Pharmacy Plus, Inc. dba Vital Care Compounder 8/9/17

Office of Pharmaceutical Quality Operations, Division II
4040 N. Central Expressway, Suite 300
Dallas, Texas 75204

August 9, 2017

CMS Case # 522183

WARNING LETTER

VIA UPS EXPRESS

Ronald D. Edwards, Pharm.D., Owner
Pharmacy Plus, Inc. dba Vital Care Compounder, LLC
115 S. 40th Avenue
Hattiesburg, Mississippi 39402-6600

Dr. Edwards:

From June 3, 2016, to July 7, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, Vital Care Compounder, LLC, located at 115 S. 40th Avenue, Hattiesburg, Mississippi, 39402-6600. This inspection was conducted after receipt of an adverse event report associated with an oral solution containing chloral hydrate produced by your firm. 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 July 7, 2016. FDA acknowledges receipt of your facility's response to the Form FDA 483, dated July 26, 2016, as well as your subsequent correspondence. FDA also acknowledges your firm's action on July 26, 2016, to recall all aseptically produced drug products within expiry. 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(a)].***1*** Receipt of valid prescriptions for individually-identified patients is one of the conditions for the exemptions under section 503A.

In addition, for a compounded drug product to qualify for the exemptions under section 503A, bulk drug substances used to compound it must: (I) comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (II) if such a monograph does not exist, be components of drugs approved by the Secretary; or (III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appear on a list developed by the Secretary through regulation ("503A bulks list") (section 503A(b)(1)(A)(i) of the FDCA).

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:

1. Your firm did not receive valid prescriptions for individually-identified patients for a portion of the drug products you produced.

2. Your firm compounded drug products using domperidone. Drug products compounded using domperidone are not eligible for the exemptions provided by section 503A(a), because domperidone is not the subject of an applicable USP or NF monograph, is not a component of an FDA-approved human drug, and does not appear on the 503A bulks list.***2***

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

As noted above, FDA received a MedWatch report dated June 2, 2016, regarding adverse events experienced by two patients associated with an oral solution

produced by your firm that was labeled as containing 100 mg/mL of chloral hydrate. FDA analysis of a sample of this product found that it contained approximately 980 mg/mL of chloral hydrate, or 980% of the label declaration for chloral hydrate. Under section 501(b) of the FDCA [21 U.S.C. § 351(b)], a drug is deemed to be adulterated if it purports to be or is represented as a drug the name of which is recognized in an official compendium and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium. The strength of your chloral hydrate oral solution differed from and greatly exceeded the labeled amount of chloral hydrate the product was purported to possess, causing it to be adulterated under section 501(b) of the FDCA.

In addition, 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 [21 U.S.C. § 351(a)(2)(A)]. For example, the investigators observed the following:

1. Your firm's **(b)(4)**, where aseptic processing occurred, was located in an unclassified room. In addition, there were stains on the HEPA filter located inside your **(b)(4)**.

2. The plastic shield, located on the front of the ISO 5 **(b)(4)** within your cleanroom, was shattered. The investigators also noted flaking plastic adhesive material underneath the hood.

3. Your firm stored sterilized vials and stoppers, used for the production of drug products intended to be sterile, in containers covered with aluminum foil in an unclassified area. Furthermore, these containers were stacked on top of one another without additional protection.

4. Your firm failed to use a sporicidal agent and sterile wipes as part of your disinfection program for the aseptic processing area.

5. Your firm failed to demonstrate through appropriate studies that your aseptic processing areas were able to provide adequate protection of the ISO 5 area in which sterile products are processed. 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 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 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)).

3. 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)).

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

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

6. Your firm failed to establish an adequate quality control unit with the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products (21 CFR 211.22(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 any human or animal 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.***3*** 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.***4*** Accordingly, these ineligible drug products are misbranded under section 502(f)(1) of the FDCA.

Further, under section 502(a) of the FDCA [21 U.S.C. § 352(a)], a drug product is misbranded if its labeling is false or misleading in any particular. As noted above, FDA analysis showed that your chloral hydrate drug product contained in excess of 900% of the labeled concentration of chloral hydrate. Because the labeling of this drug product was false, it was misbranded under section 502(a) 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 any human or animal 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 July 26, 2016, as well as your subsequent correspondence. We acknowledge your action on July 26, 2016, to voluntarily recall all aseptically produced drug products within expiry and cease aseptic drug production on July 27, 2016, until adequate corrective actions had been taken. We also acknowledge your letter, dated October 4, 2016, in which you stated that your firm would resume aseptic drug production on October 5, 2016.

Regarding the insanitary conditions observed during the inspection, some of your corrective actions appear to be adequate. However, we are unable to fully evaluate the following corrective actions due to a lack of adequate supporting documentation:

1. In your response, you stated that the **(b)(4)** has been relocated to an ISO 7 classified room. However, you did not provide supporting documentation to demonstrate that this room was certified with the addition of the **(b)(4)**. Furthermore, no documentation was provided to show that the ISO 5 **(b)(4)** was re-certified after it was moved.

2. We acknowledge your firm's corrective action to replace the ISO 5 hood within your cleanroom. However, your firm did not provide supporting documentation to demonstrate that your cleanroom was certified with the addition of the "new, larger hood."

3. We acknowledge your firm's corrective action to now store sterilized glassware within an ISO 7 environment. However, your firm did not provide supporting documentation to demonstrate how these items will be protected from contamination while awaiting use in aseptic drug protection. Furthermore, we remain concerned with the lack of a hold time for these items. Storage of sterilized items for extended periods of time increases the risk of them becoming contaminated. Your firm should ensure that these items are protected from contamination while awaiting use in sterile drug production as the use of non- sterile equipment can introduce or increase endotoxins in the finished drug product, which would be considered an insanitary condition. Moreover, glassware approved for use should be rotated such that the oldest approved items are used first.

In addition, the following corrective actions appear inadequate to address the insanitary conditions noted:

1. In your response to our observation regarding the failure to use a sporicidal agent within the aseptic processing areas, you stated that you would use "**(b)(4)**, which contains a sporicidal and will alternate that product with a dilute sodium hypochlorite solution." However, the cleaning policy provided in your response dated October 4, 2016, "**(b)(4)**", does not list **(b)(4)** as a disinfectant. Furthermore, the **(b)(4)**, referenced in your cleaning policy, for the **(b)(4)** sodium hypochlorite solutions is not sufficient to achieve adequate levels of sporicidal disinfection.

2. The smoke study video that your firm provided did not include a simulation of routine operations. In addition, your response did not include a video of the smoke study performed within the ISO 5 **(b)(4)** for our review. Conducting smoke studies under dynamic conditions helps to ensure that unidirectional airflow is maintained while personnel are working in the ISO 5 areas.

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, including the condition on receipt of a prescription for an identified individual patient prior to compounding and distributing drug products. In addition, sections 501(b) and 502(a) of the FDCA apply regardless of whether drug products you compound meet the conditions of section 503A.

Regarding observations related to the conditions of section 503A of the FDCA, FDA acknowledges your response dated July 26, 2016, in which you stated that your firm "ceased all non-patient specific sales" and destroyed "all existing non-patient specific compounded inventory." However, you did not state if you will stop compounding drug products containing domperidone.

Should you continue to compound and distribute drug products that do not meet the conditions of section 503A, 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.***5***

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 your management undertake a comprehensive assessment of operations, including facility design, procedures, personnel, processes, maintenance materials, and systems for human and animal drugs. 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.

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 working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. 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. 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. Your written notification should refer to the Warning Letter Number above (**CMS Case # 522183**).

Please address your reply to Rebecca A. Asente, Compliance Officer, at the FDA address provided. In addition, please submit a signed copy of your response to rebecca.asente@fda.hhs.gov.

If you have questions regarding the contents of this letter, you may contact Ms. Asente via (504) 846-6104 or rebecca.asente@fda.hhs.gov.

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

Cc:
Frank Gamill, Executive Director
Mississippi Board of Pharmacy 6360 I-55 North
Suite 400
Jackson, Mississippi 39211

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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 On June 9, 2016, FDA issued a final guidance titled, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act*. This guidance describes FDA's interim regulatory policy for State-licensed pharmacies, Federal facilities, and licensed physicians that compound human drug products using bulk drug substances that do not otherwise meet the conditions of section 503A(b)(1)(A)(i) while the 503A bulks list is being developed.

Specifically, the guidance sets out the conditions under which FDA does not intend to take action against a State-licensed pharmacy, Federal facility, or licensed physician for compounding a drug product using a bulk drug substance that is not the subject of an applicable USP or NF monograph or a component of an FDA-approved drug, until the substance is identified in a final rule as included or not included on the 503A bulks list. These conditions include that the substance may be eligible for inclusion on the 503A bulks list, was nominated with adequate support for FDA to evaluate it, and has not been identified by FDA as a substance that appears to present significant safety risks pending further evaluation. The bulk drug substance domperidone was nominated for inclusion on the 503A bulks list. It has been identified as a substance that appears to present significant safety risks. For additional information, see the guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf.

3 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.

4 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).

5 In this letter we do not address whether your proposed corrective actions would resolve the CGMP violations noted above.