U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Sanofi Aventis Deutschland GmbH 2/9/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-11-09

February 9, 2011

Mr. Martin Siewert, Chairman of the Board
Sanofi Aventis Deutschland GmbH
Industriepark Hochst, Building H550
Frankfurt am Main 65926
Germany

Dear Mr. Siewert:

During our September 6-10, 13-16, 2010 inspection of your pharmaceutical manufacturing facility, Sanofi Aventis Deutschland GmbH, Industriepark Hochst, Building H550, Frankfurt am Main, Germany, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's responses in October 2010 and January 2011, however we continue to have concerns related to your firm's compliance with CGMP.

Specific violations observed during the inspection include, but are not limited to the following:

1. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)]. For example,

   For example, in June 2010, your firm failed to identify the organisms recovered from a sterility test for Apidra lot #OF100. Identification of microorganisms recovered from a sterility test is essential when conducting a sterility failure investigation. In addition, the identification of organisms is also a fundamental part of any investigation of environmental or personnel monitoring excursions.

   Your firm's failure to identify organisms recovered from a sterility test was also discussed during the December 2008 inspection.

   We recognize that your firm voluntarily recalled the Apidra, Lot#0F151A, which was part of the February 2010 production campaign in which there was a significant concern regarding environmental contamination levels. We expect all procedures related to the response for an out-of-limit environmental monitoring sample or a sterility failure to include the appropriate evaluation and remedial measures, as appropriate.

2. Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during aseptic processing. [21 C.F.R. § 211.42(c)]. For example,

   a) The airflow velocity inside critical areas of the aseptic processing operations of Line **(b)(4)** was found unacceptable by FDA. The documentary evidence of *in-situ* air pattern analysis (e.g., smoke studies) reviewed during the inspection confirmed this condition.

   With respect to aseptic processing in critical areas, you should be able to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. Please note that proper design and control prevents turbulence and stagnant air in the critical areas. It is crucial that airflow patterns are evaluated for turbulence that can act as a channel for contamination, and that any deficient conditions are addressed.

   b) Your environmental monitoring program does not give assurance that environmental contaminants are reliably detected. Your practice of collecting samples from the gloves of operators, from left and right hands on alternate days is unacceptable. In addition, your SOP fails to include instructions for the location and duration of samples collected in the critical aseptic processing areas.

   An adequate environmental monitoring program should be established by your firm. It should capture meaningful data and act as an early warning system to detect possible environmental contaminants that may impact the sterility of drug products manufactured at your facility that purport to be sterile.

3. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the educatior training, and experience, or any combination thereof, to enable that person to perform the assigned functions. [21 C.F.R. § 211.25(a)]. For example,

On September 6 and 9, 2010, operators involved in the cleaning operations and aseptic connections during filling, were observed demonstrating incorrect aseptic techniques to prevent product contamination. We expect that operators who conduct operations within aseptic processing areas be properly trained and monitored to ensure that proper aseptic techniques are utilized during all operations.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. If you wish to continue to ship your products 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, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, FDA may be refusing admission of articles manufactured at Sanofi Aventis Deutschland GmbH, Industriepark Hochst, Building H550, Frankfurt am Main, Germany, into the United States. The articles are 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 Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Please identify your response with FEI # 3002807197.

If you have questions or concerns regarding this letter, contact Douglas Campbell, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
White Oak, Building 51, Room 4224
10903 New Hampshire Ave
Silver Spring, MD 20993
Tel: (301) 796-3201
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Sincerely,
/S/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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