10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter 320-18-08**

November 14, 2017

Werner Baumann
Chief Executive Officer
Bayer AG
Kaiser-Willhelm-Allee
Building W11
51368 Leverkusen
Germany

Dear Mr. Baumann:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Bayer Pharma AG at Kaiser-Willhelm-Allee, Building W11, Leverkusen, from January 12–20, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your February 10, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

Your equipment cleaning practices for non-dedicated equipment are inadequate.Your firm has several **(b)(4)** that can be used for more than one product.

A. *Equipment exterior surfaces*
During the production of your drug product **(b)(4)**, which was in a **(b)(4)**, our investigator observed a **(b)(4)** residue on the **(b)(4)** exterior surfaces. Your manufacturing area personnel stated that the residue was probably from a **(b)(4)** drug product, **(b)(4)**, which was previously processed in the same room.

After our inspection, you tested samples of tablets produced with **(b)(4)** manufactured in the same **(b)(4)** to assess the potential for cross-contamination. Your testing confirmed the presence of **(b)(4)** in **(b)(4)** tablets, which you had produced as a contract manufacturer for your customer, **(b)(4)**. **(b)(4)** recalled several lots of **(b)(4)** on **(b)(4)**, due to the cross-contamination problem.

B. **(b)(4)** *on manufacturing equipment*
In three different rooms, our investigator observed white residues in and around the **(b)(4)** of three **(b)(4)** identified as "clean." Your cleaning procedure did not include provisions for cleaning **(b)(4)** in **(b)(4)**.

Residues in and around **(b)(4)** can lead to the ingress of cross-contaminants into manufacturing equipment.

In your response, you committed to a number of corrective actions and preventive actions (CAPA) for **(b)(4)**, including reevaluating cleaning procedures and practices, assessing the effect of residues on quality and safety of products, and retraining personnel involved with cleaning.

Your response was inadequate. You did not sufficiently assess whether U.S.-shipped products manufactured with the **(b)(4)** were cross-contaminated.Additionally, you did not reevaluate your cleaning procedures, practices, and validation for other non-dedicated manufacturing equipment.

In response to this letter, provide:

- Your retrospective review supporting the safety and purity of each batch of product manufactured with your **(b)(4)** that remain within expiry in the U.S. market. Include a summary report of analytical testing results supporting your conclusions. Provide scientific justification if you to propose to exclude any batch that remains within expiry from this retrospective testing.
- A comprehensive plan to assess cleaning procedures, practices, and validations for each piece of manufacturing equipment used to manufacture more than one product. Also include your plans to ensure that powder residues are removed from room surfaces as part of product changeovers.

2. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your investigations into product quality complaints are inadequate. For example, when you investigated two complaints of leaking **(b)(4)** containing **(b)(4)** batch **(b)(4)**, you did not determine a root cause for the container-closure defect. Your **(b)(4)** supplier informed you of a **(b)(4)** defect that you did not address in your investigation. The investigation also failed to include an examination of retain samples or review past complaints to identify other instances of bag integrity defects.

Your response was inadequate because it lacked sufficient improvements to your investigation systems.

In response to this letter, provide:

- A list of all complaints received from 2014 to present that indicate potential bag non-integrity, with detailed descriptions including complaint dates, product names, batch numbers, description of complaint, exact breach locations, root causes, and CAPA. Include your final, updated investigations into the **(b)(4)** issues observed in batches **(b)(4)** and **(b)(4)**.
- A retrospective review of all investigations relating to complaints that could impact the quality of products within expiry in the U.S. market. Include an assessment of the depth of investigation, identification of potential root causes, review of related trends, and CAPA.
- A full assessment and remediation of your systems for investigating complaints, failures, and deviations to ensure they are thorough, scientifically sound, and culminate in appropriate and effective CAPA.
- Procedures requiring more thorough examination or testing of retention samples during investigations, including both the complaint batch and other potentially affected batches
- Procedures that ensure each complaint of a critical defect is carefully evaluated to determine whether marketed products may be impacted. Currently, a problem appears to be escalated only after three complaints are received for a batch.
- Improvements in your ongoing monitoring of vendor or contractor acceptability. Explain how you will ensure that vendors notify you about significant deviations or potential defects in materials (e.g., by modifying quality agreements).

3. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products, and that approves or rejects all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product (21 CFR 211.22(a) and (c)).

Your quality control unit did not sufficiently oversee adequacy of procedures at your facility to assure drug product quality.

A. *Discarded training records*
Our investigators observed discarded original personnel training records. Your procedure 3-040-127, *Use of the Schulungsdatenbank (Learning Management System) in the Supply Center Leverkusen* requires these records to be maintained. In your response, you committed to retain

original training records. However, you did not reassess your program to ensure that personnel were trained and capable of performing their assigned functions.

B. *Discarded automated visual inspection machine parameters*
In a **(b)(4)** department office waste bin, our investigators observed discarded forms used to document and set inspection parameters for your automated tablet visual inspection machinery. These parameters are used to accept or reject tablets. In your response, you noted that you documented and approved final set-up parameters, "but historically the calculations generated in support of those parameters have not been preserved." You indicate that programming the visual inspection machine to detect defects may not be a CGMP activity. We note that the parameters of this machinery are used to discriminate between acceptable and unacceptable tablets. Accordingly, entering reliable settings into machine programming is part of CGMP.

In response to this letter:

- Reassess any systems or activities associated with drug manufacturing or testing equipment that you consider "non-GMP." Provide your reassessment and describe improvements in your procedures for document handling, retention, and destruction.
- Review your training program's effectiveness, including but not limited to evaluating the reason(s) that some individuals failed to follow standard operating procedures. Summarize your CAPA.

4. Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

When reviewing audit trails, our investigator observed unreported data from in-process tablet weight checks. You programmed your in-process weight checker not to report values that varied more than **(b)(4)**% from the tablet target weight.

In your response, you committed to suspend this procedure, investigate any such values, and perform a retrospective assessment of tablet weight checker data. However, your retrospective tablet weight assessment was limited to all rejected measurements from February 1 to March 15, 2017, and about 8,000 rejected measurements representing an unspecified percentage of the total number of rejected measurements from August 1, 2016, to February 1, 2017. There was no commitment to revisit equipment qualification(s) and process validation(s) to ensure they included complete data.

In response to this letter, as part of your retrospective tablet weight assessment, explain whether your findings impact data supporting tablet manufacturing equipment qualification and manufacturing process validation studies. Provide a summary listing of equipment qualification and process validation documents that you reviewed.

Data Integrity Remediation

FDA acknowledges that, before our inspection, you began a data integrity remediation program. Our investigator documented that, as part of your data integrity remediation program, you discontinued the practice of performing "test" injections as a result of an internal assessment in June 2016. However, we noted that you only reviewed chromatographic data for **(b)(4)** and **(b)(4)** generated between January 1, 2015, and June 23, 2016.

Your action plans submitted on May 11, 2017, and August 10, 2017, did not include an assessment of other products manufactured and tested at your facility. Additionally, the retrospective review did not include data generated before January 1, 2015, used in support of drug applications submitted to FDA. Further, your retrospective review only focused on the laboratory. You did not investigate potential data integrity lapses in other manufacturing systems.

In response to this letter, provide your revised action plan. In your summary report, include other products manufactured and tested at your facility and identify any data generated before January 1, 2015, that was used to support drug applications submitted to FDA. Also, include your protocol and methodology. Summarize all laboratories, manufacturing operations, and systems covered by the assessment. Specify whether a qualified independent consultant performed interviews to ensure that the nature and scope of the problem was fully determined. Discuss the role of the independent consultant in auditing the integrity of your data and assisting with CAPA. Justify why you excluded any part of your operations or systems.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Bayer Pharma AG at Kaiser-Willhelm-Allee, Building W11, 51368 Leverkusen into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls

used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Jason F. Chancey
Consumer Safety Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3002806462.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research