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	2/9/2026-2/18/2026* FEI NUMBER 3003098680

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Dr. Niklas Schier, Site Head Marburg & Managing Director

FIRM NAME	STREET ADDRESS
CSL Behring GmbH	Emil-Von-Behring-Str. 76
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Marburg, Hassia, 35041 Germany	Licensed Biological 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 WE OBSERVED:

OBSERVATION 1

Changes to written procedures are not reviewed and approved by the quality control unit.

Specifically, your firm failed to evaluate and control a change to the (b) (4) stopper material used in (b) (4) transfer devices for the following U.S. marketed biological products: Afstyla, Berinert, Haegarda, Kcentra, Humate-P, Idelvion, Corifact, and Respreeza.

For example, there was a(n)

a) Lack of Comparability Studies:

Global Change Control (GCC) (b) (4), implemented July 7, 2021, changed the (b) (4) stopper material (b) (4) (stopper (b) (4) (b) (4)). No comparative piercing force studies or (b) (4) compatibility testing were conducted between the old and new stopper materials prior to implementation. Post-implementation testing studies (conducted 2022 - 2025) initiated in response to elevated (b) (4) complaint rates revealed a (b) (4) in piercing force (b) (4) between new stopper and old stopper and (b) (4) transfer failure rates at center offsets (b) (4) for the new stopper.

b) Inadequate Risk Assessment Scope:

The risk assessment for GCC (b) (4) failed to evaluate the impact of the stopper material

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change on (b) (4) transfer device compatibility and functionality. The risk assessment focused exclusively on manufacturing process impacts (filling machine qualification, crimping machine qualification, sterilization processes, container closure integrity) while failing to assess the stopper's critical interface with the (b) (4) transfer device, including piercing force requirements, device functionality during reconstitution, and comparative performance between old and new stopper materials.

After the change, a systematic increase in (b) (4) complaints without crimp cap deformation was observed (supporting (b) (4) stopper puncturing defect): from (b) (4) cases in 2022 to (b) (4) cases 2023, (b) (4) cases 2024, and (b) (4) cases 2025, totaling (b) (4) global complaints. Complaint rates for this specific defect pattern increased from approximately (b) (4) ppm (2022) to (b) (4) ppm (2023), (b) (4) ppm (2024), and (b) (4) ppm (2025). Approximately (b) (4) total U.S. complaints were identified within this category since 2022. To date, corrective actions have not been fully implemented to reduce the number of complaints.

OBSERVATION 2
Failure to submit biological deviation.

By 2024, your firm identified that complaints of (b) (4) without crimp cap deformation were associated with the July 2021 (b) (4) stopper material change (GCC (b) (4)). Internal investigations confirmed the new (b) (4) stopper was (b) (4) (b) (4) requiring (b) (4) piercing force (b) (4).

Despite identifying the stopper material as a contributing factor in the increase in complaint rates impacting patient use, your firm did not submit BPDRs for affected U.S. marketed products.

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Defect complaints have included:

- QE-113013 (Haegarda 2000 IU, lot (b) (4), reported Dec 1, 2025): Patient received half dose due to bent spike (associated with Adverse Event AE Case (b) (4) and (b) (4) for delay in therapy)
- QE-113522 (Kcentra 1000 IU, lot (b) (4), reported December 3, 2025): Transfer issue - (b) (4) water in the vial could not transfer to the product vial; adapter appeared faulty and product not administered
- QE-100119 (Humate-P 250 IU, lots (b) (4) and (b) (4), reported August 20, 2025): Technician spiking diluent vial with (b) (4) adapter, (b) (4) spike bending and breaking and did not puncture stopper; events occurred 2 nights in a row; products not administered
- QE-097680 (Humate-P 500 IU, lot (b) (4), reported July 31, 2025): Transfer device failed to transfer the product from one vial to the other; no visible defect but transfer failed; product not administered
- QE-087338 (Humate-P 250 IU, lot (b) (4), reported May 14, 2025): Transfer issue - diluent would not go into Humate-P vial; product not administered

At least (b) (4) U.S. complaints (2022-2025) exhibited (b) (4) without crimp cap deformation directly associated with the stopper change across multiple U.S. marketed products. Patient impacts resulting from (b) (4) reconstitution complaints include inability to reconstitute product, incorrect dosing, and treatment delays.

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OBSERVATION 3

Procedures describing the handling of all written and oral complaints regarding a drug product are not established and followed.

Specifically, you failed to adequately investigate complaints, determine appropriate root causes, implement timely corrective actions, and follow established procedures, as follows:

a) Delayed CAPA Implementation:

(b) (4) complaints increased from (b) (4) complaints ((b) (4) ppm) in 2022 to (b) (4) complaints ((b) (4) ppm) in 2023 and (b) (4) complaints ((b) (4) ppm) in 2024. Despite this escalating trend:

- Proactive Improvement QE-048540 was not initiated until July 11, 2024
- CAPA-047072 ((b) (4) modification) due date: October 12, 2026 (Not fully implemented)
- CAPA-054641 (alternate device) due date: June 30, 2026 (Not fully implemented)

b) Deficient Root Cause Classification:

For confirmed (b) (4) without crimp cap deformation, your firm classified root cause as (b) (4) or (b) (4) despite internal testing confirming stopper material as primary contributor. Examples: QE-113013, QE-100096, QE-093303, assigned (b) (4) (b) (4) QE-113522, QE-100119, QE-097680, QE-087338 assigned (b) (4) (b) (4) misalignment application vs more rigid (b) (4) stopper material." However, your own investigation ((b) (4)) confirmed the new stopper requires (b) (4) (b) (4) piercing force and that manufacturing changes to stopper material properties contributed to device failures.

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c) Severity Misclassification:

Complaints involving (b) (4) without crimp cap deformation were consistently classified as (b) (4) despite frequently resulting in inability to reconstitute product, incorrect dosing, and treatment delays. Per your firm's own severity criteria (b) (4), defects that (b) (4) should be classified as (b) (4) Complaint QE-113013 documented associated patient adverse event cases (b) (4) and (b) (4) and classified as (b) (4)

d) Deficient Investigation Scope:

Per your procedure (b) (4) when (b) (4) (b) (4) identification of all impacted batches and initiation of a deviation is required.

OBSERVATION 4

Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, Change Control (b) (4) introduced enhanced equipment cleaning procedures as part of corrective action CAPA 034616 to address bioburden excursions identified in Fraction (b) (4) during the base fractionation process in Building (b) (4). The modification involved updating the (b) (4) by (b) (4) and (b) (4) (b) (4). This revision was implemented on May 05, 2025. The original cleaning procedure for the thawing (b) (4), documented in (b) (4) (b) (4) (b) (4) specified (b) (4) with a (b) (4). Quality event investigations

concluded that this (b) (4) cleaning recipe was deemed insufficient to control increased microbial counts in the thawing process. After implementing changes to the (b) (4) cleaning recipe (e.g., modifications to temperature and (b) (4) parameters), the firm did not perform a cleaning re-validation to confirm the effectiveness of these critical changes, despite the generation of subsequent investigations.

a) QE-060555 – On October 15, 2024, a total microbial count (bioburden) for (b) (4), Batch # (b) (4) result of (b) (4) was obtained, exceeding the established action limit of (b) (4) (b) (4) in thawing (b) (4). The associated investigation was closed on May 28, 2025.

b) QE-060739 – On October 15, 2024, a total microbial count (bioburden) for (b) (4), Batch # (b) (4) value of (b) (4) was obtained, exceeding the action limit of (b) (4) (b) (4) in thawing (b) (4). The associated investigation was closed on June 06, 2025.

OBSERVATION 5

The responsibilities and procedures applicable to the quality control unit are not fully followed.

Specifically, Investigations are not completed within established timeframes. Document (b) (4) (b) (4) allows Quality Assurance (QA) to grant (b) (4) extensions for deviation closure dates (b) (4). These extensions are granted in (b) (4) at the (b) (4). Review of the deviation management system revealed that deviations remain open for extended periods, in some cases (b) (4), with (b) (4) for validated processes approved by QA for the following quality events. Although the firm's risk assessment was determined to be adequate, the investigation confirmed that in-process control (IPC) testing results met established specifications throughout the fractionation process. The Frac. (b) (4)

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is used in the manufacture of U.S. licensed products Privigen and Hizentra.

a) QE-056326 – On September 11, 2024, Fractionation (b) (4) Batch # (b) (4)(b) (4) was exceeded. The time exceeded (b) (4) was (b) (4) and the temperature (b) (4) (b) (4) The associated investigation remained open for approximately (b) (4) days and was closed on December 18, 2025.

b) QE-058819 – On October 1, 2024, Fractionation (b) (4) Batch # (b) (4) (b) (4) was exceeded. The time exceeded (b) (4) (b) (4) was (b) (4) The associated investigation remained open for approximately (b) (4) days and was closed on December 18, 2025.

c) QE-059442 – On October 4, 2024, Fractionation (b) (4) Batch # (b) (4) (b) (4) was exceeded. The time exceeded (b) (4) (b) (4) The associated investigation remained open for approximately (b) (4) days and was closed September 09, 2025.

***DATES OF INSPECTION**
2/09/2026(Mon), 2/10/2026(Tue), 2/11/2026(Wed), 2/12/2026(Thu), 2/13/2026(Fri), 2/16/2026(Mon), 2/17/2026(Tue), 2/18/2026(Wed)

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2/18/2026

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."