



Department of Health and Human Services

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

October 31, 2008

2008-DAL-WL-03

WARNING LETTER

**RETURN RECEIPT REQUESTED
CERTIFIED MAIL**

Kabir Ahmed, Ph.D.
President
Deltex Pharmaceuticals Inc.
1700 Bamore Road
Rosenberg, Texas 77471

Dear Dr. Ahmed:

An inspection of your facility, located at 1700 Bamore Road, in Rosenberg, Texas, that manufactures prescription (Rx) and over-the-counter (OTC) drug products for human use, was conducted on June 9 through July 15, 2008, by an investigator of the U.S. Food and Drug Administration (FDA). The inspection revealed that your drug products are adulterated within the meaning of Section 501 (a)(2)(B) [21 U.S.C. § 351 (a)(2)(13)] of the Federal Food, Drug, and Cosmetic Act (Act) 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 Current Good Manufacturing Practice (CGMP) regulations for drugs Title 21, Code of Federal Regulations (CFR), Part 211.

In addition, this inspection also revealed your firm is marketing unapproved drugs in violation of Section 505(a) of the Act [21 U.S.C. 355(a)] and the drugs are also misbranded in violation of Section 502(f)(1) [21 U.S.C. 352(f)(1)] and Section 502(c) [21 U.S.C. 352(c)].

The violations observed during our inspection and listed on the FDA-483 include, but are not limited to, the following:

1. Failure to follow written procedures applicable to the quality control unit and to establish adequate procedures in writing as required by 21 CFR § 211.22(d). Specifically, your SOP # QC-016-0 requires that the Quality Control Manager or designee calibrate the [(b)(4)] FT-IR

spectrometer with an internal reference standard on a [(b)(4)] basis. This was not done for six months following the last calibration on November 9, 2007. In addition, your SOP # QC-012-1, requiring the Quality Control Manager to ensure that in-house calibration of all scales and balances is performed [(b)(4)] with [(b)(4)] standard weights, was not followed. Calibrations of the [(b)(4)] Scale used to weigh active ingredients were performed with only [(b)(4)] weights for a period of 11 months (February 2007 to January 2008). Also, your SOP QC-01 0-1 "Procedure for out of spec Inspection" is inadequate in that it lacks a defined protocol for the number of retests allowed, and has no requirement for expansion of an OOS investigation to manufacturing processes and procedures or any provision for expansion on an investigation to other lots potentially impacted. We acknowledge your correspondence of September 2, 2008, in response to the FDA-483 in which you outline corrective action on the calibrations of the spectrometer and balance. The response is incomplete because it does not include the promised revised SOP addressing the deficiencies in your written procedures for handling OOS test results. Additionally, the response fails to provide any documentation of the corrective actions related to the balance and spectrometer.

2. Failure to establish laboratory controls, including determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components used in the manufacture, processing, packing, or holding of drug products as required by 21 CFR § 211.160(b)(1). Specifically, during review of laboratory documentation obtained as part of your supplier's qualification program for Phenylephrine Tannate lot no. R0510; Pyrilamine Tannate lot no. R0233; and Dextromethorphan Tannate lot no. R0250, a recurrent failure to identify each peak (or absorption band) of spectra obtained using USP <197K> FT-IR identity test for functional groups characteristic of Dextromethorphan Base, Pyrilamine Base and Phenylephrine Base, was noted.

Review of the USP <197K> FT-IR Identity test spectra obtained for the stated APIs revealed that all of the spectra generated for each API had comparable peaks in all areas of the [(b)(4)] spectrum when processing the sample tested as described in USP <197K>. The established USP <197K> Identity test method lacks the capability to detect physico-chemical changes of incoming API raw materials or distinguish one of the above referenced APIs from another. Therefore, your firm's Identity test method is considered an inadequate analysis for the identification and quantitation of in-coming tannate containing APIs (i.e., Dextromethorphan Tannate, Pyrilamine Tannate, and Phenylephrine Tannate). In addition, your firm fails to document that your identity testing procedures can detect extraneous materials in lots of incoming API's salt/base forms, that may necessitate rejection of the lot. We acknowledge the corrective actions outlined in your September 2, 2008, response. However this response lacks scientific evidence designed to demonstrate that the proposed HPLC identity test is an improvement over the USP <197> FT-IR identity testing and that it is suitable for the specific identification of tannate containing APIs. Please be aware that identity testing in the context of multiple drug components that are compounds of closely related molecular structure must be able to discriminate between the compounds. There is no assurance that the proposed use of HPLC RRT as the preferred identity test method can adequately confirm the identity of incoming lots of tannate APIs.

3. Failure to establish adequate laboratory controls, including the establishment of scientifically sound and appropriate specifications designed to assure conformance with appropriate standards of identity, strength, quality, and purity as required by 21 CFR § 211.160(b). Specifically, your firm has not established specifications for: the amount of free Tannic Acid in drug products containing tannate compounds; the assay for [(b)(4)] in bulk [(b)(4)] USP (ANDA [(b)(4)] and Benzalkonium Chloride 50% in [(b)(4)] drug product. In addition, your firm has failed to establish specifications or testing procedures for dissolution or rate of drug release for drug products containing tannates. We acknowledge your September 2, 2008 response in which you state that manufacturing of all drug products containing "tannate" compounds will cease as of September 2, 2008. However, we disagree with your assertion that there are no methods by which to determine the dissolution or drug release in "tannate" preparations. Methods for dissolution and drug release testing for other oral suspension products with approved New Drug Applications (NDAs), or Abbreviated New Drug Applications (ANDAs), that have an insoluble active pharmaceutical ingredient have been developed.

4. Failure to conduct appropriate laboratory testing, as necessary, of each batch of product required to be free of objectionable microorganisms, as is required by 21 CFR § 211.165(b). For example, your firm does not conduct any preparatory testing on drug products to assess their possible inhibitory effects on microbial growth prior to testing for the presence of microorganisms. In addition, there is no growth promotion testing on the batches of media used. We acknowledge the pledge in your September 2, 2008, response to conduct preparatory testing on most product formulations by October 31, 2008. However this response is unsatisfactory because it includes no commitment to conduct growth promotion testing on each batch of growth media used. Because of the possible impact of exposure to adverse conditions while in shipment, reliance on a suppliers' Certificate of Analysis (COA) alone is not sufficient to provide a necessary degree of assurance that the purchased media will perform adequately. The performance of each lot of growth media used should, at a minimum, be confirmed upon receipt or before the first use.

5. Failure to establish and follow appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile, as required by 21 CFR § 211.113(a). For example, your firm failed to perform antimicrobial effectiveness testing on all your finished product formulations. Your response of September 2, 2008, is unsatisfactory. The determination of [(b)(4)] alone is insufficient to show the antimicrobial/preservative characteristics of a particular drug product formulation. The effectiveness of a particular solvent system, by itself or in combination with other chemical preservatives, in controlling microbial growth should be verified by actual testing.

6. Failure to establish the reliability of the supplier's analysis, through appropriate validation of supplier's test results at appropriate intervals, as required by 21 CFR § 211.84(d)(2). Specifically, suppliers' reports of analysis are routinely accepted by your firm without appropriate validation. For example, the supplier's test results for Organic Volatile Impurities (OVI) in shipments of Citric Acid have not been verified by your firm's own testing. Also, because there are no qualified and fully characterized primary reference standards for the active pharmaceutical ingredients (API) used in tannate containing drug products, your firm's testing to confirm supplier analyses of these APIs is questionable. You assert in your response of September 2,

2008, that all the tests cited in the relevant FDA-483 item as unverified by your firm's testing are not required by the USP. This is incorrect. A test for OVI is specified in the monograph for Citric Acid, USP.

7. Failure to thoroughly investigate any unexplained discrepancy or the failure of any batch to meet any of its specifications, whether or not the batch has already been distributed, as required by 21 CFR § 211.192. Specifically, review of the HPLC assay chromatograms for release testing for Tannate Pediatric Suspension, lot #08046, revealed the presence of an unidentified peak at approximately [(b)(4)] RRT in the sample chromatogram. Your firm did not perform a timely investigation in regard to the unidentified peak. We acknowledge the tentative conclusion from your investigation, stated in your FDA-483 response, that the unknown peak represents the other active ingredient in the product, Phenylephrine Tannate. However, this determination should have been made at the time of the initial analysis. In addition, we not yet have received any documentation of the investigation, including the final conclusion and follow-up.

8. Master production and control records lack special notations as required by 21 CFR § 211.186(b)(9). Specifically, your production batch records for drug products containing tannates failed to contain a correction factor intended to formulate drug products calculating the amount of each active moiety while excluding the excess amount of other components in the API. We acknowledge your response of September 2, 2008, stating that production of all drug products containing Tannate compounds would be suspended pending more reliable determination of their molecular weights. Please be aware that, in the absence of molecular weight figures, the calculation of the quantity of active moiety can also be based on the empirical determination of the quantity of base in the API reported in the COA, provided this analysis can be reliably confirmed by your firm's testing.

Unapproved Drugs

In addition to the CGMP violation, you manufacture and market unapproved new drugs in violation of the Act at your facility at 1700 Bamore Road, Rosenberg, Texas 77471. Based on the labeling collected during the inspection of your facility, you manufacture the following prescription drugs:

- Tannate Pediatric Suspension (Phenylephrine Tannate 5 mg, Chlorpheniramine Tannate 4.5 mg);
- [(b)(4)] Pediatric Suspension Drops, (Chlorpheniramine Tannate 2 mg, Phenylephrine Tannate 6 mg);
- Duohist™ DH Liquid (Dihydrocodeine Bitartrate 7.25 mg, Chlorpheniramine Maleate 2 mg, Phenylephrine HCl 5mg);
- Ed-A-Hist DM (Dextromethorphan HBr 15 mg, Chlorpheniramine Maleate 4 mg, Phenylephrine HCl 10 mg per 5 mL);

- Bromphenex DM (Dextromethorphan HBr 30 mg, Pseudoephedrine HCl 60 mg, Brompheniramine Maleate 4 mg per 5 mL); and

- [(b)(4)] (Carbetapentane Citrate 20 mg and Guifenesin 75 mg per 5 mL).

The above products are drugs within the meaning of Section 201(g) of the Act, [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 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. Under Sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(a), (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 the drug. Based on our information, you do not have any FDA-approved applications on file for these drug products.

Additionally, the above products are misbranded because, as prescription drugs, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for use as required under Sections 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)] and because they lack required approved applications, they are not exempt from this requirement under 21 C.F.R. § 201.115. The introduction or delivery for introduction into interstate commerce of these products without approved new drug applications violates Section 301(a) and (d) of the Act [21 U.S.C. §§ 331(a) and (d)].

Your response to the new drugs violations set forth in FDA's 483 is inadequate. Tannate Pediatric Suspension, [(b)(4)] Pediatric Suspension Drops, Duohist DH™ Liquid, Ed-A-Hist DM, Bromphenex DM, and [(b)(4)] are "new drugs" that may not be introduced into or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for these drugs. There are no FDA-approved applications in effect for these drugs, therefore, your firm is violating the Federal Food, Drug, and Cosmetic Act by introducing into commerce "new drugs" that do not have FDA approval, as required under Section 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)]. Failure to promptly discontinue manufacturing, distributing, and repackaging unapproved new drugs may result in regulatory action, including seizure and/or injunction without further notice. It is your responsibility to ensure all drugs you manufacture, distribute, and repackage comply with all the requirements of the Federal Food, Drug, and Cosmetic Act.

Misbranded Over-the-Counter (OTC) Drugs

Moreover, your firm also manufactures drug products for over-the-counter use. Specifically, at least one drug product that you manufacture inappropriately bears the Rx (prescription) legend because it is an OTC drug product based on its formulation and directions for use as described in the final regulations covering Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use, 21 C.F.R. Part 341. Since this product is not subject to Section 503(b)(1) of the Act [21 U.S.C. § 353(b)(1)], it is misbranded under Section 503 (b)(4)(B) of the Act [21 U.S.C. § 353(b)(4)(B)] because it inappropriately bears the Rx legend. This product is:

- [(b)(4)] Syrup, (Dextromethorphan HBr 10 mg, Phenylephrine HCl 5mg, & Brompheniramine Maleate 2 mg per 5 mL);

In addition to the above violation, the product [(b)(4)] Syrup does not contain the required labeling information in a drug facts panel in accordance with 21 C.F.R. § 201.66. Therefore, this product is misbranded under section 502(c) of the Act [21 U.S.C. § 352i] because the information that is required to appear on the labeling is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

In the March 9, 2007, Regulatory Meeting and November 7, 2007, follow-up meeting, you were informed of the need to remove the prescription (Rx) legend from the drug products and the requirements to market these products in compliance with the applicable OTC monographs. You stated you planned to submit new drug applications for some of the drug products discussed during the meeting and cited in this letter. We have not received any such applications. You also committed in your September 2, 2008, letter to comply by November 20, 2008, with the regulatory requirements applicable to the OTC drugs you manufacture and market.

This letter is not intended to be an all-inclusive list 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 conduct a comprehensive audit of your facility and operations and assure compliance with all requirements of the Act 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 regulatory action without further notice, including, without limitation, seizure and/or 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 new drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary.

Within 15 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 similar violations as well as copies of related documentation. Please submit your corrective action plans, as communicated in your September 2, 2008, letter, to bring the OTC drugs listed above into compliance with applicable regulations. We also request that you outline the action you are taking to discontinue the marketing of the unapproved drug products listed above, or any other such drugs that you may market. 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 the products cited in this letter, your response should so indicate, including the reasons for, and the date on which you ceased manufacturing or marketing the products.

Your reply should be directed to Edwin Ramos, Compliance Officer, U.S. Food and Drug Administration, 4040 N. Central Expressway, Suite 300, Dallas, Texas 75204. If you have any questions regarding any issue in this letter, please contact Mr. Ramos at (214) 253-5218.

Sincerely yours,

/S/

Reynaldo R. Rodriguez, Jr.
District Director
Dallas District

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