DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg71, Rm 5054 Silver Spring, MD 20993-0002 (240)402-9160 orabioinspectionalcorrespondence@fda.hhs.gov	11/9/2023-11/17/2023* FEI NUMBER 3002807257

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Jaume Salles, VP & Site Head	
FIRM NAME Instituto Grifols, S.A.	STREET ADDRESS Pg Levante, Calle De Can Guasch 2
CITY, STATE, ZIP CODE, COUNTRY Parets Del Valles, Barcelona, 08150 Spain	TYPE ESTABLISHMENT INSPECTED Manufacture

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

Procedures describing the handling of written and oral complaints related to drug products are deficiently written or followed.

Specifically, SOP IG_MSP-000532_ING version 20.0 describes the process for receipt, management, and investigation of customer product quality complaints. Your firm's handling of customer product quality complaints investigation is deficient in that it does not require practice of testing retention samples of respective lots for most frequent complaints. Since 2021, your firm has received US customer product quality complaints for Fibrin Sealant [VistaSeal] categorized as biologics thawing issue as follows: 2021, 46 complaints; 2022, 31 complaints; and 2023 (Q3), 14 complaints. For example, review of selected biologics thawing issue complaint investigations 800010433, 800010845, 800010963, 800011603, and 800011859 revealed that none of the complaints investigated were supported by testing the retention samples.

There is no documented evidence that your firm retention samples were tested as part of the complaint investigation for biologics thawing issue.

OBSERVATION 2

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Susan M Jackson, Investigator - Team Biologics Shafiq Ahadi, Investigator - Team Biologics Natalya M Ananyeva, FDA Center Employee Sergey S Akimov, FDA Center Employee X Susan M Jackson Investigator - Team Biologics Signed By: Susan M. Jackson -S Date Signed: 11-17-2023 12:22:00	11/17/2023

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Specifically,

A. Your firm failed to conduct a thorough investigation and expand the investigation to assess the impact on any batch of US marketed Flebogamma drug product tested by method (b) (4) for release. The deviation investigation 300104589 was opened on 17 February 2021 for Flebogamma batch (b) (4) (non US) due to result in (b) (4) (b) (4) was not traceable to the raw data stored in QC laboratory notebook. The QC laboratory uses this same assay for release of US marketed Flebogamma. The original assay was performed on 07 February 2020, however your firm's investigation opened on 17 February 2021 failed to evaluate if there were other results in (b) (4) also not able to be traced to raw data in QC laboratory notebooks.

B. The investigation into the discrepancy of (b) (4) results with raw data in QC laboratory notebook is inadequate in that the investigation states that the present deviation did not affect the quality/safety of the product for Flebogamma batch (b) (4) (non US). Deviation investigation 300104231 failed to be extended into any other batches of Flebogamma, specifically US marketed batches of Flebogamma tested for release during the period in question. On 04 February 2021, deviation investigation 300104231 was opened for incorrect QC test results in (b) (4) for method (b) (4) (b) (4) tested on 28 April 2020. Flebogamma batch (b) (4) 10% batch was tested as a Flebogamma 5% batch. The release test results reported in (b) (4) for Flebogamma drug product batch (b) (4) was reported as (b) (4) (b) (4) due to human error. The assay result was recalculated on 05 May 2020 and documented in the QC laboratory notebook, however the recalculated value (b) (4) was not reported in (b) (4), resulting in a discrepancy with QC laboratory notebook raw data. The (b) (4) result of (b) (4) was used for the batch release and batch certificate of analysis.

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OBSERVATION 3

Deviations from written production and process control procedures are not justified.

Specifically,

Your firm's SOP IG_MSP.000577 Investigation Protocol of Analytical Deviation in the Quality Control Laboratories describes the procedure for investigating any deviation from approved procedure or specification. Analytical deviation investigation record is required, and a predefined testing plan is required to isolate and confirm OOS results. Flebogamma batch (b) (4) was initially tested as QC sample (b) (4) on 31 January 2020 and retested as QC sample (b) (4) on 07 February 2020. There is no documented evidence of a laboratory OOS investigation opened for the initial test result. The initial test result met the Method (b) (4) specification. No predefined test plan was approved for retesting Flebogamma batch (b) (4). There was no justification documented for conducting a retest on Flebogamma batch (b) (4).

Consequently, there is no justification for the average of (b) (4) within specification test values reported in (b) (4) for Flebogamma batch (b) (4), the assay results should be reported as single test value result for the batch.

OBSERVATION 4

Your firm failed to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, purity, and quality that they are purported or represented to possess.

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A. Your firm manufactured and released Fibrin Sealant (Human), 10 ml, batch, no. A04H105631, manufactured date 7/7/2023 for the US market. Your firm uses SOP IG_MSP-001932_ING, Version 8.0, Batch Final Qualification procedure to review and release the finished drug product. Final batch release Form, IG_RSAP_REG_001097_1, Version 6.0 is used to confirm results of the batch in (b) (4), a quality management platform. Batch Final Qualification procedure, SOP IG_MSP-001932_ING, Version 8.0 is inadequate, in that it does not state to document noted deviations found during the review of the final drug product. For example, during the final batch review Form, IG_RSAP_REG_001097_1, Version 6.0, Product Release Specialist must confirm (b) (4) instead of opening a deviation to investigate the discrepancy.

B. Deviation procedure Related to Manufacturing and Control Batch Protocols, SOP IG_MSP-000405_ING, Version 18.0 and the (b) (4) platform used to document deviations are inadequate. Your firm uses (b) (4) for quality notifications, CAPA, Complaints, Quality Management, quality control results and batch release review/status. All deviations are documented in (b) (4). In order to initiate a deviation in (b) (4), the user needs a material or process number, including the batch number to open a deviation. A standalone deviation found during production, and the batch review process cannot be opened without material or process number. Additional requirements such as material or process number to open a deviation limit and or hinders the platform's (b) (4)) ability to open a standalone deviation related to quality issues found outside of the identified manufacturing processes. For example, a deviation found during batch review by the Quality Assurance (QA) cannot be initiated by QA because the material or process number required by (b) (4) to open a deviation is not assigned and identified for batch review process. The firm's deviation procedures, SOP IG_MSP-000405_ING, Version 18.0, and SOP IG_MSP-002019, Version 5.0, Management of Manufacturing and Control

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Batch Notification through the (b) (4), does not identify which material or process number to use to open standalone deviation(s) found outside identified processes.

OBSERVATION 5

The written stability testing program is not followed.

Specifically,

The Protocol # BIG-RD-SOP-000282, titled "Deviations General Procedure for Stability Studies ((b) (4) Barcelona, Scientific Innovation Office)" (Version 2.0, Effective from 6-Oct-2023; Section 7.2.1 Notification) is inadequate because it permits you to not open out of specification (OOS) investigations for reoccurring OOS at different time-points and different batches, if "the notification has been created" for the first OOS result ("i.e analytical incidents under accelerated conditions that have expected results due to previous studies"). Specifically, only one OOS investigation was opened for Fibrin Sealant Batch A04G03174 as Deviation # 300116307 for the 4 ml produced at (b) (4) with OOS result 3.6% for (b) (4)". However, the reoccurring OOS results from the following batches and time-points from the same Stability Study at (b) (4) 0 hours were not investigated.

All results were out of specification limit (b) (4) for "(b) (4)" (document # IG_ESP-00030-ING):

Batch #Time PointResult, %			
A04G031741	(b) (4)		3.4
A04G031741	(b) (4)		3.6
A04G038321	(b) (4)		3.8

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Sergey S Akimov, FDA Center Employee

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A04G038321	(b) (4)		3.4
A04G038321	(b) (4)		3.8

***DATES OF INSPECTION**

11/09/2023(Thu), 11/10/2023(Fri), 11/13/2023(Mon), 11/14/2023(Tue), 11/15/2023(Wed), 11/16/2023(Thu), 11/17/2023(Fri)

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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."