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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Los Angeles District

19701 Fairchild
Irvine, California 92612-2506
Telephone (949) 608-2900

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

December 18, 2007

W/L 04-08

James L. McDaniel, President
U.S. Apothecary Labs
11100 Greenstone Ave.
Santa Fe Springs, CA 90670

Dear Mr. McDaniel:

On July 18 through July 24, 2007, the Food and Drug Administration (FDA) conducted an inspection of your manufacturing facility located at 11100 Greenstone Ave., Santa Fe Springs, CA. The inspection was reopened on August 9, 2007 for the purpose of collecting a sample. The inspection revealed significant deviations from Current Good Manufacturing Practice (CGMP) regulations in 21 Code of Federal Regulations (CFR), Parts 210 and 211, in the manufacture of the drug product, RadBlock. These CGMP deviations were listed on an Inspectional Observations (FDA 483) form issued to you on July 24, at the initial close of the inspection.

These CGMP deviations cause your drug product to be adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B) (Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act)) in that the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding fail to conform to, or are not operated or administered in conformity with, CGMP regulations [21 CFR 210 and 211]. Section 301(a) of the Act [21 U.S.C. § 331(a)] prohibits the introduction or delivery for introduction into interstate commerce of any drug that is adulterated.

Furthermore, RadBlock is an unapproved new drug within the meaning of Section 201(p) of the Act [21 U.S.C. § 321(p)] and may not be legally marketed in the United States without an approved NDA under Section 505(a) of the Act [21 U.S.C. § 355(a)]. Although Section 802 of the Act [21 U.S.C. § 382] permits the export of certain unapproved new drugs if specific requirements are met, Section 802(f)(1) of the Act [21 U.S.C. § 382(f)(1)] prohibits exportation of drugs that are not manufactured, processed, packaged, or held in substantial conformity with current good manufacturing practices. Your exportation of RadBlock is not in compliance with Section 802 of the Act [21 U.S.C. § 382], since it is not in substantial compliance with current good manufacturing practices, as delineated in the CGMP deficiencies below.

We acknowledge receipt of your two letters both dated July 25, 2007, responding to the deficiencies listed on the FDA Form 483. Examples of the deficiencies observed along with

comments regarding your FDA Form 483 response are as follows:

1. Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity [21 CFR § 211.160(b)]. Specifically, methods of analysis for Potassium Iodide tablets, USP are not scientifically sound, or validated. For example:

    a. Your firm performs a "modified dissolution" test on the Potassium Iodide Tablets, which is significantly different from the USP dissolution test. The "modified dissolution" test is not scientifically sound or validated.
    For example:

        i. Your firm's method directs to dissolve [redacted] tablets in [redacted] with an [redacted] amount of water and to stir for [redacted] on top of a hot plate; the USP method requires the use of a specific dissolution equipment (apparatus 2/paddles) and to dissolve one tablet in each of the six dissolution vessels.
        ii. Your firm does not perform an adequate calculation of the amount of dissolved active ingredient as a percentage of the label content of the dosage unit. Instead, the firm weighs the undissolved material to calculate the amount of active dissolved. No standard solution is used to measure the amount of active dissolved.
        iii. The parameters (i.e. volume, temperature, speed of mixing) for the firm's test are not defined in a written method.
        iv. The method has not been proven to be adequate (validated) for its intended use.

    b. Your firm randomly uses results from either your in-house "modified dissolution" test on Potassium Iodide tablets or the USP dissolution test (performed by [redacted]) at stability test stations for lots on stability.

    c. The weight variation reported on the Certificate of Analysis (COA) for Potassium Iodide tablets (performed by [redacted]) states "weight variation meets USP requirements". The weight variation is not conducted. The test results only state a range of tablets.

    d. There is no defined number of Potassium Iodide tablets to be used for hardness testing.

    Your response lacks objective evidence that the "modified dissolution" test is adequate for its intended use and validated. Also, your response lacks an explanation for how your testing justifies the declaration that the tablets' "weight variation meets USP requirements". Weight variation is the method used to demonstrate uniformity of dosage units. The assay is used in the actual weight variation calculation. Your firm's test results only state "a range of tablet weights is reported".

2. Failure to establish written procedures for production and process control designed to assure that drug products have the identity, strength, quality and purity that they are represented to

possess. Written procedures are not drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the Quality Control Unit [21 CFR § 211.100(a)]. For example, the validation for the Potassium Iodide tablets (RadBlock) manufacturing process is inadequate in that there is no in-process blend uniformity analysis performed to show that the blending process is adequate. Also, there is no documentation to show that the tablet coating process, which is performed by [redacted], has been validated.

3. Failure to adequately investigate a batch that does not meet its specifications [21 CFR § 211.192]. For example, no adequate laboratory investigation was performed for lot 991331 assay failure at 60 months. Your firm's contract laboratory ([redacted] performed the test and reported an initial result of 110.1%. The contract laboratory conducted an investigation and determined the method was inadequate. Your firm was notified of the OOS result and the inadequacy of the method. However, your firm instructed the contract laboratory to conduct a series of steps to attempt to obtain a passing result (i.e. shaking, filter change, and recalculating the theoretical potency). The results were then averaged for a passing result. We note that your response does not explain why the contract laboratory was instructed to recalculate the results using a theoretical potency per tablet of [redacted] mg rather than the labeled potency of 65 mg. In addition, your response fails to address whether you evaluated the contract laboratory's findings that the test method was inadequate.

4. Buildings used in the manufacture, processing, packing or holding of drug products are not maintained in a clean and sanitary condition [21 CFR § 211.56(a)]. For example:

   a. Pallets of bags of clay raw material were observed stored against the wall in the warehouse. The bags were torn, some of the material was transferred to clear plastic bags which were also torn, and powder was observed throughout the warehouse. This clay raw material was received in the year 2000.
   b. There were several dirty and dusty drums observed in the warehouse, outside the door of the blending room.
   c. The blending room doors were observed open on several days, allowing dust to be blown and/or tracked throughout the drug manufacturing facility.
   d. The areas between the storage shelves in the warehouse were observed dusty. Also, there was a visible demarcation where the area in front of the pallets that was easily accessible had been swept, while the areas between the shelves remained visibly dusty.
   e. External painted surfaces with chipped paint were observed on equipment such as the blenders and tablet presses used to manufacture Potassium Iodide tablets.

5. Your firm's written stability testing program is inadequate [21 CFR § 211.166(a)]. Specifically, your Potassium Iodide Tablets stability test protocol lacks sample size, how many samples pulled at test intervals, and incomplete test data.

6. Batch production records prepared for each batch of drug product produced do not include complete information relating to the production and control of each batch [21 CFR § 211.188]. Specifically, white-out was observed on several batch record pages and equipment log book pages and there was no notation of who made the change, when, and why. Batch records are the

documented history of production activities associated with each lot. We believe use of white-out and the lack of notation regarding the particulars of what was changed do not provide accurate documentation of recorded data, prior to batch release.

Neither this letter nor the observations noted on the FDA Form 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facilities. It is your responsibility to ensure that all drug products manufactured and distributed by your firm comply with the Act and the regulations. You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

Federal agencies are advised of the issuance of all Warning Letters pertaining to drugs so that they may take this information into account when considering the award of contracts. In addition, any pending New Drug Applications, Abbreviated New Drug Applications, or export certificate requests submitted by your firm may not be approved until the above violations are corrected.

Please respond to this office in writing within fifteen (15) working days of receiving this letter. Your response should describe the specific actions, in addition to those already submitted, you will take, or have taken, to correct the violations described above and include an explanation of how each action being taken will prevent recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which corrections will be completed.

If you have any questions or need clarifications regarding this letter prior to your written response, you may contact John Stamp, Compliance Officer at telephone number (949) 608-4464.

Your written response should be directed to:

Pamela B. Schweikert
Director, Compliance Branch
U.S. Food and Drug Administration
19701 Fairchild
Irvine, California 92612

Sincerely,

Alonza E. Cruse, Director
Los Angeles District

cc: