STI Pharma LLC 11/21/16

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WARNING LETTER
17-PHI-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

November 21, 2016

Anup K. Dam
Chairman
STI Pharma LLC
2080 Cabot Blvd W, Suite 205
Langhorne, PA 19047

Dear Mr. Dam:

The United States Food and Drug Administration (FDA) conducted an inspection of your firm, STI Pharma LLC, located at 2080 Cabot Boulevard West, Suite 205, Langhorne, PA 19047, between July 11 and July 21, 2016. The inspection revealed serious violations of Postmarketing Adverse Drug Experience (PADE) reporting requirements under section 505(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(k)) and Title 21, Code of

Federal Regulations (21 CFR) 314.80 and 314.98. Failure to comply with section 505(k) is a prohibited act under section 301(e) of the Act (21 U.S.C. 331(e)).

At the conclusion of the inspection on July 21, 2016, investigators Matthew R. Noonan, David A. Oluwo, and Namita Kothary, representing FDA, presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your written response dated August 8, 2016, to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the evidence submitted with that report, and your firm's written response, we conclude that your firm did not adhere to the applicable statutory requirements and FDA regulations for PADE reporting. Specific violations include, but are not limited to, the following:

1. Failure to develop adequate written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences (ADEs) as required by 21 CFR 314.80(b) and 21 CFR 314.98(a).

As an application holder, your firm is required to develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences (ADEs) to FDA. Your firm does not have any written procedures that describe how you, and your contractor acting on your behalf, comply with PADE regulations. Specifically:

a. Your firm does not have any written procedures that describe the surveillance and receipt of ADE information from any source, including how you monitor, receive, identify, triage, process, reconcile, and document ADEs. As the application holder and as a firm listed on product labels, you may receive ADE information directly, despite any agreements that you may have with a contractor.

1. Our inspection determined that you failed to document, or incorrectly documented, initial received dates for 70 percent of your ADE cases (16 of 23 cases). During the inspection, you stated that you do not document the receipt of incoming calls, inquiries, or postal mail before providing the information to your contractor. Without this information, you are unable to determine the actual initial receipt date of the ADE for regulatory purposes, or to reconcile the ADE information that you provided to your contractor.

As the application holder and recipient of ADE information, you are responsible for ensuring that the initial received dates for ADEs are appropriately determined and documented.

2. Our inspection determined that you failed to capture reported ADE information accurately and completely before transferring it to your contractor. For example, a consumer reported that he experienced dry mouth while "being treated for topical 'red spots' on his scalp" with your firm's product, and that his other medications included "an inhaler, but [he] did not know the drug." Your firm subsequently made various assertions (that the "red spots" were associated with aging, and that the inhaler was assumed to be an anti-inflammatory steroid that caused the dry mouth) in the report before you relayed it to your contractor. Consequently, your contractor considered these assertions to be factual when evaluating the case, and ultimately attributed the reported ADE to a theoretical concomitant medication. In another case, your firm documented a call from a consumer reporting retinal detachment and chest pains with ethambutol. This ADE was not included in your safety database, and you were unable to provide evidence that this call was evaluated or otherwise handled as an ADE.

As the application holder, you are responsible for ensuring that ADE information reported to you, or to your contactor acting on your behalf, is captured accurately and completely for subsequent evaluation and reporting to the FDA.

In your August 8, 2016, written response, you provided newly created draft SOPs (DS-000, "Safety and Pharmacovigilance Policies"; DS-001, "Processing AEs and SAEs"; DS-002, "Complaint Processing"; DS-006, "Quality Oversight of Safety"; and DS-007, "Training for Safety and Pharmacovigilance") related to the receipt of

ADEs. However, we note that these are draft SOPs, and that you did not (1) provide a target completion or implementation plan, or (2) describe how you will monitor and review your actions to ensure effectiveness and prevent recurrence. Additionally, your written response failed to describe any corrective actions that your firm plans to take. For example, you did not identify and assess the root causes of ADEs containing inaccurate or incomplete information in your safety database, to determine if you needed to update the cases and submit accurate, complete information to FDA.

b. You do not have any written procedures that describe how you evaluate ADEs against the U.S. package insert for seriousness, expectedness, relatedness (when applicable), and reportability to FDA. Your firm's agreement with your contractor states that they provide medical review and assessment on your behalf. However, neither you nor your contractor has any written procedures that define how to evaluate ADEs for seriousness, expectedness, and relatedness.

1. Your contractor's safety physician inappropriately determined expectedness of a consumer-reported serious, spontaneous postmarketing ADE described as "pure red cell aplasia while taking [e]thambutol." The safety physician considered only the Investigator's Brochure when determining expectedness of this "pure red cell aplasia." According to 21 CFR 314.80(a), expectedness for postmarketing ADEs is based on current product labeling only. Further, the safety physician stated that for the same case, he assessed this "pure red cell aplasia" as unrelated, and therefore he did not report the ADE to FDA as a 15-day Alert Report. According to 21 CFR 314.80(e), relatedness affects reportability for postmarketing ADEs from studies only.

2. Your firm inappropriately determined relatedness of an "ischemic insult" when it was reported to you from a study indicating that the suspect drug was "dexamethasone ([manufacturer] or formulation not specified)." You evaluated this serious, unexpected study-based ADE as unrelated, because you considered the ADE unlikely to be caused by your firm's product; however, you were unable to provide information justifying how you determined this. Therefore, this case was not correctly evaluated for causality (that is, asking if there is a reasonable possibility that the drug caused the ADE) or considered for submission to FDA as a 15-day Alert Report.

Additionally, your firm does not have any written procedures that describe how you evaluate ADEs, including ADEs you receive from scientific and medical literature,for reportability to FDA as 15-day Alert Reports or as nonexpedited Individual Case Safety Reports (ICSRs). As described in the case of the "pure red cell aplasia" above, you inappropriately determined that a serious, unexpected, spontaneous ADE was not reportable to FDA as a 15-day Alert Report because you assessed the ADE as unrelated. Furthermore, your most recent ethambutol Periodic Adverse Drug Event Report included seven literature articles.
However, you were unable to provide evidence that these articles were evaluated to determine if they contained reportable ADEs.

Serious and unexpected ADEs found in scientific and medical journals as case reports or as the results of a formal clinical trial are reportable to FDA as expedited 15-day Alert Reports (21 CFR 314.80(d)). Nonexpedited ADEs from scientific and medical journals are not reportable to FDA (21 CFR 314.80(c)(2)(iii)).

In your August 8, 2016, written response, you provided newly created draft SOPs (DS-001, "Processing AEs and SAEs"; DS-002, "Complaint Processing"; and DS-003, "Literature Searches") related to the evaluation of ADEs. As stated above, you did not (1) provide a target completion or implementation plan, (2) describe how you will monitor and review your actions to ensure effectiveness and prevent recurrence, or (3) describe any planned corrective actions. Your written response also fails to describe whether you conducted, or intend to conduct, a retrospective evaluation of ADEs to determine if they were correctly evaluated for seriousness, expectedness, and relatedness. For example, the Form FDA 483 includes at least two ADEs (described above) that you did not evaluate according to the 21 CFR 314.80 definitions of serious, expected, and related, and therefore you did not consider them for submission as 15-day Alert Reports.

As a result of not having written procedures for the evaluation and subsequent reporting of ADEs to FDA, our inspection determined that you failed to appropriately evaluate ADEs. Consequently, you failed to report ADE information to FDA in a timely, complete, and accurate manner.

c. You do not have any written procedures that describe how you report 15-day Alert Reports and nonexpedited ICSRs to FDA in the correct format and on time. Your firm's agreement with your contractor states that they provide regulatory submission services on your behalf. However, neither you nor your contractor has any written procedures that define how you report ICSRs to FDA, or what time frames you follow for their submission to FDA.

As of September 8, 2015, FDA requires all postmarketing drug safety reports to be submitted in an electronic format that FDA can receive, process, and archive, in accordance with the final rule "Postmarketing Safety Reports for Human Drug and Biological Products: Electronic Submission Requirements" (79 FR 33072 and 80 FR 30151). Neither you nor your contractor has an account to submit ICSRs electronically to FDA. Because you did not have written procedures for reporting postmarketing safety information to FDA, you failed to submit all nonexpedited ICSRs sent after September 8, 2015, in an approved electronic format (XML via either the Electronic Submission Gateway or the Safety Reporting Portal).

In your August 8, 2016, written response, you provided newly created draft SOPs (DS-001, "Processing AEs and SAEs"; and DS-004, "Aggregate Reporting") related to the reporting of ADEs. As stated above, you did not (1) provide a target completion or implementation plan, (2) describe how you will monitor and review your actions to ensure effectiveness and prevent recurrence, or (3) describe corrective actions. Furthermore, your written response fails to address whether you determined if all serious, unexpected, spontaneous ADEs and all serious, unexpected, possibly related study ADEs were appropriately submitted as 15-day Alert Reports to FDA in an approved electronic format. For example, you did not resubmit ICSRs sent to FDA after September 8, 2015, in an approved electronic format. You stated that you have an account for submitting ICSRs through the Electronic Submission Gateway and may also use the Safety Reporting Portal. However, as of November 7, 2016, FDA does not have a record showing that you, or your contractor acting on your behalf, has active accounts for reporting ICSRs to the FDA Adverse Experience Reporting System (FAERS) via the Electronic Submission Gateway or the Safety Reporting Portal.

Given your reliance on contractors to carry out PADE activities, we are concerned about your firm's fundamental understanding and implementation of PADE regulations, including how they relate to your use of contractors. As the application holder of two New Drug Applications and five Abbreviated New Drug Applications, you are ultimately responsible for ensuring compliance with the Act and the PADE reporting regulations. The lack of written procedures and the examples of failure to report safety information to FDA in a complete, accurate, and timely manner, raise concerns about your firm's ability to assess the safety of your drug products.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your firm. 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 correct these violations promptly may result in legal action, including injunction, without further notice. Federal agencies are advised concerning the issuance of all Warning Letters about drugs and devices, so they may take this information into account when awarding contracts. FDA may re-inspect your firm to verify that you have completed corrective actions.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at **drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov)**, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and