Inspections, Compliance, Enforcement, and Criminal Investigations

Hill Dermaceuticals, Inc.

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Food and Drug Administration
555 Winderley Pl., Ste: 200
Maitland, FL 32751

VIA FEDERAL EXPRESS

WARNING LETTER

FLA 09-13

April 27, 2009

Jerry S. Roth, President
Hill Dermaceuticals, Inc.
2650 Mellonville Avenue
Sanford, Florida 32773-9311

Dear Mr. Roth:

On September 15, 16, 17, 18, 22, 23, and 29, 2008, the United States Food and Drug Administration (FDA) conducted an inspection of Hill Dermaceuticals, Inc., your prescription dermatological drug manufacturing facility located at 2650 Mellonville Avenue, Sanford, Florida 32773-9311. The inspection revealed significant deviations from· the Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21 Code of Federal Regulations

Parts 210 and 211.

These CGMP deviations cause your prescription drugs 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 procedures or controls used for, the manufacture, processing, packing, and holding of drug products do not conform with the CGMP regulations.

A Form FDA 483, Notice of Inspectional Observations, was issued, and discussed with you and your staff at the close of the inspection on September 29, 2008. The significant violations observed during the inspection include, but are not limited to the following:

1. Your firm failed to follow its procedures for the preparation of master production and control records as required by 21 CFR § 211.186(a). Your firm's "Batch Record Recording Procedure" states that only blue or black ink can be used to record information in the Batch Record Book. However, for at least six lots, the Master Packaging Instruction sections of the batch records contained reconciliation and disposition data written in pencil, erased, and then rewritten in ink. In addition, some data that had been rewritten in ink was different from the original data that had been written in pencil. You indicated in your response that the Quality Control Unit (QCU) member associated with this practice is no longer working for the firm; however, your proposed corrective action did not include a review of other production and control records to ensure that this practice did not occur in other instances, particularly where the QCU inspector could have advised production employees to use pencil.

2. You did not thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch had been already distributed, as required by 21 CFR § 211.192. For example, your firm's contract testing laboratory **(b)(4)** reported out-of-specification (OOS) assay results for Tolak Cream, bulk lot number 08F060 and packaged lot number F080115. The laboratory also reported OOS assay results for Tolak Cream, bulk lot number 08F061, which is documented as a 500-kg batch (a typical commercial lot size for this type of product). The contract laboratory's investigation confirmed the OOS assay results. However, your firm re-submitted samples for additional testing without conducting an investigation into the root cause of the OOS assay results and invalidating the original assay results.

You indicated in your correspondence dated February 16, 2009, that these lots were not intended for distribution and were manufactured solely for the purpose

of gathering manufacturing process data, but you nonetheless determined that the test results for these research lots failed established specifications. Your Deviation Management and CAPA SOP submitted with your response dated October 31, 2008, appear to address root cause investigation in section 5.6. However, the SOP does not include specific steps to conduct an investigation of an OOS result obtained from analytical testing or specific instructions when results can be invalidated or the material re-sampled. In addition, you did not conduct an investigation into nor did you review the testing data from other potentially affected lots of Tolak, Tri-Luma, or any other of your firm's products to assure that assay results were properly invalidated for those lots. Your response does not include the date of implementation for the revised procedure or the training of personnel.

3. Your laboratory records did not include a record of all calculations performed in connection with laboratory tests as required by 21 CFR § 211.194(a)(5). For example, laboratory notebook #7, page 49, documents the assay results, but not the calculations performed in Test number DSFS D-13 and Test number TG 521 for the analysis of **(b)(4)**, lot #HI7908. The notebook does not document reference to the spreadsheet calculation used to generate the results. In addition, the assay results generated by the spreadsheet were not verified for accuracy. Your response dated February 16, 2009, states that you have established procedures to ensure that calculations of method validation studies are recorded. The Records Management SOP, Section 5.7.4.7, states that the procedures shall define what and how data is to be recorded in respective logbooks. However, this SOP omits instructions to include in the notebook the reference to the spreadsheet calculation used to generate the results, as well as the raw data and calculations. In addition, you continued to release products based on assay results generated by the spreadsheet that have not been verified for accuracy.

4. You have not established and documented the accuracy, sensitivity, specificity, and reproducibility of test methods as required by 21 CFR § 211.165 (e). For example, Your analytical methods for the analysis of the active pharmaceutical ingredient (API), as well as the preservatives **(b)(4)** and **(b)(4)**, in your Tri-Luma Cream drug product have not been verified. Your firm has not verified that the preservatives and API test methods using the **(b)(4)** System is adequate for its intended use. The **(b)(4)** system is different from the previously used Perkin-Elmer high Performance Liquid Chromatographic (HPLC) system in make, model, and column. In addition, your analysis of parabens in Tri-Hy-Ret (Tri-Luma) for Tretinoin in finished product does not identify the maximum adjustment in mobile phase to obtain a suitable resolution between peaks. Your response dated February 16, 2009, states that method validation is completed for some products; however, it does no specify the equipment that was used to perform the validation.

We have received your correspondence dated September 19, 2008, in which you stated that an outside audit of your firm has been scheduled, additional experienced staff will be hired, and test methods and processes for NDA **(b)(4)** will be revalidated.

We have also received your "interim response" to the FDA 483 dated October 6, 2008, regarding your firm's hiring of **(b)(4)** Consulting to assist your firm in preparing a corrective action plan, your search for additional personnel, and your intention to revalidate the **(b)(4)** analysis method. Furthermore, we have received your letter dated October 13, 2008, in which you notified us that your firm had recently hired a Director of Quality Unit.

We acknowledge your commitments to implement the corrective actions described in your response dated October 31, 2008, to include corrections to procedures pertaining to your quality control unit, manufacturing practices, analytical methods, documentation of manufacturing and laboratory equipment calibration.

In addition, we have also received your letter dated February 16, 2009, in which you provided a progress report to your previously proposed corrective actions. You indicated that you have implemented procedures, established written calibration programs, and are in the process of re-qualifying instruments. However, the procedures were not included in your response and you did not provide an assessment of the products on the market that were tested using improperly validated methods and unqualified equipment.

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 or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations. Please be advised that FDA is currently evaluating information about your chemistry, manufacturing, and controls (CMC) that you have submitted in new drug applications. You will be informed of our conclusions regarding this CMC information by separate correspondence.

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, without limitation, seizure and injunction. Other federal agencies

may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. 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 being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason tor the delay and the time within which you will complete the correction. If you no longer manufacture or market any of your drug products, your response should so indicate, including the reasons and the date on which, you ceased production.

Please send your response to the U.S. Food and Drug Administration, Attention: Matthew B. Thomaston, Compliance Officer, 555 Winderley Place, Suite 200, Maitland, FL 32751. If you have questions regarding any issue in this letter, please contact Mr. Thomaston at (407) 475-4728.

Sincerely,

/S/
Emma R. Singleton
Director, Florida District