Vaccines, Blood & Biologics

Sanofi Pasteur Untitled Letter

EXPRESS MAIL

July 22, 2010

Mr. Andre Dupont
Vice President Industrial Operations and Site Director
Sanofi Pasteur SA
Campus M é rieux
1541 Avenue Marcel M é rieux
69280 Marcy l'Etoile, France

Dear Mr. Dupont:

The Food and Drug Administration (FDA) conducted an inspection of Sanofi Pasteur SA, Marcy l'Etoile, France, between March 15, and April 2, 2010. During the inspection, the FDA investigators documented significant deviations from current good manufacturing practice (CGMP) requirements in the manufacture of licensed biological products and bulk drug substances. These products include IMOVAX® RABIES, Imogam® Rabies, IPOL®,

Act HIB®, and Typhim Vi®. The deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as well as requirements of your biologics license applications approved under Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations, (21 CFR) Parts 210, 211, and 600-680.

At the close of the inspection, FDA investigators issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your firm's compliance with CGMP. These include, but are not limited to, the following:

1. You failed to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, and failed to extend the investigation to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. For example:
    a. Your investigations into recurring (since 2007) Typhim Vi® out-of specification (OOS) pyrogen results, identified the pyrogenicity of the ----------(b)4)----------, used in the pyrogen testing and the manufacture of Typhim Vi®, as the most probable root cause. However, incoming raw materials, ----------(b)(4)---------- used in the manufacture of your ---(b)(4)--- have not been evaluated to rule them out as a potential root cause; and
    b. Your investigations into the numerous complaints received between February 2008 and February 2009 for Ac HIB® that was "difficult to withdraw" did not include an evaluation of the reconstitution of retain samples with the 0.4% NaCl diluent used in the marketed product.
2. You failed to report biological product deviations for lots of bulk and final drug product that represent marketed product and have failed stability at various time points [21 CFR 600.14(b)].
3. You failed to inform the FDA about each change in the production process in your approved license application [21 CFR 601.12]. For example, the use of a –(b)(4)--------- containing (b)(4) for pyrogen testing, rather then the approved -----(b)(4)-----, was not reported to the Agency.

Additionally, significant deviations in the manufacture of your bulk drug substances were observed during the inspection. The deviations violate Section 501(a)(2)(B) of the FD&C Act and Section 351(a) of the PHS Act. Specific areas of concern include, but are limited to:

CONTROL OF MICROBIAL CONTAMINATION

You failed to follow procedures designed to prevent microbial contamination, in that you did not follow your SOP 130343 entitled "Environmental Monitoring of Clean Areas," which requires Environmental Monitoring Trend Reports be written and approved within **(b)(4)** days of the end of a study period. For example:

1. The Building (b)(4) Environmental Monitoring Trend Report for December 2008 to February 2009 was approved on June 3, 2009;
2. The Building (b)(4)Environmental Monitoring Trend Report for February to July 2009 was approved on November 19, 2009;

3. The Building (b)(4) Environmental Monitoring Trend Report for January to June 2009 was approved on October 14, 2009.

BUILDINGS AND FACILITIES

You failed to perform operations within specifically defined areas, or to establish other control systems for your operations as are necessary to prevent contamination or mix-ups, in that you did not adequately label quarantined ----------(b)(4)---------- Batches ---(b)(4)--- and ---(b)(4)---. Individual bottles of these batches were stored wit bottles of (b)(4) Batch ---(b)(4)---, which were awaiting destruction.

We acknowledge receipt of your written responses dated April 21, 2010, May 17, 2010, and June 11, 2010, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. We also acknowledge your commitments made in your responses to address the items listed on the Form FDA 483.

We have reviewed your responses and have the following specific comments. The items are numbered to correspond to the observations listed on the Form FDA 483.

Form FDA 483 All Items

We acknowledge your commitment to implement corrective actions, including updating your SOPs and training your personnel in a number of areas. Please discuss implementation of global Quality Assurance oversight to ensure that adequate steps are taken for the evaluation of product impact, deviation investigations, and adequate and effective corrective and preventive actions.

Form FDA 483 Item #1D

We acknowledge your commitment to submit a supplement for your ------(b)(4)----------. For questions regarding the supplement please contact the Office of Vaccines Research and Review, Division of Bacterial, Parasitic, and Allergenic Products at 301-827-5105.

Neither the above deviations, nor the observations noted on the Form FDA 483 presented to your firm at the conclusion of the inspection, are intended to be an all-inclusive list of deviations at your establishment. It is your responsibility to ensure compliance with all requirements of the laws and regulations administered by FDA.

Your reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact Robert A. Sausville, Director, Division of Case Management, CBER at 301-827-6201.

Sincerely,

/signature/

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: Jean-Michel Khoury
Associate Vice-President, Site Quality Operations, Marcyl'Etoile
Sanofi Pasteur SA
Campus Mérieux
1541 Avenue Marcel Mérieux
69280 Marcy l'Etoile, France

Luc Kuyens, MD, MPH, DTM
Vice-President, Regulatory Affairs and Research and Development Quality Assurance
Authorized U.S. Agent
Sanofi Pasteur, Inc.
1 Discovery Drive
Swiftwater, PA 18370

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