Medaus, Inc. 3/8/18

Office of Pharmaceutical Quality
Operations, Division 2
4040 North Central Expressway,
Suite 300
Dallas, TX 75204-3158

March 8, 2018

CMS #522090

WARNING LETTER

UPS OVERNIGHT MAIL

Steven L. Russell, Owner
Medaus, Inc. dba Medaus Pharmacy
6801 Cahaba Valley Road, Suite 116
Birmingham, Alabama 35242-9609

Dear Mr. Russell,

From March 7, 2016 to March 11, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Medaus, Inc. dba Medaus Pharmacy (Medaus), located at 6801 Cahaba Valley Road, Suite 116, Birmingham, Alabama. During the inspection, the investigators noted that drug products you produced failed to meet the conditions of section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353a] for exemption from certain provisions of the FDCA. The investigators noted serious deficiencies in your practices for producing sterile drug products, which put patients at risk.

FDA issued a Form FDA 483 to your firm on March 11, 2016. FDA acknowledges receipt of your facility's response on March 26, 2016. We also acknowledge your recall of all sterile drug products within expiry due to a lack of sterility assurance, initiated in response to an FDA Requested Recall letter issued on May 3, 2016. Additionally, FDA acknowledges that the Alabama State Board of Pharmacy ("the

Board"), pursuant to a settlement agreement with your firm, issued a Final Order on July 1, 2016 requiring Medaus "not [to] engage in sterile compounding or dispensing [of] any sterile drug products…for a minimum of two years from the effective date of this Final Order,"; not to "petition the Board to resume sterile compounding... before two years from the effective date of this order"; and to "only dispense drugs on patient specific prescriptions…."

Based on this inspection, it appears that you produced drug products that violate the FDCA.

A. Compounded Drug Products Under the FDCA

Section 503A of the FDCA describes the conditions under which human drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practices (CGMP) (section 501(a)(2)(B)); labeling with adequate directions for use (section 502(f)(1)); and FDA approval prior to marketing (section 505) [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1) and 355].***1*** Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

B. Failure to Meet the Conditions of Section 503A

During the inspection, the FDA investigators noted that drug products produced by your firm failed to meet the conditions of section 503A. For example, the investigators noted that your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

Therefore, you compounded drug products that do not meet the conditions of section 503A and are not eligible for the exemptions in that section from the FDA approval requirement of section 505 of the FDCA, the requirement under section 502(f)(1) of the FDCA that labeling bear adequate directions for use, and the requirement of compliance with CGMP under section 501(a)(2)(B) of the FDCA. In the remainder of this letter, we refer to your drug products that do not qualify for exemptions under section 503A as the "ineligible drug products."

Specific violations are described below.

C. Violations of the FDCA

Adulterated Drug Products

The FDA investigators noted that drug products 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, your firm used a sporicidal agent in the ISO 5 area only once between August 2015 and February 2016. In addition, your facility was designed in a way that permits the influx of poor quality air into a higher classified area. For example, an air return is located next to the high efficiency particulate air (HEPA) filter rather than near the

floor, and pressure differentials between areas of higher quality air (ISO 8) and unclassified area are not adequately maintained. Your firm also failed to demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 areas in which sterile products are produced. Therefore, your products may be produced in an environment that poses a significant contamination risk.

Furthermore, the manufacture of the ineligible drug products is subject to FDA's CGMP regulations, Title 21, Code of Federal Regulations (CFR), parts 210 and 211. The FDA investigators observed significant CGMP violations at your facility, causing the ineligible drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations included, for example:

1. Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product as appropriate (21 CFR 211.111).

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

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 cleaning and disinfecting the room and equipment to produce aseptic conditions (21 CFR 211.42(c)(10)(v)).

5. Your firm failed to adequately design the facility with adequate separation or defined areas or such other control systems necessary to prevent contamination or mix-ups (21 CFR 211.42(b)).

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

7. 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)).

Under section 301(a) of the FDCA [21 U.S.C. § 331(a)], 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 [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 adulterated.

Unapproved New Drug Products

You do not have any FDA-approved applications on file for the ineligible drug products that you compounded.***2*** Under sections 505(a) and 301(d) of the FDCA [21

U.S.C. § 331(d)], 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. Marketing of these products, or other applicable products, without an approved application violates these provisions of the FDCA.

Misbranded Drug Products

The ineligible drug products you compounded are intended for conditions 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.***3*** Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA. The introduction or delivery for introduction into interstate commerce of these products therefore violates section 301(a) of the FDCA. It is also 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 misbranded.

D. Corrective Actions

We have reviewed your firm's response to the Form FDA 483 dated March 26, 2016, and your response dated March 30, 2016. We acknowledge your recall of all sterile drug products within expiry initiated on May 13, 2016 due to a lack of sterility assurance, in response to an FDA Requested Recall letter issued on May 3, 2016. We also acknowledge that under the Final Order issued by the Board on July 1, 2016, your firm "may not engage in sterile compounding or dispensing any sterile drug products…for a minimum of two years from the effective date of this Final Order" and "may only dispense drugs on patient specific prescriptions..."

Regarding the insanitary conditions observations in the Form FDA 483, we cannot fully evaluate the adequacy of several corrective actions described in your responses because you did not include sufficient information or supporting documentation. For example, your firm has not provided documentation to show that a pressure gauge has been installed to monitor the pressure between the ISO 8 anteroom and the unclassified warehouse, as you indicated would occur in your response dated 3/30/16. Additionally, your response dated 3/26/16 states that certification of ISO 5 environments was performed under dynamic conditions. However, your response did not include any documentation to support this statement, or a detailed description of how dynamic conditions are simulated during performance of smoke studies.

You did not address certain observations related to insanitary conditions. For example, your responses did not propose any corrective action to the deficiency in the design of your facility, specifically, return air vents located next to HEPA filters in the ceiling of the ISO 7 cleanroom, rather than near the floor level. Additionally, according to your responses, your firm has not taken any corrective action to ensure that media fills are performed under the most challenging or stressful conditions.

Please be aware that section 501(a)(2)(A) of the FDCA concerning insanitary conditions applies regardless of whether drug products you compound meet the conditions of section 503A.

Should you resume compounding and distributing drug products that do not meet the conditions of section 503A (e.g., the receipt of a prescription for an identified individual patient before a compounded drug product leaves the compounding facility), the compounding and distribution of such drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the drug CGMP regulations. Before doing so, you must comply with the requirements of section 505 and 502(f)(1) and fully implement corrections that meet the minimum requirements of the CGMP regulations.***4***

In addition to the issues discussed above, you should note that CGMP requires the implementation of quality oversight and controls over the manufacture of drugs, including the safety of raw materials, materials used in drug manufacturing, and finished drug products. *See* section 501 of the FDCA. If you choose to contract with a laboratory to perform some functions required by CGMP, it is essential that you select a qualified contractor and that you maintain sufficient oversight of the contractor's operations to ensure that it is fully CGMP compliant. Regardless of whether you rely on a contract facility, you are responsible for assuring that drugs you introduce into interstate commerce are neither adulterated nor misbranded. [*See*21 CFR 210.1(b), 21 CFR 200.10(b)]. FDA strongly recommends that if you decide to resume production of sterile drugs following a successful petition to the Board after two years from the effective date of the Final Order, your management first undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance materials, and systems. In particular, this review should assess your aseptic processing operations. A third-party consultant with relevant sterile drug manufacturing expertise should assist you in conducting this comprehensive evaluation.

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 following a successful petition to the Board after two years from the effective date of the Final Order, 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 if you have taken any specific steps to correct the violations cited in this letter, 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 following a successful petition to the Board after two years from the effective date of the Final Order, 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 violated the FDCA, include your reasoning and any supporting information for our consideration. In addition to taking appropriate corrective actions, you should notify this office fifteen (15) working days prior to resuming production of any sterile drugs in the future.

Your written notification should refer to the Warning Letter referencing CMS #522090. Please submit your written response to:

John W. Diehl
Director, Compliance Branch
U.S. Food and Drug Administration
Office of Pharmaceutical Quality Operations, Division 2
4040 North Central Expressway, Suite 300
Dallas, Texas 75204

You may submit your written response via e-mail to Mr. John Diehl at john.diehl@fda.hhs.gov.

If you have questions regarding the content of this letter, please contact Mr. Diehl at 214- 253-5288, or Rebecca Asente, Compliance Officer, at 504-846-6104.

Sincerely,
/S/
Monica R. Maxwell
Program Division Director
Office of Pharmaceutical Quality Operations, Division 2

Steven L. Russell
(b)(6), (b)(7)(C)

Larry D. Stephens, Co-Owner
Medaus, Inc. dba Medaus Pharmacy
6801 Cahaba Valley Road, Suite 116
Birmingham, Alabama 35242-9609

Larry D. Stephens
(b)(6), (b)(7)(C)

Susan Alverson, Executive Secretary
111 Village Street
Birmingham, Alabama 35242

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1 We remind you that there are conditions other than those discussed in this letter that must be satisfied to qualify for the exemptions in section 503A of the FDCA.

2 The specific products made by your firm 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 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) [21 U.S.C. 321(p)] of the FDCA because they are not generally recognized as safe and effective for their labeled uses.
3 Your ineligible drug products are not exempted from the requirements of section 502(f)(1) of the FDCA by regulations issued by the FDA (see, e.g., 21 CFR 201.115).
4 In this letter, we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.