Hartley Medical Center Pharmacy, Incorporated 4/21/16

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED

April 21, 2016

WL #29-16

Mr. William A. Stuart, Owner/President
Hartley Medical Center Pharmacy, Inc.
113 W. Victoria Street
Long Beach, CA 90805

Dear Mr. Stuart:

From June 29, 2015, to July 8, 2015, U.S. Food and Drug Administration (FDA) investigators conducted an inspection of your facility, Hartley Medical Center Pharmacy, Inc., located at 113 W. Victoria St, Long Beach, CA 90805-2162. During the inspection, the FDA 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, our investigators noted that your firm produced sterile **(b)(4)** from non-sterile components and then stored them in **(b)(4)** containers, which were subsequently punctured multiple times throughout the assigned expiry period of up to **(b)(4)** days. Puncturing a container compromises the integrity of the container closure system, and each puncture increases the chances of contamination. The production process observed at your facility, including the storage conditions of **(b)(4)**, represents a potential lack of control for bioburden and further **(b)(4)** sterilization performed by your firm would not remove bacterial endotoxin. This was noted to be of particular concern as some of the drug products you produced from these **(b)(4)** were intended for intrathecal administration, and you do not test each of your finished drug products to ensure that the amount of endotoxin is within an acceptable limit.

Our investigators also noted that your firm did not use a sporicidal agent or sterile wipes, and used non-sterile sanitizers as part of your disinfection program for the

aseptic processing areas. Therefore, your products may be produced in an environment that poses a significant contamination risk.

FDA issued a Form FDA 483 to your facility on July 8, 2015. FDA acknowledges receipt of your firm's responses to the Form FDA 483, dated July 21, 2015; September 22, 2015; November 23, 2015; January 14, 2016; and March 22, 2016. FDA acknowledges your actions on August 17, 2015, and February 4, 2016, to voluntarily recall certain drug products purported to be sterile.

Based on this inspection, it appears that you are producing 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 qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practices (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 that must be met for drug products to qualify for the exemptions under section 503A of the FDCA.

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 sections 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 subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. The FDA investigators observed

significant CGMP violations at your facility, causing your 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. In addition, your compounded drug products 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)]. 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

The FDA investigators noted 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, our investigators noted that your firm produced sterile **(b)(4)** from non-sterile components and then stored them in **(b)(4)** containers, which were subsequently punctured multiple times throughout the assigned expiry period of up to **(b)(4)** days. Puncturing a container compromises the integrity of the container closure system, and each puncture increases the chances of contamination. The production process observed at your facility, including the storage conditions of **(b)(4)**, represents a potential lack of control for bioburden and further **(b)(4)** sterilization performed by your firm would not remove bacterial endotoxin. This was noted to be of particular concern as some of the drug products you produced from these **(b)(4)** were intended for intrathecal administration, and you do not test each of your finished drug products to ensure that the amount of endotoxin is within an acceptable limit.

Our investigators also noted that your firm did not use a sporicidal agent or sterile wipes, and used non-sterile sanitizers as part of your disinfection program for the aseptic processing areas. Therefore, your products may have been produced in an environment that poses a significant contamination risk.

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 cleaning and disinfecting the room and equipment to produce aseptic conditions [21CFR 211.42(c)(10)(v)].
2. 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)].
3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination [21 CFR 211.28(a)].
4. 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)].
5. Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing area [21 CFR 211.42(c)(10)(iv)].

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. Corrective Actions

FDA acknowledges your action on August 17, 2015, to voluntarily recall three lots of Prolotherapy with Phenol (RX **(b)(6), (b)(7)(C)**, RX **(b)(6), (b)(7)(C)**, and **(b)(6), (b)(7)(C)**, due to non-sterility concerns. FDA also acknowledges your action on February 4, 2016, to voluntarily recall all sterile products produced on February 3, 2016, due to an uncertainty in the quality assurance of sterile drug products produced under the Laminar Air Flow Workbench (LAFW), which was not operating properly on February 3, 2016.

FDA further acknowledges receipt of your responses to the Form FDA 483, dated July 21, 2015; September 22, 2015; November 23, 2015; January 14, 2016; and March 22, 2016, and your statement in the July 21, 2015 response that your firm "understand[s] the observations made during the inspection and plan[s] to make changes to [y]our facility and quality assurance program to comply with the FDA." Although several of your proposed corrective actions appear adequate, others are deficient. For example, in response to our observation of inadequate cleaning and disinfection, you indicated that you purchased sterile disinfectants and sterile wipes. You also indicated that you have added a sporicidal agent to your routine cleaning and disinfection of work surfaces. However, your SOP for cleaning and disinfection did not specify the contact time for sporicidal disinfection in the ISO 5 work areas.

In response to our observation regarding **(b)(4)**, you indicated that you developed a container closure integrity test for the **(b)(4)** and plan to demonstrate the sterility of the **(b)(4)** throughout its expiry. However, this test only confirms the sampled portion is sterile and does not validate the integrity of the container. Additionally, the tested portion may not have detectable microbial contamination after the **(b)(4)** container loses integrity, but the amount of bacterial endotoxin may still increase. Your proposed corrective action is not adequate to demonstrate container closure integrity. Therefore, your response does not indicate how you will ensure your finished product is sterile and the amount of endotoxin is within an acceptable limit after multiple punctures to the **(b)(4)** containers.

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 aseptic processing operations. 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 valid prescription for an identified-individual patient.

In addition, if you were to continue to manufacture and distribute 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 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. As indicated above, such drug products would also be subject to new drug approval requirements in section 505 and the requirement to be labeled with adequate directions for use in section 502(f)(1), among other requirements of the FDCA.

D. 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 (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. 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 be addressed to:

CAPT Daniel W. Cline, Acting Director
Compliance Branch
U.S. Food & Drug Administration
19701 Fairchild
Irvine, CA 92618

If you have questions regarding any issues in this letter, please contact Ms. Mariza Jafary at (949) 608-2977 or via email at mariza.jafary@fda.hhs.gov.

Sincerely,
/S/
CDR Steven E. Porter, Jr.
Los Angeles District Director

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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.