

# Inspections, Compliance, Enforcement, and Criminal Investigations

## Bayer HealthCare - Bayer Schering Pharma AG 8/5/09



Department of Health and Human Services

Public Health Service  
Food and Drug  
Administration  
CENTER FOR DRUG  
EVALUATION AND  
RESEARCH  
Division of Manufacturing  
and Product Quality  
International Compliance  
Team

### Warning Letter

**Via FedEx**

**WL: 320- 09- 09**

August 5, 2009

Dr. Franz-Josef Renneke  
Site Manager  
Bayer HealthCare - Bayer Schering Pharma AG  
Ernst-Schering-Str 14  
59192 Bergkamen  
Germany

Dear Dr. Renneke:

This letter is regarding a March 2-10, 2009 inspection of your active pharmaceutical ingredient (API) facility in Bergkamen, Germany, by U.S. Food and Drug Administration (FDA) Investigator Jose Cruz and Chemist Miguel Martinez. The inspection revealed significant deviations from U.S. current good manufacturing practices (CGMP) in the manufacture of non-sterile APIs. These deviations were listed on an Inspectional

Observations FDA Form (FDA-483) issued to you at the close of the inspection.

These CGMP deviations cause your APIs to be adulterated within the meaning of Section 501(a)(2)(B) [21 USC 351(a)(2)(B)] of the Federal Food, Drug, and Cosmetic Act (the Act). Section 501(a)(2)(B) states that drugs are adulterated when they are not manufactured, processed, packed, and held according to current good manufacturing practices. Failure to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have reviewed your April 7, 2009 written response to the FDA-483 observations. We acknowledge that some corrections appear to have been completed or will soon be implemented. However, your response does not adequately address some of the deficiencies. Specific violations found in the inspection include, but are not limited to:

1. Laboratory controls are deficient in that your firm has established procedures that allow for the averaging of out-of-specification (OOS) and within-specification analytical test results from separate samples. The use of these approved procedures resulted in API batches being released to the U.S. market based on passing averaged assay results. Refer to FDA-483 Observation #2c and 2d. For example:

a. *GMP Directive #CMSD08-50-01-1, Handling of Out-of-Specification Results*

This procedure allows for the averaging of results into specification. It provides for the reportable, or averaged result, rather than the individual test results to be compared against the established specifications. The reported (average) result is defined as the final analytical result reported and compared against the specification. An individual value found outside the established specification is not defined as an DOS if, when averaged, the reportable result remains within specifications. An ODS result is defined as a reportable result (average) that is outside the defined acceptance criteria (e.g. specification).

b. *LIMS (Laboratory Information Management System) procedure:*

The inspection revealed that results for individual tests are calculated individually by the **(b) (4)** system and then averaged by your firm's Laboratory Integrated Management System (LIMS). The averaged result (not individual results) is then corrected for water content, if necessary. The release specification is applied only to the averaged result and not to the individual results. Refer to FDA-483 Observation #2d.

The investigators were informed during the inspection that the analyst is the first person to review the individual results. If the individual results do not vary more than **(b) (4)**, the average of the results is permitted according to procedure #QCB.PKA00132, *Determination of Values and Rounding of Results*. This procedure allows the analyst to make the decision to re-inject the samples or to accept the assay result and continue documenting the values obtained as final results without conducting an investigation.

2. Your quality management system fails to ensure that APIs manufactured and released by your firm meet established specifications. Refer to FDA-483 Observation #1.

Specifically, the API batches shown below were released based on reportable assay results obtained from the average of two independent sample results. One of the sample results was out-of-specification (ODS) while a second result was within specification. The averaged passing reportable assay result was compared against the established specifications, and the batches were released to the marketplace.

See Table A for examples:

Table A

API Product Name	Batch Number	Assay Results	Release Specification	QA Approved Date	Release Date for Distribution
Drospirenone, <b>(b) (4)</b>	88100260	<b>(b) (4)</b>	<b>(b) (4)</b>	February 08, 2008	February 11, 2008
Drospirenone, <b>(b) (4)</b>	88101020	<b>(b) (4)</b>	<b>(b) (4)</b>	April 05, 2008	April 07, 2008

Continuation: Table A

Batch Assay Release QA Release

API Product Name	Batch Number	Assay Results	Release Specification	Approved Date	Date for Distribution
Drospirenone, (b) (4)	88303430	(b) (4)	(b) (4)	September 23, 2008	September 24, 2008
Drospirenone, (b) (4)	88201160	(b) (4)	(b) (4)	April 25, 2008	April 28, 2008
Drospirenone, (b) (4)	88100210	(b) (4)	(b) (4)	February 01, 2008	February 06, 2008
Ethinylestradiol (b) (4)	88100590	(b) (4)	(b) (4)	February 14, 2008	(several dates) May 5, 2008 To March 5, 2009
Norethisterone acetate (b) (4)	88303790	(b) (4)	(b) (4)	September 09, 2008	February 05, 2009
Norethisterone acetate (b) (4)	88303830	(b) (4)	(b) (4)	September 23, 2008	September 29, 2008

In regards to items 1 and 2 described above:

In your April 7, 2009 response you reported that you had conducted a retrospective investigation that extended to all "U.S. relevant" (i.e., sent to facilities that further processed them into finished drug products intended for the U.S. market) API batches produced between 2007 and 2009. You identified nine additional incidents where OOS results were averaged with passing results. In all cases, your firm concluded that no analytical errors had been identified and that the values were true DOS results. Your firm

concluded that these OOS results were within the accepted variation of the analytical method and that the quality of these batches was not affected. We disagree with your rationale and conclusion. An assay test is used to determine potency, not method variability. The validation of your analytical method should address robustness or variability, while system suitability is designed to address instrument variation performance, which was met in each of these instances. We believe that these results were true ODS values and that these batches should not have been released for distribution.

In your written response, you indicate that your current procedure allows the average of two individual sample preparation results, if the difference of the single values does not exceed **(b) (4)** absolute. You state that this is appropriate averaging and in line with the FDA OOS guidance document. We disagree with your rationale and interpretation of the FDA OOS guidance. Your firm prepares two to three separate samples, which are assayed individually. We expect you to treat each of these results independently, and not to average an OOS result with a passing individual result. The hiding of an OOS result in the average is an unacceptable practice. Please refer to the October 2006 *Guidance for Industry-Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Products*, that states in part IV.C.1.b., "Reliance on averaging has the disadvantage of hiding variability among individual test results. For this reason, all individual test results should normally be reported as separate values. "Your revised *DRAFT SOP QCB.PKA00132, "Determination of Values and Rounding of Test Values"* appears adequate, in that going forward you will treat each individual test result independently and will only average values that are within-specification. Please submit a translated version of the revised SOP once it is approved, along with appropriate training documentation.

We remain concerned with your released and distributed API batches used in the manufacture of finished products intended for the U.S. market, in which the reportable results were based on the average of out-of-specification and within-specification analytical test results. Include in your response to this letter a complete list of all API batches shipped to the U.S. (also include lot numbers, date of shipment, customer name and address), using reportable passing average results consisting of out-of-specification and passing results. Please inform this office of any additional corrective action you plan to take to correct this violation.

We are concerned that *GMP Directive #CMSD08-50-01-1, Handling of Out of Specification Results*, is a corporate directive that may be in place in other manufacturing and testing facilities. Provide in your response to this letter the corrective and preventive actions implemented throughout your corporation to address this deficiency, and ensure that adulterated APIs have not been shipped into the U.S.

We recognize that your SOP has been revised and submitted as a DRAFT revision

of procedure #QCB.PKA00775, Version 5.1 for Handling of out of Specification Test Results (OOS) during Chemical or Physical Test Methods, Microbiological Contamination and Endotoxin testing. However, most of it is in the German language. Please submit an English translation once it is approved. Also include with your written response to this letter, the revised corporate GMP Directive CMS D08-50-01-1, for Handling of Out-of-Specification Results.

The inspection reported that your analysts had been trained to average passing and OOS results, and to report the average passing results. Please submit the translated training records for all analysts demonstrating that they have been trained in your new revised procedures.

Additionally, please submit your finished product sampling procedure and your scientific rationale for this procedure.

3. The Quality Unit failed to maintain responsibility and authority to review and conduct investigations. Your firm failed to conduct adequate investigations that included scientific justification to support conclusions. In addition, the investigations did not include proper corrective actions. For example:

a. Out-of-specification (OOS) results were disregarded, and no OOS investigations were conducted after obtaining individual OOS assay results during release and stability testing of your APIs. Instead, the OOS and passing results were averaged to obtain a reportable result within-specification, as referenced in item 2 of this letter. Our investigator documented two stability intervals where individual OOS stability sample results were averaged with within-specification stability results, and no OOS investigation was conducted. Examples of this practice were observed during the forty-eight month stability interval (25°C/60%) for **(b) (4)** (Batch # **(b) (4)**) and Medroxy Progesterone Acetate, **(b) (4)** (Batch # **(b) (4)**). The first batch showed duplicate assay results of **(b) (4)** and **(b) (4)**, with a specification of **(b) (4)**. The second batch showed duplicate assay results of **(b) (4)** and **(b) (4)**, with a specification of **(b) (4)**.

Refer to FDA-483 Observation #4a. We disagree with your rationale and conclusion submitted in your response for the reasons stated above in items 1 and 2 of this letter.

b. Norethindrone Acetate **(b) (4)** lot # **(b) (4)** was rejected (for destruction) because it was found with levels of **(b) (4)** for the impurity **(b) (4)**. Your firm did not conduct an investigation to determine a root cause for the high level of impurity. Refer to FDA-483 Observation #9.

Your response states that this high impurity was a single event, and from a scientific view it is very unlikely in the NETA process because the **(b) (4)** is much more stable due to the **(b) (4)** functionality. Please supply supporting documentation for your conclusion.

c. OOS investigations did not adequately determine root cause, or provide for corrective actions to prevent recurrence. Investigation report #s 87302220 and 87201360, related to an out-of-specification (OOS) result in the polarimetry test, and an OOS result in the assay by potentiometer titration. These reports respectively concluded that the OOS result was caused by a weighing error, and by the **(b) (4)** solvent used to conduct the test. However, when our investigator reviewed and discussed the investigations with your firm's personnel, he discovered that the real root cause for the OOS result was the use of an incorrect test method, and an improperly executed procedure for the equilibration of the electrode in **(b) (4)** (not the solvent itself), respectively. No corrective action was addressed in the investigation. In addition, investigation report # 82190246, related to an out-of-specification result in the melting point test, concluded that the OOS result was caused by not having sufficient amount of sample in the capillary (filling sample technique). No corrective action was addressed and/or documented to correct and prevent recurrence. Refer to FDA-483 Observation #4c. Your response lacks explanation and documentation to support your conclusions.

Your April 7, 2009, written response reports that you are revising your OOS standard operating procedure (SOP) to emphasize the importance of conducting and documenting a thorough investigation of all OOS test results, including determining root cause analysis and evaluation of corrective and preventative actions. Your response indicates that the SOP became effective and training was completed by May 2009. Provide copies of the translated revised procedure and training records.

Your written response should also include the corrective action under consideration, or implemented to address the OOS test result examples (a and c), cited on the FDA-483 under Observation 4, and FDA-483 Observation 9. Provide a description of the corrective actions for each example cited, along with expected dates of completion, as well as a more comprehensive review to ensure the revised OOS SOP's overall adequacy.

4. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment. Refer to FDA-483 Observation #5. For example:

The inspection revealed that production equipment, specifically the surface of the **(b) (4)** on production vessel **(b) (4)**, used in the manufacturing process of Ethinylestradiol API, was not maintained in a clean condition even though the equipment was labeled cleaned, and had been inspected and verified as cleaned by the Production Department Shift Supervisor. This **(b) (4)** is in direct contact with the product when inside the vessel. Your response lacks an explanation and documentation to support your conclusion that the operator may not have detected the brown residue, because the equipment was wet when examined.

In your response to this Warning Letter, explain where the "inorganic substance insoluble in water or inorganic solvents" that you identified as the residue originated from. Additionally, your response mentions that the residue was removed by flushing with diluted **(b) (4)**. Explain if this procedure is part of your routine cleaning procedure, and if your routine cleaning procedure is capable of removing the residue.

The CGMP deviations identified above, or on the FDA-483 issued to your firm, are not to be considered an all-inclusive list of the deficiencies that may exist at your facility. FDA inspections are audits, which are not intended to determine all CGMP deviations or violations that exist at a firm. If you wish to continue to ship your APIs to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, this office may recommend withholding approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act [21 U.S.C § 381(a)(3)], in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practices within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C § 351(a)(2)(B)].

Please respond to this letter, with requested documents translated in English, within thirty days of receipt, and identify your response with FEI# 3002808295. Please contact Denise DiGiulio, Compliance Officer, at the address and telephone number shown below, if you have any questions or concerns regarding this letter.

U.S. Food & Drug Administration  
Center for Drug Evaluation and Research  
Division of Manufacturing and Product Quality  
International Compliance Branch  
White Oak, Building 51  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993  
Tel: 301-796-3667  
Fax: (301) 847-8741

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Field Investigations HFC- 130, 5600 Fisher's Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5655, or by fax at (301) 443-6919.

Sincerely,  
Richard L. Friedman, M.S.  
Director  
Division of Manufacturing and Product Quality  
Office of Compliance  
Center for Drug Evaluation and Research