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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Food and Drug Administration
New Orleans District
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Nashville, TN 37217-1003

Telephone: 615-366-7801
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February 1, 2008

WARNING LETTER NO. 2008-NOL-08

FEDERAL EXPRESS
OVERNIGHT DELIVERY

Thomas J. Young, Chief Executive Officer
Vintage Pharmaceuticals, LLC
120 Vintage Drive
Huntsville, Alabama 35811-8216

Dear Mr. Young:

During an inspection of your pharmaceutical manufacturing facility, located at 120 Vintage Drive, Huntsville, Alabama, on July 16 – 20, 23-25, and August 8, 2007, investigators from the United States Food and Drug Administration documented significant violations of the Current Good Manufacturing Practice (CGMP) regulations in Title 21, *Code of Federal Regulations*, Parts 210 and 211 (21 CFR 210 and 211). These violations cause your firm's 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 addition, this inspection also revealed your firm is marketing unapproved new drugs in violation of Sections 301(a) and (d) and 505(a) of the Act [21 U.S.C. 331(a) and (d) and 355(a)] and the drugs are misbranded in violation of Section 502(f)(1) of the Act [21 U.S.C. 352(f)(1)].

I. The CGMP violations include, but are not limited to, the following:

A. Failure to adequately investigate evidence of microbiological contamination and failure to maintain a complete record of data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation [21 CFR 211.192 and 211.194(a)(4)]. Specifically, the following was noted regarding the investigation conducted by your firm to identify microbial growth in a sample of pre-gelatinized starch, lot #

- The Vintage " " report number states after growth was observed in , and inoculated into and "appropriate media for identification by the system". Further, your investigation report states the results were uncertain due to a

In contrast, our investigators found laboratory notebooks contained no record of the results of the reported testing on media, and no record of the results of identification testing using the system. Please explain why your response to Form FDA 483 (483) does not state the reason these test results were not documented.

- The investigation report and your September 6, 2007, 483 response state after initial testing failed to positively identify the growth observed in retesting was conducted on a new sample collected from the lot. The report states the isolate from the original sample was not retested because there was insufficient sample remaining after the initial testing. The report also states the colony growing on was not detected during the retest on a new sample.

  It is unclear why there would not have been a sufficient amount of the original sample remaining to obtain a new isolate, which we believe would have increased the chance of identifying the microorganism. Additionally, in contrast to your investigation report, during the inspection, Vintage personnel told our investigators retesting was not conducted on the original sample because the isolate from the original sample was lost.

  We note Vintage SOP requires documentation of the results and rationale for any re-sampling and re-testing conducted during an investigation, however, there is no mention in your records the original isolate was lost. Please clarify this difference in the information we received from your firm.

- Your September 6, 2007, 483 response concludes since tests conducted using the system found a low probability of identifying the growth initially observed in it is not likely the microorganism was objectionable.

  We do not agree with your conclusion. We believe there can be numerous technical reasons why the probability for identification was low, which are unrelated to the clinical significance or pathology factors of the microorganism.

- Your laboratory test data shows during the tests conducted with a new sample, growth was observed on , which is used to selectively isolate *Pseudomonas aeruginosa*. There is no mention of this test result in your investigation report and, although there was an inconclusive report, there is no indication additional testing was conducted to positively identify the microorganism.

B. Failure to follow established test procedures and failure to record the initials or signature of the person who performs each test and the date each test is performed [21 CFR 211.160(a) and 211.194(a)(7)].

- Our review of your test data corresponding to the investigation of microbial contamination in pre-gelatinized starch, lot found the volume of used in the retest with a new sample from this lot was not recorded. Although the sample size for the retest

our investigators could find no documentation showing the volume of enrichment broth was adjusted for the increased sample size, as required by Vintage SOP , and USP Chapter 61, "Microbial Limit Tests."

Your September 6, 2007, 483 response acknowledges the SOP was not followed as the amount of was not adjusted for the increased sample size, but states this was deliberate and justified to increase the probability of recovering microorganisms. Moreover, you assert increasing the concentration of the sample was not a problem because the sample maintained solubility without falling out of solution, re-crystallizing or forming sediment. You state your SOP has been revised to allow for adjusting the amount of diluent to achieve the desired concentrations and maintain the material in solution.

We do not agree with your response. First, it is not acceptable for your analyst to ignore or deviate from your firm's approved SOPs unless the deviation is recorded and justified, as well as approved by appropriate organizational and quality control units. Secondly, it appears the revised SOP permits analysts to vary the amount of diluent during a retest, without validation and without oversight by the appropriate organizational and quality units. Lastly, your revised SOP is not appropriate because it permits your analysts to base adjustments to the amount of diluent during a retest solely on maintaining the sample in solution, and without assuring through appropriate preparatory testing the increased sample concentration will not inhibit the recovery of microbial growth. A validated concentration should be used for all microbial limit testing.

- Vintage SOP requires retests, conducted as part of an investigation of out-of-specification (OOS) or out-of-trend test results, not be performed by the original analyst. However, our inspection found laboratory notebook entries for the original testing and retesting, conducted as part of the aforementioned OOS investigation of microbial growth in pre-gelatinized starch, lot #, were signed by the same analyst. Vintage personnel told our investigators the person who signs the notebook entry is not necessarily the person who conducts the analysis, and the analyst usually can be identified by the handwriting.

  It is not appropriate for anyone other than the analyst who conducted the test and entered it into the laboratory notebook to sign and date the entry. It also is not appropriate to rely on handwriting analysis to determine who performed the work. The CGMP regulations in 21 CFR 211.194(a)(7) require laboratory records contain the signature and date of the person who performs each test.

- The testing of capsules, lot #, Vintage SOP and procedures specified in USP Chapter 61, "Microbial Limit Tests," were not followed because when tests revealed growth on , the was not conducted to confirm the presence of *Staphylococcus aureus*. Your September 6, 2007, 483 response describes alternative tests conducted using differential media not specified in your SOP, which indicated the growth was not *Staphylococcus aureus*. We do not agree with your response stating it was acceptable to deviate from your SOPs and from procedures specified in USP Chapter 61. Your

laboratory records contain no written justification and no record of approval by the appropriate organizational and quality units of your firm for the use of the alternative test methods.

C. Failure to follow appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile [21 CFR 211.113(a)].

Prior to our July 16, 2007, et al, inspection, you failed to follow Vintage SOP [redacted] " which required: [redacted]

The inspection initially found your firm had over 13 months of environmental monitoring data. There was no record showing isolates obtained from air samples were being identified; and, during the inspection, our investigators were told there was no record of environmental trending data. Subsequently, our investigators were provided with a report dated July 19, 2007, which contained environmental trending data for January through June 2007, which established action and alert limits. Additionally, your September 6, 2007, 483 response acknowledges SOP [redacted] was not followed, in which environmental trending reports were not prepared and alert and action limits were not initially established after the period of May 26 through December 2006.

Your September 6, 2007, 483 response asserts the microorganisms isolated from air samples were identified but the records pertaining to the identifications were not reviewed by the investigators. However, during the inspection, our investigators were provided with the log book for [redacted], including the page dated July 19, 2007, which does not show isolates from air samples had been identified.

Your promised corrections to the above observation in your September 6, 2007, 483 response appear to be adequate. However, we request you provide us with the rationale for the environmental alert and action limits set by your firm.

D. Failure to establish scientifically sound and appropriate test procedures designed to assure in-process materials and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] .

Microbial test methods were not validated properly because preparatory tests, as required by USP Chapter 61, "Microbial Limit Tests," were not conducted adequately to assure the inhibitory properties were neutralized during microbial limits testing of the following drug products: Acetic Acid Otic Solution, USP; Benzoyl Peroxide 5% and 10%; Bacitracin Ointment; Hydrocortisone Cream 1% and 2.5%; Hydrocortisone Lotion 2.5%; Micronazole Cream 2%; Multi-Vit with Fluoride, 0.5 mg, drops; Multi-Vit with Fluoride and Iron, 0.25 mg, drops; Nystatin Oral Suspension; Nystatin Topical Cream; Oralseptic Spray (cherry); Povidone Iodine Solution; Povidone Iodine Ointment 10%; Q-Tussin PE; Triamcinolone Acetonide Cream 0.01%; Tussiden C Liquid; and, Vitamin A & D Ointment.

Your September 6, 2007, and September 13, 2007, 483 response letters report the results of new preparatory testing had been conducted for all of the above products. Your response states the new preparatory testing showed additional inactivation procedures were necessary and microbial test methods were modified accordingly. You state where test methods were modified, Vintage tested representative retention samples of currently marketed products using the modified test methods to verify the absence of any microbial contamination.

While the actions described in your responses appear to be generally adequate, we are unclear about some parts of the responses. For example, during the inspection, Vintage identified preparatory test failures (i.e., failure to recover target microorganisms) for the following products: Hydrocortisone Cream 1%; Hydrocortisone Lotion 2.5%; Triamcinolone Acetonide Cream 0.1%; and, Vitamin A & D Ointment. However, your September 6, 2007, 483 response states the more recent preparatory tests exhibited positive growth, thus confirming the findings of the original preparatory tests and no microbial test method modifications were necessary. Please explain this inconsistency.

We also note in the records of preparatory tests attached as exhibit 1 to your September 6, 2007, 483 response, the data recorded in several of the tables appears to be inconsistent with the narrative descriptions of test results in the same document. For example, for Multi-Vitamin with Fluoride Drops 0.5%, an "N/A" is recorded in each table for the results of testing to recover *Aspergillus niger* and *Candida albicans* growth. We interpret the "N/A" to mean tests were not conducted to detect these microorganisms, yet the narrative with each table describes test results relating to these microorganisms (i.e., the narrative descriptions of test results specify either growth or no growth was found). Please provide clarification of all test results reported in exhibit 1 for *Aspergillus niger* and *Candida albicans*.

E. Failure to withhold each lot of components from use until the lot has been sampled, tested or examined as appropriate, and released for use by the quality control unit [21 CFR 211.84(a) and (e)].

Records corresponding to the investigation of microbial growth in a sample of [redacted], indicate the lot was released before the investigation report was signed by the Quality Control Director and by other officials of your firm. Additionally, the records indicate the lot was released and material from this lot was dispensed for production prior to the date the laboratory test data was verified by the Microbiology Manager. The following was noted:

- The Certificate of Analysis indicating the lot met all specifications and was acceptable for use was signed and dated on January 18, 2007.
- The '[redacted]' shows the signatures of the Microbiology Manager and Quality Control Director, both dated January 22, 2007, with the comment the product is released. The same form includes the signatures of other individuals of Vintage's quality, manufacturing and R&D units, which are dated between January 24, 2007 and January 30, 2007.

- Inventory records show on February 2, 2007, a portion of this lot was dispensed for use in the manufacture of finished drug product.

- Laboratory notebook pages containing the microbial test data for this lot show the data was verified by the Microbiology Manager on February 12, 2007.

II. In addition to the CGMP violations, you manufacture and market unapproved new drugs in violation of the Act at your facilities, located at 120 Vintage Drive, Huntsville, Alabama 35811-8216; and, 3241 Woodpark Boulevard, Charlotte, North Carolina 28206-4212. Furthermore, your wholly owned subsidiary, Qualitest, distributes unapproved new drugs in violation of the Act.

Based on the information your firm submitted to FDA's Drug Registration and Listing System and the labeling collected during the inspection of your facilities, located at 120 and 150 Vintage Drive, Huntsville, Alabama, you are marketing: Tussiden C Liquid (codeine phosphate and guaifenisin); Hyoscyamine Sulfate Capsules Timed Release; Yohimbine HCl; Phenazopyrine HCl; and, Salsalate Tablets.

These products are drugs within the meaning of 21 U.S.C. 321(g) because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are new drugs within the meaning of the 21 U.S.C. 321(p) because they are not generally recognized as safe and effective for their labeled uses. Under 21 U.S.C. 331(d) and 355(a), a new drug may not be introduced into or delivered for introduction into intestate commerce unless an FDA-approved application is in effect for the drug.[1] Based on our information, you do not have FDA-approved applications on file for these drug products. These drugs also are misbranded pursuant to 21 U.S.C. 352(f)(1) because they lack adequate directions for use and they are not exempt from the requirement under 21 CFR 201.115. The interstate distribution of these products without approved new drug applications violates 21 U.S.C. 331(a) and (d).

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations existing at your facility. You are responsible for investigating and determining the causes of the violations identified above and preventing their recurrence or the occurrence of other violations. It is your responsibility to assure your firm complies 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 but not limited to seizure and injunction. Other Federal agencies may take this warning letter into

[1] FDA is aware some firms market products they claim are "grandfathered" under the 1938 Act or the 1962 Amendments to the Act, as defined by Section 201(p)(1) of the Act [21 U.S.C. 321(p)(1)] and Section 107(c)(4) of the 1962 Amendments. The grandfather clauses in the Act have been construed very narrowly by the courts (see the appendix of our marketed unapproved drugs CPG, http://www.fda.gov/cder/guidance/6911fnl.htm, lines 323-329). Companies claiming their products are grandfathered are responsible for fully documenting their products' grandfathered status. Any company marketing a product on this basis must provide documentation including, but not limited to, pre-1938 or pre-1962 labeling to demonstrate the product meets all criteria for grandfather status, including the product as marketed today has the same formulation, strength, dosage form, route of administration, indications, intended patient population, and other conditions of use as the pre-1938 or pre-1962 product. For additional information, please refer to 21 CFR 314.200(e).

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. A reinspection may be necessary.

As noted above, we received your written responses, dated September 6 and 13, 2007, addressing the deviations noted on the 483 issued to you at the conclusion of the inspection on August 8, 2007. We have commented above on several parts of the responses we feel are inadequate.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps 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 for the delay and the time within which you will complete the correction. If you no longer manufacture or market any of your products, your response should so indicate, including the reasons for, and the date on which, you ceased production.

Your response should be directed to Mark W. Rivero, Compliance Officer, U.S. Food and Drug Administration, at the above address. Should you have any questions concerning the contents of this letter, or if you desire a meeting with the agency staff, do not hesitate to contact Mr. Rivero at (504) 219-8818, extension 103.

Sincerely,

Carol S. Sanchez
Acting District Director
New Orleans District

Enclosure: Form FDA 483, dated August 8, 2007