DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 3 0 2006

WARNING LETTER

OEWL-06-01

EXPRESS MAIL

Mr. David J. Williams
Senior Vice-President, Vaccines
Sanofi Pasteur, Inc.
Discovery Drive
Swiftwater, Pennsylvania 18370

Dear Mr. Williams:

The Food and Drug Administration (FDA) conducted an inspection of Sanofi Pasteur, Inc. (Sanofi), Discovery Drive, Swiftwater, Pennsylvania, between April 18 and April 28, 2006. During the inspection, FDA investigators documented significant deviations from current good manufacturing practices (CGMP) in the manufacture of licensed biological products and Fluzone® monovalent concentrate batches. These deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 issued a Form FDA 483, Inspectional Observations, that described a number of significant objectionable conditions relating to your facility's compliance with CGMP. Significant deviations observed during the inspection include, but are not limited to, the following:

1. Failure to keep equipment and supplies used in work on or otherwise exposed to any potentially pathogenic agent separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination [21 CFR 600.11(e)(5)]. Hallway 135 in building 37 (Fluzone® production floor), which connects directly to the sterile gowning suite used for sterile processing and to the equipment airlock for passing equipment in and out of the sterile filtration room, does not provide for adequate segregation of early production materials from materials used in sterile processing. During sterile filtration of influenza concentrate lot U08182, this common hallway was utilized to transport already-sterilized equipment into the equipment airlock as well as to transport soiled equipment and carts containing inoculated eggs, for personnel traffic, and to transfer reagents between rooms.

2. Failure to establish a system for maintaining equipment to control aseptic conditions; failure to follow appropriate written procedures to prevent microbial contamination of drug products purporting to be sterile; and failure of the quality control unit to ensure that errors are investigated [21 CFR 211.42(c)(10)(vi), 211.113(b), and 211.22(a)]. For example, when leaks were found in the HEPA filters for final product aseptic filling in room 181 in Building 37 on June 7 ([redacted]) and on December 5, 2005 ([redacted]), the firm did not generate deviations even though the leaks violated the "Acceptance Criteria" in the firm's SOP (Number 21C22 Revision Number 06). Moreover, the firm did not investigate to determine whether using those filters had any product impact.

3. Failure to follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. For example, during aseptic filling operations for Menomune, an operator was observed with head and torso over partially stoppered vials while loading vials onto lyophilization trays.

4. Failure to establish the accuracy, sensitivity, specificity, and reproducibility of test methods employed by your firm [21 CFR 211.165(e)]. Eleven analytical methods have not been validated or qualified since your 2001 commitment to validate or qualify all test methods.

5. Failure to report any event and relevant information associated with the manufacturing of a licensed biological product that represents a deviation from current good manufacturing practice, applicable regulation, applicable standards, or established specifications that may affect the safety, purity, or potency of a distributed biological product as required by 21 CFR 600.14(b). For example, you failed to report to FDA that:

    a) product complaints were received concerning glass in the product (complaints CO2005-00209 Decavac™ Lot U1212CA and CO2004-08344 TD Lot U1188AA), which your investigation concluded were missed during the 100% inspection of the product; and

    b) stability testing ([redacted]) at the [redacted]-month time point for DT Adsorbed PF Lot U1047AA was not performed.

6. Failure to inform CBER about a change to your licensed product stability testing program [21 CFR 601.12(a)]. You reduced the stability testing time points for Tripedia® from [redacted] and [redacted] months to [redacted], and [redacted] months without submitting a supplement (also, see comment below on Laboratory and Controls System Observation 6.)

Additionally, significant deviations in the manufacture of your monovalent concentrate that is used to formulate Influenza Virus Vaccine, Fluzone® were observed during the inspection. These 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 not limited to:

INVESTIGATION OF FAILURES

1. Eleven Fluzone® (preservative formula and no preservative formula) monovalent concentrate lots manufactured between February 2006 and April 2006 failed sterility. There were significant deficiencies in the investigation of these sterility failures. For example:

   a) Your firm increased non-routine surveillance monitoring to further evaluate the Fluzone® manufacturing facility (building 37). However, there was no plan in place specifying the locations to be tested, sampling methods to be used, and corrective actions to be assigned and implemented where and when microbial contamination was noted (see comment below on your response to Quality System Observation 1A.)

   b) Investigational aseptic processing simulation studies did not include pre-filtration operations and cleaning activities that are performed prior to sterile filtration of the monovalent concentrate. Consequently, you did not test whether the separation between pre-filtration and post-filtration activities was adequate to prevent pre-filtration activities, including cleaning, from contaminating sterile material.

   c) Only microbiological samples containing colonies exhibiting morphological gram negative characteristics were further identified, even though some gram positive organisms were isolated among the samples from the sterility failures.

   d) The [redacted] microbiological method used to increase environmental monitoring surveillance was not validated.

   e) There was no scientifically sound justification for not re-sampling portions of the failed monovalent concentrate lots that did not test positive to determine the extent of the contamination.

   f) Organisms isolated from routine environmental monitoring in the Building 37 Influenza Virus Vaccine manufacturing facility were not identified to help determine the route of contamination.

PRODUCTION AND PROCESS CONTROLS

2. Sterile vent filters used on the [redacted] sterile influenza bulk concentrate tank and on the [redacted] dispensing siphon unit are not integrity tested by your firm after sterile filtration.

3. Operators performing level 1 cleaning between Fluzone® pre-filtration and sterile filtration operations were observed traveling between grade C areas (less clean) and grade B (cleaner) areas.

4. During routine cleaning of grade A areas in the influenza manufacturing facility, excess disinfectant solution was not removed as required by your cleaning/disinfecting procedures.

5. Review of batch production records for Fluzone® by the quality control unit does not include product contact equipment sterilization records. This issue was previously cited on the Form FDA 483 issued to your firm on March 18, 2005 (Observation #5.)

6. The wet/dry vacuum is used to clean the floors of your production areas. However, the vacuum's HEPA filter has not been evaluated to ensure that airborne particulates are not dispersed into the production areas.

LABORATORY CONTROLS

7. The bioburden sampling size of [redacted]mL was not representative of the lot size in determining pre-sterile filtration bioburden levels.

8. Qualification studies for Fluzone® non preserved monovalent concentrate bioburden testing had not been performed. Samples of both non preserved and preserved formulations were collected in [redacted]

The deficiencies described in the Form FDA 483 and this letter are indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your drug product [21 CFR 211.22]. Please describe in detail how Sanofi will attain CGMP compliance with regard to deviation investigations. Please include in that description how Sanofi will use all of the relevant information to conduct a root cause analysis, to ensure that adequate steps are taken to evaluate whether deviations impact product, and to implement effective corrective and preventive actions.

We acknowledge receipt of your written response dated May 19, 2006, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter; however, we believe that your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our comments and requests for further information regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Production System, item 1B:

As noted above, eleven Fluzone® (preservative formula and non preservative formula) monovalent concentrate lots manufactured between February 2006 and April 2006 failed sterility. No data have been submitted to exclude the hallway as a contributor to the sterility failures. We disagree with your conclusion that hallway 135 and adjacent critical processing areas continued to demonstrate state-of-control. Your response indicates that you will continue to explore on-going improvements to product and personnel flow during the current 2006 production campaign; and will explore options for spatial and/or temporal segregation for subsequent campaigns, including the potential relocation of filtration activities to separate sterile filtration from egg

related processing. Please be aware that your reply should provide specific details of corrective actions.

Production System, item 6:

In your response to this letter please update us on the status of your plans to apply a post-use integrity testing method to the influenza process after sterile filtration.

Production System, item 8:

Your response indicates that you believe your practice of reporting [redacted] working seed changes to FDA in an Annual Report follows FDA's "Guidance for Industry: Changes to and Approved Application: Biological Products." Specifically, you point to example number 11 in Section IV of that Guidance, which lists as an example of an item that may be submitted as an Annual Report change: "Establishment of a new Working Cell Bank derived from a previously approved Master Cell Bank according to an SOP on file in the approved license application." We acknowledge that supplement BL 103926/5042, which was approved on February 19, 2004, contained the statement, "[redacted]" However, the SOP you submitted with that supplement does not contain sufficient detail about your process for establishing a new working seed, and the purpose of the supplement was not to obtain FDA approval of that process such that you could thereafter report working seed changes only in annual reports. Before you submit working seed changes through annual reports, we request that you submit a supplement specifically for that purpose, that contains detailed procedures on your process for establishing new working seeds.

Production System, item 9b:

Your response states that [redacted] Master Seed Lots vials stored at [redacted]°C have been blocked from use in manufacturing and that an approved procedure (SOP A000739, version 6.0, "Receipt, Storage and Inventory of Microbiological Cultures, Prepared Serums and Antigens") is in place to ensure that future [redacted] Seed Lots are stored in the appropriate back-up storage location. A copy of your procedure should be available for review at the next inspection.

Production System, item 13:

Your response indicates that qualification studies for solutions used in final product formulation and manufacture of product intermediates will be initiated by Q4 2006 and reports on the completed studies finalized by Q3 2007. Your response also indicates that qualification studies for growth media hold times and for the remaining production solutions will be initiated by Q4 2007 and reports on the completed studies finalized by Q3 2008. The completion dates for these qualification studies appear excessive and we recommend that you reevaluate your proposed timeframe so that these studies are completed in a timely manner.

Quality System, item 1A:

We acknowledge your commitment to revise SWI J003906, "Surveillance Environmental Monitoring Procedure." Please submit a copy of the revised version with your response to this letter.

Quality System, item 1D:

We disagree with your response. Your response states that since all OOSs were not repeatable, the contamination was not extensive. This is not necessarily the case. Retesting of the negative bottles, as well as the positive bottles, would have provided important information on the extent of the contamination.

Quality System, item 3:

Your response is not acceptable. The quality control unit is responsible for review of all production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed. This issue was previously cited on the Form FDA 483 issued to your firm on March 18, 2005.

Quality System, items 4 & 6:

Your response states that you will revise your procedure SWI J003642, "Quality Assurance Compliance Procedure for Evaluating and Reporting Biological Product Deviations" to include specific instructions for the filing of biological product deviation reports in association with missed stability time points and complaints. Please conduct your reviews and product impact assessments for the products identified in observations 4 and 6 and submit retroactively to CBER the corresponding product deviation reports concerning the missed stability time points and product complaints.

Facility and Equipment System, item 2:

Your response indicates that you will revise SOP A004357, "Certification of HEPA Filtered Equipment" to require an investigation be conducted to assess product impact when HEPA filters used in production do not meet specifications. Further, your response states that you are confident in the quality of the lots produced in the areas cited in the observation based on the continuous cleaning systems and ongoing successful environmental monitoring results. We recommend that you perform a retrospective product impact assessment for lots produced using the failed HEPA filters cited in the observation.

Laboratory Controls System, item 6:

We acknowledge that in your response [redacted] reduction in stability testing. For future changes like those, however, we would expect you to file a prior-approval supplement under 21 CFR 601.12(b), given the substantial potential of such change to have an adverse effect on the potency of the product.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as

management to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, and applicable federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in FDA initiating regulatory action without further notice. Such action may include license suspension and/or revocation, seizure, and/or injunction.

Please notify us in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, ORA/OE/Division of Compliance Management and Operations, HFC-210, 15800 Crabbs Branch Way, Rockville, MD 20855. If you have any questions regarding this letter, please contact Jacqueline Little, Ph.D., Team Biologics Compliance, Division of Compliance Management and Operations, at (240) 632-6850.

Sincerely,

David K. Elder
Director
Office of Enforcement

cc: Damian Braga
President, U.S.
Sanofi Pasteur, Inc.
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Swiftwater, Pennsylvania 18370