U.S. Department of Health & Human Services

U.S. Food and Drug Administration



# Inspections, Compliance, Enforcement, and Criminal Investigations

## Sanofi-Aventis U.S. LLC

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054
Telephone (973) 331.4900

January 28, 2011

**WARNING LETTER**

**CERTIFIED MAIL**
**RETURN RECEIPT REQUESTED**

Gregory Irace
President and Chief Executive Officer (CEO)
Sanofi-Aventis US LLC
55 Corporate Drive
Bridgewater, New Jersey 08807

**11-NWJ-06**

Dear Mr. Irace:

The Food and Drug Administration (FDA or "Agency") inspected Sanofi-Aventis (Sanofi) pharmaceutical facility located at the address above from April 16, 2010 through May 13, 2010. The inspection focused on Sanofi's compliance with Postmarketing Adverse Drug Experience (PADE) reporting requirements. FDA's inspection found that your firm failed to comply with the postmarketing reporting requirements under 21 U.S.C. § 355(k) [Section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act)] and its corresponding regulations in Title 21 of the Code of Federal Regulations (21 C.F.R.) Section 314.80 and 314.81. Such failure to comply with Section 505(k) of the Act and its corresponding regulations is a prohibited act under Section 301(e) of the Act [21 U.S.C. § 331(e)]. Therefore, FDA concludes that Sanof has engaged in prohibited acts in violation of Section 301(e) of the Act.

Sanofi's deviations from FDA's reporting requirements observed during the inspection include, but are not limited to, the following: inadequate written procedures for the surveillance, receipt, evaluation, and reporting of adverse events as required by 21 CFR 314.80(b), failure to submit serious and unexpected adverse drug experience (ADE) reports within 1 calendar days to FDA under 21 CFR 314.80, and failure to include all postmarketing studies in the Annual Report to FDA under 21 CFR 314. 81.

We acknowledge receipt of your June 3, 2010, July 28, 2010 and October 27, 2010 written responses to the FDA-483 Inspectional Observations issued to your firm on May 13, 2010. We have determined that your response and promised corrective actions are inadequate to address the deficiencies identified.

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

1. **Failure to review, evaluate, and submit adverse drug experience (ADE) reports that are both serious and unexpected to FDA within 15 calendar days of initial receipt of the information as required by 21 CFR 314.80(c)(1)(i). For example, approximately 185 initial 15-day reports were submitted late for the time period of January 1, 2009 to March 31, 2010. The following are examples of initial 15-day reports that were submitted late to FDA.**

| Product | Mfr. Control No. | Date Received By Mfr. | Date Sent to FDA | Days Late |
|---|---|---|---|---|
| Glyburide | 200916879GDDC | 1/18/2007 | 7/17/2009 | 896 |
| Glibenclamide | 200916952GDDC | 4/3/2007 | 7/20/2009 | 824 |
| Glibenclamide | 200919278GDDC | 5/25/2007 | 8/27/2009 | 810 |
| Furosemide | 200911209EU | 2/4/2008 | 3/17/2009 | 392 |
| Eligard | A03200803546 | 9/8/2008 | 2/4/2009 | 134 |
| Allegra D | 200914109US | 2/20/2009 | 5/15/2009 | 69 |
| Apidra | 200918792GDDC | 6/10/2009 | 8/19/2009 | 55 |
| Multaq | A03200905040 | 11/05/2009 | 01/22/2010 | 63 |
| Multaq | D01200903859 | 9/15/2009 | 1/20/2010 | 112 |
| Multaq | A03200905053 | 10/28/2009 | 1/15/2010 | 64 |
| Amaryl | 2009SA011907 | 11/24/2009 | 1/8/2010 | 30 |
| Plaquenil | 2009SA006087 | 12/1/2009 | 2/3/2010 | 49 |
| Lovenox | 2009SA007588 | 12/4/2009 | 1/25/2010 | 37 |

2. **Failure to submit follow-up PADE reports to FDA within 15 calendar days of receipt of new informatio concerning post marketing 15 day reports as required by 21 CFR 314.80(c)(1)(ii). Specifically, approximately 127 follow-up reports were submitted late for the time period of January 1, 2009 to March 31, 2010. The following are examples of 15-day follow-up reports which were submitted late to FDA:**

| Product | Mfr. Control No. | Date Received By Mfr. | Date Sent to FDA | Days Late |
|---|---|---|---|---|
| Furosemide | 200910549FR | 1/15/2009 | 6/30/2009 | 151 |
| Ambien | A03200902916 | 7/10/2009 | 2/24/2010 | 214 |
| Lantus | 200917792US | 10/23/2009 | 3/2/2010 | 115 |
| Lantus | 200915406US | 10/28/2009 | 3/2/2010 | 110 |
| Lovenox | 200812498US | 4/18/2008 | 12/21/2009 | 597 |

Sanofi's responses to the violations described in numbered paragraphs 1 and 2 above state that Sanofi has committed efforts to ensure FDA compliance through improvements in infrastructure, training and internal processes However, your corrective action plan does not adequately address procedural deficiencies critical to preventing late submission of 15-day alert and follow-up reports to FDA. For example, your standard operating procedures (SOPs) for adverse drug experience (ADEs) US PV-002 v04 *Handling Unsolicited Individual Case Safety Reports for registered/Marketed Products in the United States* dated April 5, 2010, fails to provide written adverse drug experience definitions required to assess and evaluate adverse drug experiences for the submission of individual cas safety reports including 15-day alert reports. Also, the procedure lacks clear and concise work instructions for employees to promptly investigate and follow-up on reports not containing the minimum criteria (*i.e.*, an identifiable patient, and identifiable reporter, a suspect drug, and a serious, unexpected adverse experience) for submission to FDA.

The "Adverse Event Reporting Form," used by your call center contractors for the receipt of adverse drug experience reports, fails to correctly identify the adverse outcomes required to determine the seriousness of an adverse drug experience. Failure to correctly identify the outcomes of any serious adverse drug experience could lead to inaccurate data entry into your call center database, **(b)(4)**, and on the MedWatch 3500A Form (Box 2). Indeed, it appears deficiencies in written procedures such as these may have contributed to the late reporting and non-reporting of 15-day reports that are identified in this warning letter. Yet, in your written responses, you also failed to identify all of the causes of late reporting. Your should conduct a thorough root-cause analysis of your reporting systems and procedures in order to identify all potential deficiencies which led to the reporting violations and amend your procedures and implement any necessary changes accordingly to ensure that the violations are not repeated.

In addition, we remain concerned that your **(b)(4)** adverse drug experience reporting system has not been fully validated, and may have resulted in inaccurate assessment and untimely submission of 15-day alerts. The current application was released into production on November 9, 2009 using an Interim Validation report (IVR) that is still not final. Critical issues (deviations) identified in your interim validation report during the inspection included the following, but is not limited to: lack of training for your **(b)(4)**support team, incomplete SOPs and Work Instructions, and inaccurate data migration of legacy adverse experience cases from your previous adverse drug experience database, **(b)(4)**. Currently, your **(b)(4)** system does not display accurate clock dates on MedWatch forms for cases which were initially entered in **(b)(4)** and later entered into **(b)(4)** due to the receipt of additional information (follow-up) for the same cases. MedWatch forms printed out from **(b)(4)** for these migrated cases are documented as initial 15-day reports, instead of follow-up reports. Also, the report date in Block B5 of the MedWatc form is the print date, not the actual date of submission. Shortcomings such as these affect the accuracy, reliability,

consistency of the system and your firm's ability to discern invalid or altered electronic records or make timely submissions to FDA as required. Your response states that you have hired a consultant, **(b)(4)**, to assist with resolving these computer system issues. To date, however, we have not received any response from you indicating that you or your contractor has evaluated or determines the root cause of these issues, or taken steps to resolve them or re-validate your computer system to correct deficiencies.

Please provide the status of your corrective action regarding any revised written procedures related to ADE reportin and updated computer system validation in your response to this letter.

3. **Failure to include all other postmarketing studies in Annual Reports as required by 21 CFR 314.81(b)(2)(viii). Specifically, NDA Annual Reports submitted to FDA for marketed drug products were incomplete and did not include all other postmarketing studies for studies such as:**

   a. Apidra (study APIDR_L_02012)
   b. Eloxatin (studies OXALI_L_00737 and OXALI_L_00869)
   c. Ketek (study TELIT_L_05072)

   **In addition, your firm did not include summaries of completed, unpublished clinical trials conducted by, or otherwise obtained by, the applicant as required by 21 CFR 314.81(b)(2)(vi)(b). Examples o completed clinical trials reported late include:**

   a. Ambien (zolipidem tartate)
   b. Apidra (insulin glulisine injection)
   c. Eloxatin (oxaliplatin injection)

Information obtained from FDA's inspection revealed that your firm failed to report the status of the studies associated with the marketed drugs mentioned above. Your firm stated during the inspection, that in March 2008, Sanofi made the decision to start including foreign clinical trials that were conducted by, or on behalf of your firm in the company's database for NDA Annual Reports. Yet, information obtained during the inspection, as described above, indicates that your firm has still failed to report on the status of certain foreign postmarketing clinical trials or studies. Moreover, we are troubled that your firm did not disclose to FDA, until the 2010 inspection, that it did not report on foreign trial or studies prior to 2008.

During the inspection, a review of your **(b)(4)** noted that it instructed your employees or designee that studies filed to a Sanofi-Aventis IND should not be included in the NDA Annual Reports. FDA regulations, 21 CFR 314.81(b)(2), require that all IND and NDA clinical trial studies associated with an approved drug be reported in the NDA Annual Reports.

We have reviewed your corrective and preventive action plan and the revised NDA Annual Reports, **(b)(4)**, effective date June 7, 2010, and have determined that they are still inadequate. The deficiencies noted in the procedure include: lack of definition of terms used in the reporting postmarketing studies (i.e., postmarketing study, postmarketing study requirement, and postmarketing study commitment); the procedure eliminates trials and studies that should be included in the "*Status of other postmarketing studies"* section of the NDA Annual Report; **(b)(4)** suggests that only the status of "ongoing" clinical trials that were conducted should be included under **(b)(4)**. The procedure should include current status (i.e., cancelled, delayed, or terminated) of all postmarketing studies since the last annual report. Your response only addresses studies identified since 2008. Your response to the Warning Letter should include a retrospective analysis of all clinical studies that were conducted by, or on behalf of your firm for all NDA products held by Sanofi to ensure that they have been properly identified and reported, and describe the specific steps you have taken to prevent future violations.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. It is your responsibility to ensure compliance with all requirements of federal law and FDA regulations. You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including injunction. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. FDA may re-inspect to verify corrective actions have been completed.

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.

We also recommend that you contact, Andrew Ciaccia at Andrew.Ciaccia@fda.hhs.gov, or 973-331-4904, within five day of receipt of this letter. Your reply should be sent to the following address: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054.

Sincerely,
/S/
Diana Amador-Toro
District Director
New Jersey District

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**Links on this page:**