# Buderer Drug Company Inc 9/20/16

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**Department of Health and Human Services**

Public Health Service
Food and Drug Administration
Cincinnati District Office
6751 Steger Drive
Cincinnati, OH 4523 7
Telephone: (513) 679-2700
FAX: (513) 679-2771

**Via United Parcel Service**

**WARNING LETTER**
**CIN-16-506509-22**

September 20, 2016

Matthew J. Buderer, Vice President
Buderer Drug Company, Inc.
26611 Dixie Hwy, Suite 119
Perrysburg, OH 43551-1765

Dear Mr. Buderer:

Between December 14, 2015, and January 4, 2016, a U.S. Food and Drug Administration (FDA) investigator conducted an inspection of your facility, Buderer Drug Company, Inc., located at 26611 Dixie Hwy, Suite 119, Perrysburg, OH 43551-1765. During the inspection, the investigator noted that you were not receiving valid prescriptions for individually-identified patients for a portion of the drug products you were producing. In addition, the investigator observed serious deficiencies in your practices for producing sterile drug products, which put patients at risk. For example, the investigator observed partially stoppered vials being transferred from the ISO 5 area through the ISO 7 area prior to placing them into the **(b)(4)**. Also, the investigator noted that the depyrogenated glassware used in the preparation of products intended to be sterile was stored in an unclassified area without any data to support that the glassware remained pyrogen free throughout the storage period. Moreover, your firm's **(b)(4)** parameters used to depyrogenate the glassware had not been determined to be effective at removing pyrogens. Furthermore, you do not test each batch of your finished drug products intended for intrathecal administration to ensure that the amount of endotoxin is within an acceptable limit. This is of particular concern as the endotoxin limit for these products is significantly lower than other parenteral drug products.

FDA issued a Form FDA 483 to your firm on January 4, 2016. FDA acknowledges receipt of your facility's responses dated January 15, 2016, and May 15, 2016. 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 may qualify for exemptions from three sections of the FDCA: compliance with current good manufacturing practice (CGMP) requirements, 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 necessary to qualify for the exemptions under section 503A. During the FDA inspection, the investigator 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.

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

## B. Violations of the FDCA

The drug products that you manufacture and distribute without valid prescriptions for individually-identified patients are misbranded drugs in violation of section 502(f)(1) of the FDCA. 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 such drugs is also subject to FDA's CGMP regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. The FDA investigator observed significant CGMP violations relating to aseptic processing at your facility, causing drug products intended or expected to be sterile that were manufactured and distributed without a prescription to be adulterated within the meaning of section 501(a)(2)(B) 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 for them 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].

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, the FDA investigator 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 the drug products to be adulterated under section 501(a)(2)(A) of the FDCA. For example, the investigator observed partially stoppered vials being transferred from the ISO 5 area through the ISO 7 area prior to placing them into the **(b)(4)**. Also, the investigator noted that the depyrogenated glassware used in the preparation of products intended to be sterile was stored in an unclassified area without any data to support that the glassware remained pyrogen free throughout the storage period. Moreover, your firm's **(b)(4)** parameters used to depyrogenate the glassware had not been determined to be effective at removing pyrogens. Furthermore, you do not test each batch of your finished drug products intended for intrathecal administration to ensure that the amount of endotoxin is within an acceptable limit. This is of particular concern as the endotoxin limit for these products is significantly lower than other parenteral drug products.

The FDA investigator also observed 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:

1. Your firm failed to establish and follow processing procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile (21 CFR 211.113(b)).

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

3. Your firm failed to ensure drug product containers are cleaned and sterilized to remove pyrogenic properties to assure suitability for their intended use, and depyrogenation processes are validated (21 CFR 211.94(c)).

4. 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)).

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 of the components used to make the drug and results in the drug being adulterated.

**C. Corrective Actions**

We have reviewed your firm's corrective actions, as documented in your January 15, 2016, and May 15, 2016, responses. Although some proposed corrective actions are adequate, others could not be fully evaluated because your response did not include sufficient information or supporting documentation. For example, your response did not include data to support that the **(b)(4)** parameters can achieve effective depyrogenation of your glassware. Your firm's response indicated that you started an endotoxin testing program to validate storage of your depyrogenated glassware in an unclassified area and you set beyond-use dates of less than **(b)(4)**; however, you did not provide further documentation for evaluation of the endotoxin results. Also, you did not provide your revised SOPs or log records regarding your "more robust" environmental monitoring program, which includes **(b)(4)** sampling, **(b)(4)** and **(b)(4)** sampling on a **(b)(4)** basis. Furthermore, you stated in your May 2016 response that the endotoxin testing for your stock solutions and finished sterile drug products, including intrathecal products, have been sent to a third party testing facility and you are still awaiting the final results.

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. 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. In addition, 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, as amended by the Food and Drug Administration Safety and Innovation Act (Pub.L. 112-144, Title VII, section 711).

You should also correct the violations of FDCA sections 502(f)(1) noted above.

**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 working days of receipt of this letter, please notify this office in writing if you have taken any specific steps to correct violations. Please include the reference number listed above and 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 15 working days, state the reason for the delay and the time within which you will complete the corrective action. Your written notification should be addressed to:

Mark Parmon, Compliance Officer
FDA Cincinnati District Office
U.S. Food and Drug Administration
6751 Steger Drive
Cincinnati, OH 45237

If you have questions regarding any issues in this letter, please contact Mr. Parmon via email at mark.parmon@fda.hhs.gov or by phone at (513) 679-2700 ext. 2162.

Sincerely,
/S/
Steven B. Barber
District Director
Cincinnati District

[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.