Inspections, Compliance, Enforcement, and Criminal Investigations

Sovereign Pharmaceuticals, LLC 1/29/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Dallas District
4040 North Central
Expressway
Dallas, Texas 75204-3128

January 29, 2013

Ref: 2013-DAL-WL-28

WARNING LETTER

Sent via UPS Overnight

David Brown, Co-Owner
Ralph Brown, Co-Owner
Sovereign Pharmaceuticals, LLC
7509 Flagstone St.
Fort Worth, TX 76118

Dear Messrs. Brown:

During our January 18 - February 2, 2012, inspection of your pharmaceutical contract manufacturing facility located at 7590 Sand St., Fort Worth, TX, our investigators and our review of documents collected during the inspection identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products 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 facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

In addition, this inspection also revealed that your firm is marketing unapproved drugs in violation of Sections 301(d) and 505(a) of the Act (21 U.S.C. §§ 331(d) and 355(a)) and/or misbranded drugs under Sections 502(f)(2) or 502(a) of the Act.

We have conducted a detailed review of your firm's response and note that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated July 12, 2012.

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

CGMP Violations

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 CFR § 211.192]. For example:

> a. Your investigation of the content uniformity failure of Symax SR, lot YJB10, is inadequate. Your investigation concluded that the failure was a result of the blend mixing for **(b)(4)** instead of the required **(b)(4)**. However, you failed to evaluate your completed process validation(s) to determine whether your mixing process (including

your mixing time which appears to be a critical parameter) is adequately controlled. In addition, you have no assurance that your blends are homogenous because you do not conduct in-process testing.

b. Your investigation of the out of specification percent yield for Liquibid PD-R Tablets, lot YPE11 is inadequate. According to your investigation, the low yield was due to your rejection of drug product contaminated with particulate matter. You stated that a malfunctioning mixer, **(b)(4)**, was the source of the particulate contamination. You failed to investigate the possible contamination of other lots of product manufactured using the same mixer and stated this was an isolated incident without any justification.

This is a repeat observation from the October 2004 inspection.

2. Your firm has not established written procedures to monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR § 211.110(a)]. For example:

a. You do not test in-process blend samples for adequacy of mixing to ensure uniformity and homogeneity for Acetaminophen and Hydrocodone Bitartrate Tablets.

b. You do not test in-process blend samples for adequacy of mixing to ensure uniformity and homogeneity for **(b)(4)** Tablets.

In your response, you state that the Office of Generic Drugs (OGD) did not require routine blend uniformity testing as a condition of approval of your ANDAs and therefore you eliminated the in-process blend uniformity testing. Your control strategy as described remains inadequate because in-process testing of the blend to demonstrate adequacy of mixing and homogeneity is a CGMP requirement.

Unapproved and/or Misbranded Drug Products

Your firm manufactures several drugs for over-the-counter use. For example, the products identified below, Certuss, Certuss-0, Trexbrom, Tekral, Rescon GG, Rescon, Rescon OM, and Liquibid D-R, are drugs within the meaning of Section 201(g)(1)(B) of the Act (21 U.S.C. § 321 (g)(1)(B)), because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and under section 201 (g)(1)(C) of the Act (21 U.S.C. § 321 (g)(1)(C)), because the products are intended to affect the structure or function of the body.

For the reasons described below, Certuss, Certuss-0, Trexbrom, Tekral, Rescon GG, Rescon, and Rescon OM fail to comply with the formulation and labeling requirements of the monograph regulations that set forth conditions of general recognition of safety and effectiveness for such products. Since we are not aware of any other evidence establishing such products are generally recognized as safe and effective, these products are new drugs within the meaning of Section 201 (p) of the Act (21 U.S.C. § 321 (p)) because they are not generally recognized as safe and effective for their labeled uses. As "new drugs," your products are subject to the new drug provisions of section 505 of the Act, (21 U.S.C. § 355) and absent an FDA approved application the products are unapproved new drugs. Under Sections 301 (d) and 505(a) of the Act (21 U.S.C. §§ 331 (d) and 355(a)), a new drug may not be introduced into or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for it.

Additionally, as described below in the respective product sections the product Rescon GG is also misbranded under 502(f)(2) of the Act because the product's labeling fails to bear the required warnings for expectorant drug products. Lastly, the product Liquibid D-R is misbranded under 502(a) of the Act because the principal display panel describes the product as a "Decongestant/Moisturizer" when such is not the case.

Certuss, Certuss-D, and Trexbrom

Certuss, Certuss-D, and Trexbrom contain the active ingredient chlophedianol, which is an acceptable antitussive active ingredient. However, chlophedianol cannot be combined with the particular active ingredients phenylephrine (in the case of Trexbrom) or guaifenesin (in the cases of Certuss and Certuss-D) because there is no way to write adequate directions for use that would meet the dosing direction and dosage limit requirements for each individual active ingredient (21 CFR 341.40). For example, the monograph states phenylephrine and guaifenesin are to be dosed every 4 hours (21 CFR 341.80(d)(1) and 21 CFR 341.78(d), respectively) and chlophedianol is to be dosed every 6 to 8 hours (21 CFR 341.74 (d)(1)). Therefore, if chlophedianol is used in combination with either phenylephrine or guaifenesin, there is no way to write directions for use with a dosing interval that works for each of these active ingredients.

Tekral

This product contains the active ingredients diphenhydramine HCI 50mg and pseudoephedrine HCI 60mg and the directions for use section of the labeling states this product is to be used for adults and children 12 years of age and over every 4 to 6 hours. The description of the drug product on the principal display panel states that this product is an antihistamine/antitussive/nasal decongestant and the active ingredient section of the drug facts labeling describes diphenhydramine HCI as an anithistamine/antitussive. Diphenhydramine HCI 50mg is an acceptable antihistamine active ingredient when given every 4 to 6 hours (21 CFR 341.72(d)(7)). However, when diphenhydramine is used as an antitussive it should be dosed at 25mg every 4 hours (21 CFR 341.74(d)(1)(v)). Since Tekral contains diphenhydramine 50mg to be used every 4 to 6 hours the formulation/directions for use of this product do not meet requirements described in the final cough/cold monograph for antitussive drug products.

Rescon GG

This product contains a pictorial of the ear along with the claim Eustachian tube decongestant that appears on the principal display panel. The Uses section of the drug facts labeling also states "relieves congestion of sinuses, eustachian tubes .... " Eustachian tube decongestant is not acceptable indication under the final cough/cold monograph. The product labeling is also missing important Warning information. For example, the labeling does not state the following warning required for expectorant drug products, "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or where cough is accompanied by excessive phlegm (mucus) unless directed by a doctor," see 21 CFR 341.78(c)(2).

Rescon and Rescon OM

Rescon and Rescon OM contain the active ingredient dextromethorphan hydrobromide 20mg and dextromethorphan 10mg respectively. The labeled directions for use for both products state that they are to be used every 4 to 6 hours. For adults and children 12 years of age and over, dextromethorphan hydrobromide 10mg to 20mg is an acceptable antitussive active ingredient when given every 4 hours or 30mg every 6 to 8 hours (21 CFR 341.74(d)(1)(iii)). Since these products are to be used every 4 to 6 hours the amount of dextromethorpan hydrobromide is acceptable when used every 4 hours but insufficient when used every 6 hours. Therefore, the formulation/directions for use for these products do not meet the requirements described in the final cough/cold monograph for antitussive drug products.

Liquibid D-R

This product contains the active ingredients guaifenesin 400mg and phenylephrine HCI 10mg. The drug facts panel appropriately describes these ingredients as an expectorant for guaifenesin and a nasal decongestant for phenylephrine. However, the principal display panel misleadingly identifies this product as a decongestant and moisturizer when the product's stated purpose is as a decongestant and expectorant.

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 drug applications listing your facility, 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 and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections.

Additionally, if you no longer manufacture or distribute the drug product(s) at issue, provide the date(s) and reason(s) you ceased production.

Your response should be sent to the Food and Drug Administration, Dallas District Office, 4040 N. Central Expressway, Suite 300, Dallas, TX 75204, to the attention of Elvia J. Cervantes, Compliance Officer. Should you have any questions concerning this letter, you can contact Elvia Cervantes at (214) 253-5236.

Sincerely,
/S/
Reynaldo R. Rodriguez, Jr.
Dallas District Director

Miles B. Davis, R.Ph., Ph.D., President and CEO
Sovereign Pharmaceuticals, Ltd.
7590 Sand St.
Fort Worth, TX 76118-6977

cc: David E. Brown, Chief Executive Officer
Capellon Pharmaceuticals, LTD
7509 Flagstone St.
Fort Worth, Texas 76118

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