Advanced Physician Solutions, Inc. 11/3/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Los Angeles District Office
Pacific Region
19701 fairchild
Irvine, CA 92612
Telephone: (949) 608-2900
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WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

November 3, 2015

WL# 3-16

Mr. David Kohanbash, Joseph Kohan, and Tooraj Bereliani, Owners
Advanced Physician Solutions, Inc., d/b/a Advanced Compounding Pharmacy
7225 Fulton Ave
North Hollywood, CA 91605-4111

Dear Mr. Kohanbash, Mr. Kohan, and Mr. Bereliani:

From January 12, 2015, to January 16, 2015, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Advanced Physician Solutions, Inc., d/b/a Advanced Compounding Pharmacy, located at 7225 Fulton Avenue, North Hollywood, CA 91605-4111.

During the inspection, investigators noted you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, the investigators observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigators observed an external air conditioning unit installed on the cleanroom wall across from the hoods where aseptic production occurs. Your firm had no data to indicate that a HEPA filter was installed in the air conditioner and made no assessement to determine if airflow from the air conditioner affected operations within the hoods. The investigators also observed an aseptic compounding **(b)(4)** used for **(b)(4)** sterilizing non-sterile components, located in an area of unclassified air quality. In addition, the investigators noted that non-sterile cleaning wipes were used to apply disinfectants to the ISO 5 work surfaces. Furthermore, the investigators

found that your firm failed to demonstrate through appropriate studies that your aseptic compounding **(b)(4)** and hoods are able to provide adequate protection of the ISO 5 area in which sterile drug products are produced. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA issued a Form FDA-483 to your firm on January 16, 2015, and subsequently issued an amended Form FDA-483 on February 26, 2015. FDA acknowledges receipt of your firm's response to the Form FDA-483, dated February 6, 2015.

Based on this inspection, it appears that you produced drugs that violate the Federal Food, Drug, and Cosmetic Act (FDCA).

A. Compounded Drugs Under the FDCA

Section 503A of the FDCA [21 U.S.C. § 353a] describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA: compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B) of the FDCA) [21 U.S.C. § 351(a)(2)(B)]; labeling with adequate directions for use (section 502(f)(1) of the FDCA) [21 U.S.C. § 352(f)(1)]; and FDA approval prior to marketing (section 505 of the FDCA) [21 U.S.C. § 355]. Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

During the FDA inspection, the investigators observed that your firm does not receive valid prescriptions for individually-identified patients for a portion of the drug products you produce.

Accordingly, the drugs you compound without valid prescriptions for individually-identified patients are not entitled to the exemptions in section 503A of the FDCA.

In addition, we remind you that there are a number of other conditions that must be satisfied to qualify for the exemptions in section 503A of the FDCA.[1]

B. Violations of the FDCA

Because the drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are not the subject of approved applications, they are unapproved new drugs and misbranded drugs in violation of section 505(a) and 502(f)(1) of the FDCA, respectively. In addition, drug products that are intended or expected to be sterile were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health, causing them to be adulterated within the meaning of section 501(a)(2)(A) of the FDCA [21 U.S.C. § 351(a)(2)(A)]. Furthermore, because you manufacture and distribute a portion of your drugs without valid prescriptions for individually-identified patients, the manufacture of those drugs is also subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21, *Code of Federal Regulations* (CFR), Parts 210 and 211. FDA investigators observed significant CGMP violations at your facility, causing such drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA

Unapproved New Drug Products

You do not have any FDA approved applications on file for the drug products for which you have not obtained valid prescriptions for individually-identified patients**.[2]** Under sections 301(d) [21 U.S.C.§ 331(d)] and 505(a) of the FDCA, a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under section 505 of the FDCA is in effect for the drug. Your marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

You compound drug products for which you have not obtained valid prescriptions for individually-identified patients that are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners; therefore, adequate directions for use cannot be written so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(1) of the FDCA, and they are not exempt from the requirements of section 502(f)(1) of the FDCA [*see, e.g.*, 21 CFR § 201.115].

The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA [21 U.S.C, § 331(a)]. Further, it is a prohibited act under section 301(k) of the FDCA [21 U.S.C. § 331(k)] to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being misbranded.

Adulterated Drug Products

Additionally, FDA investigators observed that drug products in your facility that were intended or expected to be sterile were prepared, packed, or held under insanitary conditions, whereby they may have become contaminated with filth or rendered injurious to health, causing your drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigators observed an external air conditioning unit installed on the cleanroom wall across from the hoods where aseptic production occurs. Your firm had no data to indicate that a HEPA filter was installed in the air conditioner and made no assessement to determine if airflow from the air conditioner affected operations within the hoods. The investigators also observed an aseptic compounding **(b)(4)** used for **(b)(4)** sterilizing non-sterile components, located in an area of unclassified air quality. In addition, the investigators noted that non-sterile cleaning wipes were used to apply disinfectants to the ISO 5 work surfaces. Furthermore, the investigators found that your firm failed to demonstrate through appropriate studies that your aseptic compounding **(b)(4)** and hoods are able to provide adequate protection of the ISO 5 area in which sterile drug products are produced.

The FDA investigators also noted CGMP violations at your facility, causing the drug products for which you have not obtained valid prescriptions for individually-identified patients to be adulterated under section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to establish an adequate system for maintaining equipment used to control the aseptic conditions (21 CFR 211.42(c)(10)(vi)).

2. Your firm failed to establish and follow an adequate written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

3. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

4. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

5. Your firm failed to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

6. Your firm does not have, for each batch of drug product purporting to be sterile and/or pyrogen-free, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product (21 CFR 211.167(a)).

Under section 301(a) of the FDCA the introduction or delivery for introduction into interstate commerce of any drug that is adulterated is a prohibited act. Further, it is a prohibited act under section 301(k) of the FDCA to do any act with respect to a drug, if such act is done while the drug is held for sale after shipment in interstate commerce and results in the drug being adulterated.

C. Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product

Section 503A of the FDCA also addresses the compounding of commercially available drug products. For a drug to satisfy the conditions in section 503A, a pharmacist or physician may “not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product” [21 U.S.C. § 353a(b)(1)(D)].

Section 503A also provides that a drug product is not essentially a copy of a commercially available drug product if it includes a change from the commercially available product that was made for an identified individual patient, and a prescribing practitioner determined that the change produces a significant difference for that patient between the compounded drug product and the commercially available drug product [21 U.S.C. § 353a(b)(2)].

During the inspection of your facility in January 2015, FDA investigators observed that your firm compounded 17-hydroxyprogesterone caproate (17-P). 17-P is the active ingredient in Makena, which FDA approved in February 2011 for the reduction of the risk of certain preterm births in women who have had at least one prior preterm birth. Your compounded 17-P appears to be essentially a copy of the commercially

available drug product Makena and may not be entitled to the exemptions for certain compounded drugs in section 503A of the FDCA.

D. Corrective Actions

In addition to your February 2015 letter responding to the FDA Form 483 and noting some remedial steps, FDA acknowledges your letter, received on April 14, 2015, in which you state your firm had "discontinue[ed] business as of April 3, 2015", and letters, dated May 6, 2015 and May 13, 2015, from Todd Mizeski of Frier Levitt, LLC, stating that "there are no plans to perform sterile compounding." Further, FDA acknowledges your action on May 18, 2015, to voluntarily recall all aseptically produced drug products intended to be sterile that were within expiry.

If you decide to resume operations in the future, before resuming production of sterile drugs, FDA strongly recommends that your management immediately undertake a comprehensive assessment of your operations, including facility design, procedures, personnel, processes, materials, and systems. In particular, this review should assess your aseptic processing operations and design. A third party consultant with relevant sterile drug manufacturing expertise could be useful in conducting this comprehensive evaluation.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies
regardless of whether the drugs are compounded and distributed after receipt of a prescription for an identified individual patient. If you decide to resume operations, you must correct all insanitary conditions at your firm.

In addition, if you were to continue to manufacture and dispense drug products without valid prescriptions for individually-identified patients, the manufacture of such drugs would be subject to FDA's drug CGMP regulations (21 CFR Parts 210 and 211), among other requirements described above, and, before doing so, you should fully implement corrections that meet the minimum requirements of 21 CFR Part 211 in order to provide assurance that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity.

E. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations 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 ensure that your firm complies with all requirements of federal law, including FDA regulations.

If you decide to resume sterile operations, 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.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations, or you may inform us that you do not intend to resume production of sterile drugs. If you intend to

resume production of sterile drugs in the future, please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. In addition to taking appropriate corrective actions, you should notify this office prior to resuming production of any sterile drugs in the future.

Your written notification should be addressed to:

William S. Vitale, DMD, Compliance Officer
FDA Los Angeles District Office
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

If you have questions regarding any issues in this letter, please contact Dr. Vitale via email at Bill.Vitale@fda.hhs.gov or by phone at 949-608-2919.

Sincerely,
/S/
LCDR Steven Porter, Acting Director
Los Angeles District

Cc: VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

David Kohanbash
(b)(4), **(b)(6)**

Joseph Kohan
(b)(4), **(b)(6)**

Tooraj Bereliani
(b)(4), **(b)(6)**

Cc:
Virginia Herold, Executive Officer
California State Board of Pharmacy
1625 N. Market Boulevard, Suite N-219
Sacramento, CA 95834

David M. Mazzera, Ph.D.
Chief, Food and Drug Branch
California Department of Public Health
1500 Capitol Avenue, MS-7602
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[1] For example, section 503A also addresses anticipatory compounding, which includes compounding (not distribution) before receipt of a valid prescription order for an individual patient. We are not addressing anticipatory compounding here.

[2] The specific products made by your firm are drugs within the meaning of section 201(g) [21 U.S. C. § 321(g)] of the FDCA because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases and/or because they are intended to affect the structure or any function of the body. Further, they are “new drugs” within the meaning of section 201(p) of the FDCA [21 U.S.C. §321(p)] because they are not generally recognized as safe and effective for their labeled uses.