DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Ave, Bldg71-5128 Silver Spring, MD 20993-0002 240-402-8906 orabioinspectionalcorrespondence@fda.hhs.gov	4/22/2024-4/30/2024* FEI NUMBER 3002806769

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Joaquin Alberto, Vice President of Quality and Regulatory

FIRM NAME	STREET ADDRESS
Medion Grifols Diagnostics AG	Bonnstrasse 9
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Dudingen, Fribourg, 3186 Switzerland	IVD 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

The (b)(4) does not demonstrate that the (b)(4) was developed following the approved (b)(4) plan.

Specifically, you did not achieve the specific negative results or meet the performance criteria as defined in your (b)(4) validation's Performance Protocol, start of study July 1st, 2019 for your Data-Cyte Extend 0.8%, which is a four vial kit used to detect unexpected anti-bodies in an Anti-D preparation.

In your (b)(4) validation, the Performance Protocol, start of study July 1st, 2019, states in part "According to SOP-002750, (b)(4) is considered as a negative reaction" . Negative reactions in SOP-002750, dated February 14, 2019, are (b)(4) . The Performance Protocol further states "All the antibody (b)(4) plasma must give negative results, Plasmas with unexpected antibodies must give result that correspond to the unexpected antibody (see list at end of protocol)".

Multiple results, including plasma samples (b)(6) (b)(7)(C) were reported as negative. However, per your procedure SOP-002750 "Reading and Interpreting results in Immunohematology techniques" these should have been interpreted as (b)(4) . Per SOP-002750, the result interpretation for (b)(4) is a (b)(4) and is not a negative or positive. The IFU for the DG 8 cards used for this test states "If poorly anti-coagulated plasma or incompletely clotted serum is used, fibrin residues may trap non-agglutinated red blood cells at the top of the gel, appearing as a pinkish or reddish layer. Although the results could be correctly interpreted, in a negative reaction the false appearance of a mixed-field could lead to a misinterpretation. In case of incompletely clotted serum samples, it is recommended to re-clot the serum and repeat the test."

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	Richard T Riggie, Investigator Creighton T Tuzon, Investigator Elias N Paz Alonzo, FDA Center Employee	X Richard T Riggie Investigator Signed By: Richard T. Riggie -S Date Signed: 04-30-2024 04:56:52	4/30/2024

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There is no deviation or any other documentation in the (b)(4) that explains why the values for (b)(4) were accepted as (b)(4). Your protocol titled "Performance Protocol" start date July 1st, 2019 allowed for repeating unexpected results, "Any unexpected result obtained with the test lot should be repeated. If the result is confirmed, the Project Manager should be informed and the cause investigated." The results that appear to show (b)(4) reactions were not repeated and were accepted as negative results achieved the same as (b)(4) results. SOP-002750 states "(b)(4) is considered a negative result, however this result must be reported to the QC manager. QC manager will make decision about accepting or rejecting the release of the product based on: 1) the (b)(4) results, 2) (b)(4) observation of the DG Gel-cards, 3) additional testing (if applicable)".

Since July 2019, you have manufactured and distributed (b)(4) lots of Data-Cyte Extend 0.8% to the United States. There is currently (b)(4) lots available within expiration, Lot (b)(4), expiring (b)(4) and Lot (b)(4), expiring on (b)(4).

OBSERVATION 2

Procedures to control environmental conditions have not been established.

Specifically,

As of 05 APR 2024, your firm has not established environmental monitoring control procedures for your ISO (b)(4) in your Quality Control/ (b)(4) (b)(4) Laboratory. The ISO (b)(4) (b)(4) is in uncontrolled room (b)(4) and is used for (b)(4) preparations and testing, which, in part, is used for (b)(4) of your firm's manufactured Reagent Red Blood Cells.

Since January 2023, for example, your firm has manufactured and distributed (b)(4) lots of Search-Cyte Plus 0.8% Reagent Red Blood Cells totaling (b)(4) vials (b)(4) to the U.S. that are intended for

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the detection of unexpected antibodies in gel techniques.

OBSERVATION 3

Corrective and preventive action activities and/or results have not been adequately documented.

Specifically,

Your firm conducted 43 Corrective and Preventive Actions (CAPA) from 2021-2024. During review, 6 out of 12 CAPA records did not adequately document effectiveness verification of actions taken to ensure that a corrective action to prevent recurrence of nonconforming product and other quality problems were appropriate and effective in eliminating the cause of the nonconformance. For example,

1. CAPA 200028372 was initiated on 10 DEC 2021 from customer complaints of leakage after (b)(4) due to (b)(4) on the (b)(4) of the (b)(4) of the caps that were (b)(4) and would occasionally move or fall from the cap (b)(4) of the vials. Corrective Actions included new supplier qualification and the use of a version of caps that contain (b)(4). Your CAPA and Effectiveness Check Planning concluded that an Effectiveness Check Plan was not required and that, "no effectiveness check needed, since this issue is tracked and trended through the complaint tracking and trending process. Additional actions will be identified and taken through that process, if required." CAPA 200028372 was closed on 01 OCT 2023.

2. CAPA 200034172 was initiated on 21 FEB 2023 from a customer complaint of leakage of (b)(4) (b)(4), and DG Gel (b)(4) upon arrival. Corrective Actions included updating SOP-002653 (b)(4) Bottling (entitled Abfüllen von Essential), implementation of documentation of the filling process, and training of filling team operators. Your CAPA and Effectiveness Check Planning concluded that an Effectiveness Check Plan is required and that within the (b)(4) implementation, a check will be conducted to ensure that the new form is correctly filled and attached to the appropriate batch record. However, your form Filling Process QC

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Products (entitled Abfüllprozess QC-Produkte), Ver. 1.0, Effective 27 FEB 2023, does not specify cap closure specification for manually closed caps. CAPA 200034172 was closed on 04 SEP 2023.

OBSERVATION 4

An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Specifically,

1. You became aware and received multiple customer complaint reports from March 2021 to Jan 2024. There were 19 false negative and one weaker than expected reports, and 2 false positive reports, that were not properly evaluated for MDR reportability and reasonably suggested that a device malfunction likely occurred. For example,

   a. Customer complaint #800009431 reported on July 29, 2022, regarding incorrect results due to false negative testing results for a patient with a history of anti-E. The facility reported that on July 26, 2022, antibody detection testing in using Search-Cyte TCS 0.8% RRBCs lot (b)(4), expiry (b)(4) produced 1+ produced positive result for cell #2 as expected. The test sample was sent to a different facility on July 26, 2022, for antibody identification where they tested the samples using the firm's Data-Cyte Plus 0.8% RRBCs lot (b)(4), expiry (b)(4), with DG Gel 8 Anti-IgG cards lot (b)(4), expiry (b)(4). All cells were negative, despite the presence of three (b)(4) cells in the panel: cell 4 (b)(4), cell 10 (b)(4), and cell 11 (b)(4). The same sample was tested manually using a different manufacturer's Panel (b)(4) lot (b)(4), expiry (b)(4). The untreated panel cells gave a 2+ positive for both (b)(4) cells in the panel: cell 3 (b)(4)) and cell 6 (b)(4), and enzyme treated panel cells gave a 4+ positive reaction for both cells 3 and 6.

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b. Customer complaint # 800005244 for several customer reports observing a reactivity that deviates from the corresponding antigen table: false negative reactions for Fya typing for cell #10 of Data-Cyte Plus 0.8% lot (b)(4). In your BPDR # 829303 you identified a device malfunction with possible root cause of contamination with trace amounts of (b)(4) solution during the bulk manufacturing. You were aware via customer complaints and confirmed a failure of your device to perform its essential function and an MDR was not submitted.

c. Customer Complaint #800011055, for unexpected negative results for several samples with known Anti-E, obtained with Cell 10 of firm's product Data-Cyte Plus 2 0.8%, (b)(4) (b)(4), lot (b)(4), exp. (b)(4). The customer stated that they properly identified anti-E using other testing methodologies and (b)(4) as an (b)(4) media but did not provide testing documentation to the firm.

d. Customer complaint # 800004523 regarding report regarding two events of unexpected negative results for anti-K during antibody screening with two samples from a (b)(4) (b)(4) female, with no prior antibodies or transfusion history were collected on (b)(4) (b)(4). The first event was observed on 04 March 2021 at the customer's (b)(4) location with the first sample. It was tested with the firm's Search-Cyte TCS 0.8%, ref. (b)(4), lot (b)(4), exp. (b)(4), DG Gel 8 Anti-IgG Card, (b)(4) (b)(4) (lot unknown), and the (b)(4) instrument. Negative reactions were observed with all three cells. Visual review of the batch listing report showed visually negative cell (b)(4), with a very slight irregularity in the cell (b)(4) for cell 2 (b)(4) (b)(6) (b)(7)(C) (b)(4) (b)(6) (b)(7)(C) only. The second event was observed on 04 March 2021 at their (b)(4) location where the second sample was sent for titer testing. Antibody screening was repeated with the firm's Search-Cyte TCS 0.8%, ref. (b)(4), lot (b)(4), exp. (b)(4) (b)(4), DG Gel 8 Anti-IgG Card, ref. (b)(4), lot (b)(4), exp. (b)(4), and the (b)(4)

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instrument. Negative reactions were observed with all three cells. Visual review of the traceability report shows visually negative cell (b)(4) that agree with the instrument algorithm reaction grade assignments. There was reports of a slight irregularity in the (b)(4) of microtube (b)(4) (donor (b)(4) (b)(6) (b)(7)(C)). Antibody identification testing was performed using Data-Cyte Plus 0.8%, (b)(4), lot (b)(4), and DG Gel 8 Anti-IgG cards, (b)(4) lot (b)(4), and the (b)(4) instrument. Cell 2 (donor (b)(4) (b)(6) (b)(7)(C)) and cell (b)(4) (donor (b)(4) (b)(6) (b)(7)(C)) were 1+ positive, while all other cells were negative. This reactivity pattern is consistent with an anti-K antibody.

False negative reactions of IgG antibodies, such as the (b)(4) and (b)(4) system examples listed above, can cause hemolytic transfusion reactions that would likely cause or contribute to a death or serious injury.

***DATES OF INSPECTION**

4/22/2024(Mon), 4/23/2024(Tue), 4/24/2024(Wed), 4/25/2024(Thu), 4/26/2024(Fri), 4/29/2024(Mon), 4/30/2024(Tue)

X Creighton T Tuzon
Investigator
Signed By: Creighton Tuzon -S
Date Signed: 04-30-2024 04:57:23

X Elias N Paz Alonzo
FDA Center Employee
Signed By: Elias N. Paz Alonzo -S
Date Signed: 04-30-2024 04:57:58

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Annotations to Observations

Observation 1: Not annotated

Observation 2: Not annotated

Observation 3: Not annotated

Observation 4: Not annotated

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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."