DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Via UPS

July 29, 2016

Dr. Barry R. Goldspiel
Acting Chief, Pharmacy Department
National Institutes of Health
Clinical Center Pharmacy Department
10 Center Drive, Building 10, Room 1C240
Bethesda, MD 20892-1196

Dear Dr. Goldspiel:

From May 19, 2015 to May 29, 2015, U.S. Food and Drug Administration (FDA) investigators inspected the NIH Clinical Center Pharmacy Department, Building 10, 10 Center Drive, Bethesda, MD 20892. We inspected the following areas:

- the Pharmaceutical Development Section (PDS), where you produced drugs for Phase 1 and Phase 2 clinical trials
- the Intravenous Admixture Unit (IVAU), where you produce sterile drugs for administration to patients at the NIH Clinical Center.

In the PDS, our investigators observed significant violations of current good manufacturing practice (CGMP) requirements for finished pharmaceuticals, causing your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

In the IVAU, our investigators observed that your 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 FD&C Act, 21 U.S.C. § 351(a)(2)(A).

We have reviewed your initial response, dated June 19, 2015, as well as all subsequent correspondence. Additionally, we have considered the discussions and materials provided to us at our face-to-face meetings on September 17, 2015 and April 29, 2016.

Pharmaceutical Development Section (PDS)

During our inspection, our investigators observed specific CGMP violations including, but not limited to, the following:

1. You failed to establish a 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).

2. You 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. You failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems for aseptic processing necessary to prevent contamination or mix-ups. 21 CFR 211.42(c)(10).

4. You failed to have facilities used in the manufacture, process, packaging and holding of drug products of appropriate construction to facilitate cleaning, maintenance, and proper operations. 21 CFR 211.42(a).

5. You failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. 21 CFR 211.192.

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

On May 22, 2015, during our inspection, you issued a hold on all production in the PDS. Shortly thereafter, you put additional controls in place to assess the quality of the products you had already produced and, subsequently, you produced only a small volume of non-sterile drug products for which you considered the production operations to be lower risk. In your May 27, 2016, response to our questions and comments dated April 25, 2016, you indicated that ongoing work in the PDS had been decommissioned. If you plan to resume or initiate production at PDS, please notify us in writing.

Intravenous Admixture Unit (IVAU)

During our inspection, our investigators observed specific insanitary conditions, including, but not limited to, the following:

1. You had inadequate separation of your aseptic processing area from your common pharmacy, with uncontrolled flow of personnel and no pressure differentials between the two areas. Furthermore, you had not adequately segregated non-hazardous drug operations from hazardous drug operations.

2. You did not use a sporicidal disinfection agent in the cleaning and disinfection program for ISO 7 and ISO 5 areas.

3. An operator produced drug products intended to be sterile with an exposed wrist and exposed facial hair.

We also note that you failed to conduct procedures that are critical to ensure that you identify and remediate insanitary conditions at your facility. For example, you failed to demonstrate through appropriate studies that your hoods are able to provide adequate protection of the ISO 5 area in which sterile drug products are produced.

You have taken significant steps to resolve the insanitary conditions identified during the inspection. For example, personnel are now wearing properly fitting gowning items and you have provided additional operator and supervisory training on proper gowning. You also promptly began using a sporicidal agent in your routine cleaning of the IVAU and have worked with your consultants to develop a more robust cleaning and disinfection standard operating procedure (SOP). Additionally, you have reduced the traffic in closest proximity to your aseptic work areas. To further reduce risks to Clinical Center patients, you have assigned more conservative beyond use dates (BUDs) to your products. Furthermore, you are continuing to work with your consultants to implement related operational and facility design improvements, including a more robust procedure for characterization of the air flow in the ISO 5 classified hoods where you produce sterile drugs.

You submitted plans for an interim IVAU space to us in May and June, 2016. These plans represent a substantial improvement over your current IVAU. Therefore, we encourage you to move into the interim IVAU as quickly as possible. You have indicated that you intend to move into the interim IVAU by October 31, 2016. If your target date is delayed for any reason, please notify us in writing with an explanation for that delay.

We acknowledge your statement that you are designing and building a new IVAU space that will meet or exceed all relevant regulatory requirements. You also committed to develop a catalogue of robust SOPs that reflects current standards and meets the needs of the IVAU.

Although your described corrective actions and plans for future action address the specific observations cited on the FDA Form 483 (483) issued for the IVAU, you are responsible for identifying any additional and future insanitary conditions and promptly taking corrective actions. It is your responsibility to ensure compliance with all requirements of federal law, including FDA regulations.

Send your reply to:

Timothy Pohlhaus, PhD
Senior Policy Advisor
U.S. Food and Drug Administration
White Oak Building 51, Room 4320
10903 New Hampshire Avenue
Silver Spring, MD 20993

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov

Please identify your response with FEI 3011547221.

Sincerely,

_____/s/_____
Thomas Cosgrove, JD
Acting Director
Office of Compliance
Center for Drug Evaluation and Research