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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Food and Drug Administration
San Juan District
Southeast Region
466 Fernandez Juncos Ave
San Juan, Puerto Rico 00901

Telephone: 787-474-9500
Facsimile: 787-729-6658

March 26, 2008

WARNING LETTER
SJN-2008-01

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Raul Sanchez, President
Farmacia La Salud Inc.
200 Rafael Cordero Avenue, Suite 140
Caguas, PR 00725-3757

Dear Mr. Sanchez:

On May 10-31, 2007, the Food and Drug Administration (FDA) conducted an inspection of your facility located at Rafael Cordero Avenue # 200, Caguas, PR 00725. Our investigators, accompanied at the beginning of the inspection by a representative from the Puerto Rico Health Department, Drugs and Pharmacy Division, documented serious violations of the Federal Food, Drug, and Cosmetic Act (FDCA). You submitted a response to the FDA-483 dated January 22, 2008. As explained below, your production and distribution of drug products violates the 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.[1]

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 drug, 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)).[2] 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,"[t]he . . . list of factors is not intended to be exhaustive." Some of the factors identified in the CPG include considering whether a firm:

- compounding drugs that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. However, in certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient;

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[1] In August 2006, the U.S. District Court for the Western District of Texas issued a ruling in *Medical Center Pharmacy v. Gonzales* interpreting, among other things, the application of the "new drug" provisions of the FDCA to compounded drugs. *See Medical Center Pharmacy v. Gonzales,* MO-04-CV-130, (W.D. Tex, Aug. 30, 2006). The government has appealed this decision to the U.S. Court of Appeals for the Fifth Circuit. Pending resolution of this appeal, FDA is abiding by the district court's decision in the Western District of Texas and with respect to the plaintiffs covered by the decision.

[2] 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 that 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.

- compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions; and

B. Factual Background

Our investigation found that your firm has exceeded the practices associated with traditional extemporaneous compounding and that your operation is more akin to that of a drug manufacturer. Your firm produces large volumes of inhalation solution products in anticipation of receiving prescriptions, including copies or essentially copies of FDA-approved commercially available products.

From May 2006 to May 2007, you produced more than —— batches (approximately ——— unit dose vials) of different inhalation solution products. These include:

- budesonide 0.25 mg/albuterol 0.83%/ipratropium 0.02% ———;
- budesonide 0.33 mg/albuterol 0.83%/ipratropium 0.02% ———,
- budesonide 0.50 mg/albuterol 0.83%/ipratropium 0.02% ———
- levalbuterol 0.63 mg/budesonide 0.33 mg/ipratropium 0.02% ———
- levalbuterol 1.44 mg/budesonide 0.33 mg/ipratropium 0.02% ———
- levalbuterol 0.63 mg/ipratropium 0.02% ———
- levalbuterol 1.44 mg/ipratropium 0.02% ———
- levalbuterol 0.63 mg/budesonide 0.33 mg ———);
- levalbuterol 1.44 mg/budesonide 0.33 mg ———;
- budesonide 0.33 mg/albuterol 0.083% ———, and
- budesonide 0.33 mg/ipratropium 0.02% ———

Some of these compounded solutions are copies or essentially copies of FDA-approved, commercially available products, including:

- albuterol 0.083%/ipratropium 0.02% (———) - There is an FDA-approved, commercially available product that contains albuterol 0.083%/ipratropium 0.017%. We are not aware of any legitimate medical need for this insignificant difference in strength, and your firm has no documentation of patient-specific medical need for this variation;
- budesonide 0.25 mg ———, 0.33 mg ———, and 0.5 mg ———) - There is an FDA-approved, commercially available product that contains budesonide 0.25 mg and 0.5 mg. Thus, your budesonide 0.25 mg and 0.5 mg drug products are copies of the FDA-approved products. With respect to your budesonide 0.33 mg drug product, we are not aware of any legitimate medical need for this insignificant difference in strength from the FDA-approved 0.25 mg drug product, and your firm has no documentation of patient-specific medical need for this variation; and
- levalbuterol 0.73 mg ——— 1 mg ——— and 1.44 mg ——— - There is an FDA-approved, commercially available product that contains levalbuterol 0.63 mg and 1.25 mg. We are not aware of any legitimate medical need for this insignificant difference in strength between your products and the FDA-approved products, and your firm has no documentation of patient-specific medical need for this variation.

Further, from January 2007 to April 2007, your firm distributed approximately ——— vials of inhalation solution products to patients in Puerto Rico. Upon arrival at your firm, the investigator observed a considerable amount of inhalation solution products, including ——— plastic vials of inhalation solution from seventeen different product formulations prepared between April 23, 2007, and May 8, 2007. We do not believe that such production volume is consistent with that of a pharmacy that is engaged in the traditional practice of extemporaneous pharmacy compounding.

Further, the Puerto Rico Department of Health (PRDH) determined that your firm's operations were not in conformance with the applicable laws of Puerto Rico. One of PRDH's observations was that your firm's operations were comparable to a drug manufacturer.

FDA is seriously concerned about the public health risks associated with the large-scale production of inhalation solutions by firms not meeting the laws and regulations applicable to drug manufacturing. The volume of inhalation solution products that your firm produces, including its production of copies or near-copies of commercially available, FDA-approved drugs, exceeds the scope of traditional pharmacy compounding and is akin to the activities of a drug manufacturer.

C. Violations of the FDCA

Unapproved New Inhalation Solution Products

The inhalation solution products made by your firm are drugs within the meaning of section 201(g) of the FDCA [21 U.S.C. § 321(g)]. These products are new drugs as defined by section 201(p) of the FDCA [21 U.S.C. § 321(p)], because they are not generally recognized by qualified experts as safe and effective for their labeled uses. No approved application pursuant to section 505 of the FDCA [21 U.S.C. § 355] is in effect for these products. Accordingly, their introduction or delivery for introduction into interstate commerce violates sections 505(a) and 301(d) of the FDCA [21 U.S.C. §§ 355(a) and 331(d)].

Misbranded Inhalation Solution Products

Your firm's inhalation solution products are misbranded under section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] because their labeling fails to bear adequate directions for use and they are not exempt from this requirement under title 21, Code of Federal Regulations (C.F.R.), part 201, section 115 (21 C.F.R. § 201.115).

Your firm's operation exceeds the scope of a traditional pharmacy that regularly engages in dispensing prescription drugs upon receiving a prescription in the course of its professional practice. Thus, your firm is subject to the registration and listing requirements under section 502(o) of the Act [21 U.S.C. § 352(o)]. Failure to comply with these requirements causes your products to be misbranded as they are manufactured in an establishment not duly registered under section 510 of the Act [21 U.S.C. § 360], and the drugs have not been listed as required by section 510(j) of the Act [21 U.S.C. § 360(j)].

Adulterated Inhalation Solution Products

Your firm's inhalation solution products are adulterated under section 501(a)(2)(B) of the FDCA [21 U.S.C. § 351(a)(2)(B)] because the controls and procedures used in the manufacture, processing, packing, and holding of the inhalation solution products do not conform to Current Good Manufacturing Practice (CGMP) regulations set forth in 21 C.F.R. Parts 210 and 211. Our investigator documented significant violations of CGMP regulations including, but not limited to, the following:

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of inhalation solution products purporting to be sterile, as required by 21 C.F.R. § 211.113(b). For example, your firm: (a) failed to perform validation studies to demonstrate the efficacy of your autoclave sterilization cycles; (b) has no scientific data to support the practice of filtering different inhalation products with the same ——— filter; and (c) has not performed media-fill testing.

   We acknowledge your response to the FDA-483 dated January 22, 2008, and your claimed corrective actions. However, the responses to the above inspectional observations are inadequate for several reasons. The response states that your firm is in the process of validating the "cleaning and sanitization" procedures used. However, mere sanitization of product contact equipment is insufficient to maintain the aseptic conditions necessary for sterile drug processing. In addition, your response indicates your firm's intent to not validate the autoclave used for sterilization of some of your product contact equipment and to possibly cease sterilization of this equipment altogether. Finally, the response provides no evidence that your firm's practice of multiple uses of a sterile filter and refrigerated storage between production runs is adequate to prevent microbial contamination of the sterile inhalation products.

2. Failure to test each batch of inhalation solution product purporting to be sterile and/or pyrogen-free to determine conformance to such requirements, as required by 21 C.F.R. § 211.167(a). Specifically, as a manufacturer of sterile drug products, your firm has not conducted sterility testing on any finished inhalation solution batches delivered to patients.

   We acknowledge your response to the FDA-483, in which you describe batch testing every three months for the products and assert that the limited testing is appropriate for a compounding pharmacy. However, as explained above in this letter, your firm's production of inhalation solution products exceeds the scope of traditional compounding and is more akin to the activities of a drug manufacturer. Your firm's production of these drugs is subject to the CGMP requirements for finished drug products. The regulation, 21 C.F.R. § 211.167(a), requires testing of each and every batch of drug product purporting to be sterile and or pyrogen-free.

3. Failure to test each batch of inhalation solution product to determine conformance to final specifications, including identity and strength of each active ingredient, before release and distribution, as required by 21 C.F.R. § 211.165(a). Specifically, as a manufacturer of sterile drug products, your firm does not conduct product testing on all batches of inhalation solution product prior to release.

We acknowledge your response to the FDA-483 stating that insurance rules require provision of the drug product to the patient within 24 to 48 hours. However, because technology exists to conduct identity and strength testing within this time frame, we do not accept your firm's claim that these rules prevent compliance with the above cited regulation.

4. Failure to establish written procedures for cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of inhalation solution product, as required by 21 C.F.R. § 211.67(b). Specifically, your firm has not conducted cleaning validation studies for the non-dedicated equipment used in the manufacturing of 18 different inhalation solutions.

   We acknowledge your response to the FDA-483 and your claimed corrective actions, including your firm's greater reliance on dedicated equipment, use of improved cleaning materials and efforts to validate your cleaning procedures. However, the response is unsatisfactory since if fails to provide any documentation of revised cleaning procedures or their validation.

5. Failure to withhold each lot of components, inhalation solution product containers, and closures from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit, as required by 21 C.F.R. § 211.84(a). Specifically, your firm does not perform testing or examination for each component used in the manufacturing of albuterol, ipratropium, budesonide, and levalbuterol products.

   We acknowledge your response to the FDA-483 but find it to be inadequate with respect to the inspectional observation mentioned above. Under the CGMP regulations, reliance on a certificate of analysis for assurance of the quality, purity and identity of drug components is permissible only if a firm conducts a specific identity test on each lot of component and establishes the reliability of the supplier's analyses through validation of the supplier's test results at appropriate intervals.

6. Failure to prepare batch production and control records for each batch of inhalation solution product containing complete information relating to the production and control of each batch including documentation that each significant step in the manufacturing, processing, packing, or holding of your inhalation solution products was accomplished, as required by 21 C.F.R. § 211.188(b). Specifically, your batch records do not document significant production parameters, e.g., mixing time, heating temperatures/times, and equipment to be used.

   We acknowledge your response to the FDA-483 but we note that although it appears to adequately address the above mentioned inspectional observations, the response provides no documentation of the corrective actions.

7. Failure to assure all inhalation solution products meet applicable standards of identity, strength, quality, and purity at the time of use by establishing an expiration date determined by appropriate stability testing, as required by 21 C.F.R. § 211.137(a). Specifically, your firm failed to conduct stability testing on your finished inhalation

solution products to support your assigned 90 day expiration date. It is important for your firm to understand the factors - besides the stability of a specific active ingredient - that should be considered in determining a suitable expiration date. These factors include the stability of the inactive ingredients, the interaction of active and inactive ingredients, the manufacturing process, the dosage form, the container closure system, the conditions under which the inhalation solution product is stored and handled (e.g., your budesonide inhalation solution is packaged in a clear plastic vial within a brown bag) and the length of time between initial manufacture and final use.

We acknowledge your response to the FDA-483 and the claimed corrective actions, including the development of data to scientifically establish a 90-day expiration date for your products, but note that the response provides no documentation of stability studies. Please be aware that verbally informing patients to keep light-sensitive products, such as the Budesonide, in its outer protective packaging until time of use is insufficient. Such warnings should be included on the product label.

8. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding an inhalation solution product, as required by 21 C.F.R. § 211.198. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of an inhalation solution product to meet any of its specifications and, for such inhalation solution products, a determination as to the need for an investigation in accordance with 21 C.F.R. § 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA in accordance with 21 C.F.R. §§ 310.305 and 514.80, as required by 21 C.F.R. § 211.198(a). Specifically, your firm's complaint procedure lacks a provision for the quality control unit to review complaints to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the FDA. While the current inspection noted that your firm referred patients reporting adverse drug experience to their physicians, your firm failed to determine whether the complaint represented a serious and unexpected adverse drug experience which is required to be reported to FDA.

Your response to the relevant observations in the FDA-483 is inadequate. The response claims the creation of a new form to document possible adverse events but there is no documentation of this new form. The response also fails to address the deficiencies of the complaint handling procedure itself.

9. Failure to establish a written distribution procedure to include a system by which the distribution of each lot of inhalation solution product can be readily determined to facilitate its recall if necessary, as required by 21 C.F.R. § 211.150(b). Specifically, your firm lacks a written distribution procedure for your inhalation solution products.

Your response appears to address the relevant observations in the FDA-483 but provides no documentation of the claimed corrective actions. Also, the response does

not address the establishment of written procedures requiring the use of the new log sheets.

Your firm's inhalation solution products are in violation of section 301(a) of the FDCA [21 U.S.C. § 331(a)] because introduction or delivery for introduction into interstate commerce of adulterated or misbranded inhalation solution products is a prohibited act. FDA will not exercise enforcement discretion with regard to these and the other violations cited in this letter.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility in connection with your products. 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 assure that 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, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts.

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 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.

Address your reply to Margarita Santiago, Compliance Officer, at the address above. If you have questions regarding the contents of this letter, please contact Ms. Santiago at (787) 474-4789.

Sincerely,

Maridalia Torres
District Director
San Juan District

Enclosures: CPG Section 460.200; Form FDA 483, dated May 31, 2007

cc: