S.R. Burzynski Manufacturing Facility 6/13/16

Department of Health and Human Services

Public Health Service
Food and Drug
Administration

Via UPS
Return Receipt Requested

Warning Letter 320-16-17

June 13, 2016

Dr. Stanislaw R. Burzynski
President
S.R. Burzynski Manufacturing Facility
12707 Trinity St.
Stafford, TX 77477-4212

Dear Dr. Burzynski:

The U.S. Food and Drug Administration (FDA) inspected your clinical supply manufacturing facility, S.R. Burzynski Manufacturing Facility at 12707 Trinity St., Stafford, Texas, from March 9 to 19, 2015.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because the methods used in, or the facilities or controls used for, the manufacturing, processing, packing, or holding of your drug products do not conform to CGMP, your drug products are 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).

We reviewed your firm's response received on April 10, 2015, in detail and note that it lacks sufficient corrective actions. Poor CGMP conditions at a manufacturing facility can ultimately pose life-threatening health risks to patients. This concern is particularly acute for immunocompromised individuals who may receive your firm's **(b)(4)** drug products.

Our investigators observed specific violations including, but not limited to, the following.

1. 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).Your firm also failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. 21 CFR 211.63

Your poor facility and equipment design inadequately protects the sterile **(b)(4)** product during manual manipulations, poses a substantial hazard to product sterility, and presents an unreasonable risk to patient safety. For example, you manually process materials in an ISO 5 (class 100) clean zone on a **(b)(4)** open to the surrounding ISO 7 (class 10,000) clean room environment. This arrangement permits the ingress of low quality air into the aseptic processing environment.

Furthermore, you have not established and followed appropriate written procedures to ensure that your intensively manual aseptic process is capable of reproducibly yielding sterile **(b)(4)** units. At the time of the inspection, your firm's most recent process simulation (media fill) to assess aseptic process control was conducted in 2010, yet your firm aseptically manufactured approximately **(b)(4)** batches of sterile **(b)(4)** drugs between December 2010 and March 2015. Your firm's failure to perform routine process simulations on at least a semi-annual basis means your firm cannot ensure that your aseptic process remains in control and results in the routine production of sterile **(b)(4)** drugs for administration to patients.

Your firm also failed to establish and follow appropriate written procedures to prevent microbiological contamination of sterile **(b)(4)** products. Your firm manufactured drugs by **(b)(4)** materials that were stored under non-sterile conditions, increasing product contamination risk. Your firm collected **(b)(4)** and transferred these **(b)(4)** to a large **(b)(4)** container sealed with a loose fitting lid. Your firm also collected the **(b)(4)** and transferred those to the same large **(b)(4)** bin. You held the **(b)(4)** and **(b)(4)** in a non-sterile state for an extended period of time, more than **(b)(4)** from the transfer of the oldest batch **(b)(4)** to the **(b)(4)** bin. When sufficient **(b)(4)** and **(b)(4)**, you used them to manufacture a new batch of drugs. These uncontrolled conditions exposed the product to contamination from bioburden and hazardous microbial byproducts (e.g., endotoxin).

2. Your firm 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)

Cleaning and Disinfection Procedures

Your firm lacks documented evidence that your operators cleaned and disinfected the manufacturing room and equipment properly to produce aseptic conditions. Our investigators also observed that operators did not conduct cleaning and disinfection in a manner appropriate to maintain the aseptic environment.

Environmental and Personnel Monitoring

Your firm lacked sufficient environmental monitoring of the critical ISO 5 clean zone, the ISO 7 aseptic processing room (in which the ISO 5 clean zone is located), and the adjacent ISO 7 support rooms.

When our investigators asked for your environmental monitoring documentation, the only documentation you could provide for the ISO 7 support rooms surrounding the aseptic processing room was from 2005. Due to the interdependence of the various rooms that make up an aseptic processing facility, monitoring of the surrounding support areas is essential to ensure adequate environmental control. A lack of sufficient environmental monitoring reduces the likelihood of detecting contamination of your sterile **(b)(4)** drugs.

In addition, your personnel monitoring program to maintain microbiological contamination-free gloves and gowns did not include all operators who aseptically manufacture your sterile **(b)(4)** drug products.

Equipment to Control Aseptic Conditions

Your firm was unable to produce documented evidence that the high-efficiency particulate air (HEPA) filters function properly to control the aseptic conditions in the ISO 5 clean zone. You manually produced sterile **(b)(4)** drug products in an environment of unknown air quality.

3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination. 21 CFR 211.28(a)

The garbing (consisting of face masks, hair nets, gloves, and suits without hoods) used at your facility is not adequate to protect the drug product from microbiological contamination during sterile processing. During your demonstration of cleaning and disinfection practices for your aseptic processing room, our investigators observed an operator who wore eye makeup with no eye protection. The operators wore clothing that allowed for exposed skin on their faces and necks. Furthermore, personnel reused these suits on multiple aseptic processing production days, with no cleaning or sterilization between uses. Rather than instructing operators to dispose of used suits after each **(b)(4)**, the procedure your firm used at the time of the inspection instructed cleanroom operators to “store the suit in a clean place for next entry.” Your failure to ensure that personnel wear clothing appropriate to protect the drug product from contamination increases the significant risk to product sterility in your aseptic processing operation.

4. Your firm failed to subject each lot of a component with potential for microbiological contamination that is objectionable in view of its intended use to microbiological tests before use. 21 CFR 211.84(d)(6)

Your firm failed to ensure that the **(b)(4)** you use to manufacture your drug product was adequate for **(b)(4)** drug manufacture. Your firm prepares **(b)(4)** using an **(b)(4)** system that lacks adequate qualification, validation, maintenance, and monitoring to

ensure **(b)(4)** of suitable quality. For example, your firm used a **(b)(4)** system for **(b)(4)** production. Your firm also did not test **(b)(4)**. Your lack of robust design, control, and monitoring increases the risk of impurities (including endotoxins) in the **(b)(4)** your firm uses in sterile **(b)(4)** drug manufacturing.

Conclusion

Although you indicated in your firm's response received on April 10, 2015, that you were developing new procedures and performing some personnel training, simply revising procedures and retraining personnel are inadequate to correct the problems described above. For example, there are inherent flaws in your facility design that promote the influx of poor quality air into the aseptic processing (ISO 5) zone where the sterile product is exposed. These and other conditions observed at your firm and discussed in this Warning Letter create contamination hazards that cannot be adequately addressed by changes to procedures and training of the type you propose. In sum, the violations discussed in this Warning Letter compromise the sterility assurance of your products and demonstrate significant risks to patient safety, especially because immunocompromised individuals may receive your firm's drugs.

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. Hiring a consultant does not remove your firm's obligation to fully comply with CGMP. Your firm remains responsible for ensuring that the drugs you manufacture have appropriate identity, strength, quality, and purity.

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

After you receive this letter, you have 15 working days to respond to this office in writing. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your completion date and reasons for delay.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts.

Until you completely correct all violations and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer.

Send your reply to:
Lynnsey Renn, Ph.D.
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359

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 1626573.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research