University Of Michigan 9/28/17

Division of Pharmaceutical
Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
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September 28, 2017

WARNING LETTER

Case# 518396

UPS NEXT DAY
SIGNATURE REQUIRED

Stanley S. Kent, R.Ph.
Chief Pharmacy Officer
University of Michigan Medical Center
1500 E. Medical Center Drive
Ann Arbor, MI 48109-5000

Dear Mr. Kent:

From June 6, 2016, to June 29, 2016, U.S. Food and Drug Administration (FDA) investigators inspected your facility, University of Michigan Medical Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5000. During the investigation, 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 June 29, 2016. FDA acknowledges receipt of your facility's response, dated July 15, 2016. Based on this inspection, it appears that you produced drug products that violate the Federal Food Drug and Cosmetic Act (FDCA).

A. 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, the investigators observed operators transferring components, containers and supplies from the ISO 7 cleanroom into the ISO 5 hood without disinfection. Investigators also observed that operators demonstrated poor aseptic practices, such as resting their gloved hands and sterile gown sleeves in the ISO 5 working area during aseptic processing. Your firm also uses non-sterile wipes for cleaning the ISO 5 hoods. In addition, your ISO 7 cleanroom **(b)(4)** was noted to contain surfaces that are not easily cleanable such chairs, computer equipment, damaged floor seam with crevices, ceiling tiles with surface damage, including small indentation and peeling. Furthermore, your firm failed to demonstrate through appropriate studies that the hoods are able to provide adequate protection of the ISO 5 area in which sterile products are being produced. Therefore, your products were produced in an environment that poses a significant contamination risk.

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.

B. Corrective Actions

We have reviewed your firm's response to the Form FDA 483

Regarding the insanitary condition observations in the Form FDA 483, we are unable to fully evaluate some of your corrective actions due to lack of adequate supporting documentation:

1. You stated that you trained your staff on the importance of proper hand positioning inside the ISO 5 work areas. However, you did not provide an updated copy of your procedures or your training records.

2. You stated that your material transfer process has been improved as all "wipe-able" surfaces will be disinfected with **(b)(4)** prior to placement into the ISO 5 areas. However, your procedure failed to describe in detail how other surfaces will be sanitized.

3. You state that the floors, ceiling tiles, and rust like substances have been removed or fixed. However, your firm failed to provide supporting documentation of the repairs.

You did not address the following observations related to insanitary conditions: Lack of smoke studies under dynamic conditions inside the ISO 5 work areas and the use of non-sterile wipes

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.

FDA strongly recommends that your management 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.

C. 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 15 working days, state the reason for the delay and the time within which you will complete the correction.

Please send your electronic reply to: ORAPHARM3_RESPONSES@fda.hhs.gov

Attn: Tina M. Pawlowski, Compliance Officer
U. S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Refer to the Unique Identification Number (Case# 518396) when replying. If you have questions regarding the contents of this letter, please contact Tina M. Pawlowski by phone at (313) 393-8217.

Sincerely,
/S/
Nicholas F. Lyons
Director of Compliance
Division of Pharmaceutical Quality Operations III