitoring of processes leading to the production of pre-sterile bulks involves the use of, in part, calculated action levels. A bioburden related deviation listing was reviewed, and it was noted that some organisms were not identified to the species level. The SOP, Identification of Incoming Microbial Cultures, CS-000-BB-153, defines speciation to the genus and species ***or*** only to the genus level. Some Deviations were selected for review to verify your firm's approach to speciation & its use in investigations.

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 60 Eighth Street, Atlanta, Georgia 30309 404 - 253 - 1169 Industry Information: www.fda.gov/oc/industry	28 APR - 06 MAY 2022
	FEI NUMBER 1050373

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

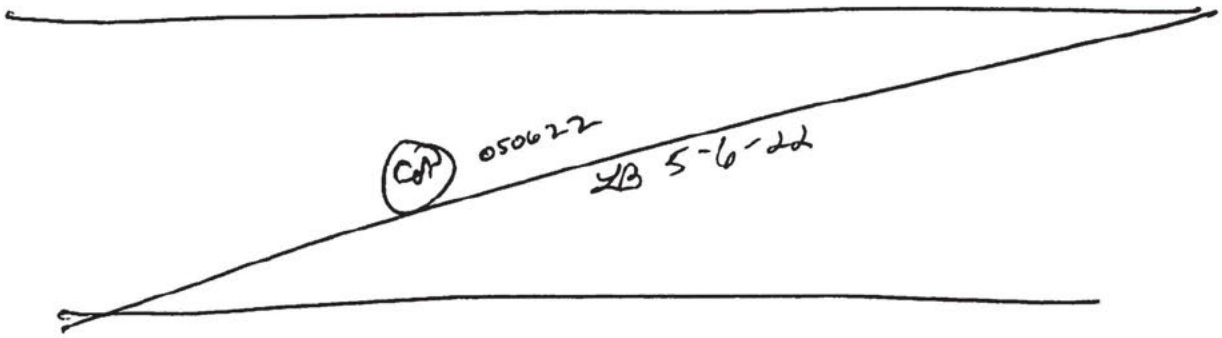
TO: Douglas B. Burns, Ph.D., President

FIRM NAME	STREET ADDRESS
Grifols Therapeutics LLC	8368 U.S. 70 Business Hwy West
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Clayton, North Carolina 27520	Biologic Drug Manufacturer

(i) Deviation 300099828 was created for detection of Trichoderma species recovered in a sample taken from (b) (4) (Batch (b) (4)), determined to be 20 CFU/mL. Given that a mold culture was identified, your firm reflexed the speciation to a 3rd party laboratory. Two species of Trichoderma were identified as possibilities (T. citrinoviride & T. reesei) but a definite species was not determined. Your firm did not consider more accurate assays given that, as per your QC sterility & microbiology manager, the method used (b) (4) analysis) has a limitation regarding specificity in the detection of yeast and molds. The investigation only addressed the finding to the genus level and did not address the possible species.

(ii) Deviation 300112264 was created for, in part, the detection of Pseudomonas species recovered in a sample taken from (b) (4) Albumin AFP Non-sterile bulk (Batch (b) (4)), determined to be 17 CFU/mL. The speciation was done in-house, and your firm's method was not able to provide a definite single species, only a grouping of possible species (P. chlororaphis, P. aureofaciens, P. aurantiaca, P. putida-biotype B, & P. vancouverensis). The investigation only addressed the issue to the genus level and did not address the possible species. In addition, more robust testing was not conducted.

(iii) Deviation 300108061 was created for, in part, the detection of Pseudomonas species recovered in a sample taken from (b) (4) Albumin AFP Non-sterile bulk (Batch (b) (4)), determined to be 31 CFU/mL. The speciation was done in-house, and your firm's method was not able to provide a definite single species but did indicate two possible species (P. flourescens-biotype G, and P. Taetroleus). The investigation only addressed the issue to the genus level and did not address the possible species. In addition, more robust testing was not conducted.



SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ulla Lee Susan Jackson Laurel G. Beer	Gene Arcy, CSO Susan Jackson, CSO Laurel Beer, CSO	05/06/2022

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."