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DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

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WARNING LETTER
NWE-12-07W

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

March 21, 2007

Michael W. Licamele, CEO and Owner
ComputeRx/Broncho-Dose, Ltd.
35-55 Ontario Street
Stratford, CT 06615-7153

Dear Mr. Licamele:

On May 31, 2006, and June 2, 5, 6, and 9, 2006, the Food and Drug Administration (FDA) inspected ComputeRx/Broncho-Dose, Ltd. (ComputeRx), located at 35-55 Ontario Street, Stratford, CT 06615. Our investigators observed and documented serious violations of the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA and FDA's Regulatory Approach to Compounding

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view is that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective" for their labeled uses. *See Weinberger v. Hynson, Westcott & Dunning,* 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"). There is substantial judicial authority supporting FDA's position that compounded drugs are not exempt from the new drug definition. *See Prof'ls & Patients for Customized Care v. Shalala,* 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug . . . provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy,* 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd, Wedgewood Village Pharmacy v. United States,* 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither

pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are rarely FDA-approved and thus lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. *See Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to the compounding of human drugs is articulated in Compliance Policy Guide section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (*see Notice of Availability*, 67 *Fed. Reg.* 39,409 (June 7, 2002)).[1] The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. As stated in the CPG, these factors are "not intended to be exhaustive." *See* CPG section 460.200 ["Pharmacy Compounding"].

B. Factual Background

Your firm purports to be a compounding pharmacy; however, our investigation has determined that your firm's operation exceeds the scope of traditional pharmacy

[1] Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Ninth Circuit's ruling in *Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001), that Section 503A included unconstitutional restrictions on commercial speech and those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

practice. Your firm's activities are not consistent with a pharmacy engaged in extemporaneous compounding, but rather are akin to a pharmaceutical manufacturer. Our findings in support of this conclusion include the following:

- Your firm manufactures budesonide inhalation drug products in the following strengths: 0.2mg/2.5ml, 0.3mg/2.5ml, 0.4mg/2.5ml, 0.6mg/2.2ml, 0.7mg/2.5ml, 1.0mg/3.6ml, and 2.0mg/5.0ml. An FDA-approved, commercially available budesonide product is available in the following strengths: 0.25mg/2.0ml and 0.5mg/2.0ml. We do not view as a meaningful distinction the mere differences in strength between your firm's products and the FDA-approved product with which they compete. Nor are we aware of any legitimate medical need for these differences in formulation. These concerns are especially significant given the large volume of drugs that your firm produces. For instance, over a 6-month period, ComputeRx manufactured the following number of units of budesonide inhalation solution 1.0mg/3.6ml:

  - [redacted] (November 2005);
  - [redacted] (December 2005);
  - [redacted] (January 2006);
  - [redacted] (March 2006);
  - [redacted] (April 2006).

  Furthermore, from June of 2005 through May of 2006, your firm dispensed more than [redacted] prescriptions, of which more than [redacted] prescriptions were for compounded drugs. ComputeRx is licensed in twelve different states, and [redacted] of its drug products are shipped outside of the State of Connecticut.

We also have significant concerns about the quality of your firms compounded inhalation drugs. During an inspection on December 16, 2005, FDA collected a sample of budesonide 2.0mg/5.0ml unit dose inhalation solution packages from lot number 11728 (sample number 354451). This sample was tested for potency and was found to be subpotent at [redacted] of the labeled potency claim. On June 6, 2006, your firm conducted a recall of budesonide 2.0mg/5.0ml oral inhalation solution as a result of FDA's analysis.

During the current inspection, FDA collected a sample of budesonide 1.0mg/3.6ml unit dose inhalation solution packages from lot number 12007 (sample number 371524). This sample was tested for potency and was found to be subpotent at [redacted] of the labeled potency claim. FDA notified you of the testing results and you indicated that an investigation was underway, and that the affected lot [redacted]

C. Violations of the Food Drug and Cosmetic Act

Based on the above, we do not believe that your firm is operating as a retail pharmacy engaged in extemporaneous compounding that would justify our exercising enforcement discretion. Your firm is in violation of the following sections of the FDCA:

Section 505 [21 U.S.C. § 355]
The oral inhalation solutions manufactured by your firm are drugs within the meaning of section 201(g) of the FDCA [21 U.S.C. § 321(g)]. They are new drugs within the meaning of section 201(p) of the FDCA [21 U.S.C. § 321(p)], and may not be introduced or delivered for introduction into interstate commerce under section 505(a) of the FDCA [21 U.S.C. § 355(a)] without approved applications. No approved application is in effect for these drugs and their distribution violates sections 505(a) and 301(d) of the FDCA [21 U.S.C. §§ 355(a), 331(d)].

Section 502(a) [21 U.S.C. § 352(a)]
ComputeRx's inhalation drug products are misbranded within the meaning of section 502(a) of the FDCA [21 U.S.C. § 352(a)] because the drugs' labels are false and misleading. Specifically, as FDA's sample analyses showed, the products are subpotent in comparison with their labeled potency.

Section 502(f)(1) [21 U.S.C. § 352(f)(1)]
ComputeRx's inhalation drug products are misbranded within the meaning of section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] in that their labeling fails to bear adequate directions for the uses for which they are being offered, and they are not exempt from this requirement under 21 CFR § 201.115.

Section 502(o) [21 U.S.C. § 352(o)]
ComputeRx's inhalation drug products are misbranded under section 502(o) of the FDCA [21 U.S.C. § 352(o)] in that they are manufactured in an establishment not duly registered under section 510 of the FDCA [21 U.S.C. § 360], and the articles have not been listed as required by section 510(j) of the FDCA [21 U.S.C. § 360(j)]. Your facility is not exempt from registration and drug listing under 21 CFR § 207.10 or section 510(g) of the FDCA [21 U.S.C. § 360(g)], because it is engaged in the manufacture and distribution of drugs in a fashion that exceeds the regular course of the practice of the profession of pharmacy.

Section 501(c) [21 U.S.C. § 351(c)]
ComputeRx's inhalation drug products are subpotent and therefore adulterated under section 501(c) of the Act [21 U.S.C. § 351(c)] in that their strength differs from that which they purport or are represented to possess.

During a previous inspection on December 16, 2005, FDA collected a physical sample of budesonide 2.0mg/5.0ml solution for oral inhalation unit dose packages from lot number 11728 (sample number 354451). The [redacted] was made on December 12, 2005, and had an expiration date of November 30, 2006. The sample was tested for potency and was found to be sub-potent at [redacted] of label claim for potency.

We acknowledge that, following notification of the laboratory results by FDA, your firm conducted a voluntary recall of all lots of budesonide 2.0mg/5.0ml oral inhalation solution, including lot number 11728. A total of [redacted] of drug products) were covered by the recall. On June 2, 2006, our investigators witnessed the voluntary destruction of all remaining units of the drug product in inventory at your firm. We also acknowledge that, since the recall was initiated, your firm has decided to [redacted] the 2.0mg/5.0ml strength of budesonide oral inhalation solution.

During the current inspection on June 6, 2006, FDA collected a physical sample of budesonide 1.0mg/3.6ml solution for oral inhalation unit dose packages for lot number 12007 (sample number 371524). The [redacted] batch was made on [redacted] and had an expiration date of [redacted]. The sample was tested for potency and was found to be subpotent at [redacted] and [redacted] of the label claim for potency.

We acknowledge that all units of this lot of drug product were [redacted] by your firm and [redacted] We also were informed that the product would [redacted] and that an investigation would be conducted. The final [redacted] lot number 12007 is unknown.

Section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)]
ComputeRx's inhalation drug products are adulterated within the meaning of section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)] in that the controls and procedures used in the products' manufacturing, processing, packing, and holding do not conform to current good manufacturing practice regulations set forth at 21 CFR Part 210 and 211. Deviations from these regulations include, but are not limited to, the following:

1. Failure to have appropriate laboratory determination of satisfactory conformance to final specifications for your inhalation drug products prior to release [21 CFR § 211.165(a)]. For example, none of the 26 batches of budesonide 2.0mg/5.0ml solution for oral inhalation that were manufactured from September 30, 2002, through April 4, 2006, were assayed for potency before their release and distribution to consumers.

2. Failure to establish adequate procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR § 211.113(b)]. For example, no media fills to validate the aseptic filling process for budesonide have been conducted.

3. Failure to have a system for monitoring environmental conditions in the aseptic processing areas [21 CFR § 211.42(c)(10)(iv)]. For example, you do not perform, nor do you have any procedures addressing, air sampling for viable and non-viable particles or microbiological monitoring of surfaces and equipment in the aseptic processing areas.

4. Failure to have an adequate system for cleaning and disinfecting the room used for aseptic processing [21 CFR § 211.42(c)(10)(v)]. There are no procedures for the cleaning and maintenance of this room.

5. Failure to conduct appropriate laboratory testing to determine that each batch of sterile drug product is free of objectionable microorganisms [21 CFR § 211.165(b)]. For example, your in-house sterility testing used on finished product testing, including budesonide 2.0mg/5.0ml, lot number 11728, has not been validated.

6. Failure to establish appropriate written procedures for production and process control designed to assure that your firm's inhalation drug products have the identity, strength, quality, and purity that they purport or are represented to possess [21 CFR § 211.100(a)]. For example, some lots of your budesonide oral inhalation solution, both the 1.0mg/3.6 ml and 2.0mg/5.0ml strengths, have been found subpotent upon analysis by FDA and your contract laboratory. We informed you of the FDA results on June 29, 2006. You indicated that an investigation was underway and that the product was [redacted] We requested but have not yet received information regarding the results of your investigation or the disposition of the subpotent lot. Your formulation and mixing procedures do not assure the declared potency of this drug product. Information collected during the inspection indicates that there may be a solubility problem associated with this product. Your formulation procedures must be designed to assure product potency throughout the expiry period.

   Additionally, there are no written procedures for other significant operations used to manufacture your budesonide drug products, including in-process controls for aseptic filling, drug product quarantine and release, and testing and release of raw materials.

7. Failure of drug products to bear an expiration date determined by appropriate stability data to assure that they meet applicable standards of

identity, strength, quality, and purity at the time of use [21 CFR § 211.137(a)]. For example, you do not have stability data to justify and support the assigned 11-month expiration date used on your budesonide 2.0mg/5.0ml inhalation solution drug product.

8. Failure to establish and maintain written procedures applicable to the quality control unit [21 CFR § 211.22(d)]. For example, you do not have any procedures describing the responsibilities of the quality control unit, such as procedures for approving the release of a batch, approving raw materials, approving formulas in the master records, and approval of the results of sterility tests.

9. Failure to establish complete batch production and control records for each drug product, and for each batch size [21 CFR § 211.188]. For example, your batch records for lot number 11728 of budesonide 2.0mg/5.0ml do not document the actual weights of raw materials used to manufacture this batch. This lot of drug product was recalled by your firm because it was subpotent.

10. Failure to establish and maintain written procedures describing the handling of complaints, including provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications, a determination as to the need for an investigation of an unexplained discrepancy, and explaining the reasons for the failure of the batch or any of its components to meet specifications [21 CFR § 211.198(a)]. For example, your procedure, "Protocol For Resolving Complaints From Medicare Beneficiaries," fails to contain provisions for evaluation, review, and determination as to the need of an investigation by a quality control unit.

We acknowledge your written response dated July 17, 2006, to the FDA-483 inspectional observations issued to your firm on June 9, 2006. In your response, you have restated your position that you are a pharmacy subject to state licensure and regulation as a pharmacy, not a drug manufacturer. We disagree. FDA considers your operations to exceed the scope of traditional pharmacy compounding and fall within the scope of drug manufacturing. You also stated that you would "review and consider adopting procedures and practices that address the observations in the 483." You further stated that you will "set-up SOPs to address quarantine of raw materials, testing raw material, release of raw materials, in-process controls, and quarantining finished product." However, no specific information is provided. Your response is not satisfactory and does not address all of the deviations noted in the FDA-483.

The above deficiencies should not be construed as an all-inclusive list of violations that may exist at your facility, and they may not be limited to the above-cited drug products. It is your responsibility to ensure adherence to each requirement of the FDCA and its regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations and prevent their recurrence. Failure to promptly do so may result in regulatory action without further notice, including seizure and/or injunction.

We request that you reply in writing, within 15 working days of receipt of this letter, stating the action that you will take to correct all the noted violations, including an explanation of the steps taken to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. We do not require a response for budesonide 2.0 mg/5.0mL solution for oral inhalation, lot number 11728, since the subject lot was recalled and destroyed; however, please indicate the final disposition of budesonide 1.0mg/3.6mL solution for oral inhalation, lot number 12007, and any other budesonide lots that might have been affected by the subpotency results.

Your reply should be directed to the attention of Bruce R. Ota, Compliance Officer, at Food and Drug Administration, One Montvale Avenue, 4th floor, Stoneham, MA 02108. If you have questions concerning the violations noted, please contact Bruce R. Ota at 781-596-7762.

Sincerely,

Gail T. Costello
District Director
New England District Office

cc:

Michelle B. Sylvestre
Drug Control Agent and Board Administrator
Connecticut Commission of Pharmacy
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