B. Braun Medical Inc 5/12/17

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration
Los Angeles District
19701 Fairchild Road
Los Angeles, CA 92612

WARNING LETTER

UNITED PARCEL SERVICE
SIGNATURE REQUIRED

May 12, 2017

WL # 30-17

Mr. Sergio Casas
Acting General Manager
Vice President and General Manager
B. Braun Medical, Inc.
2525 McGaw Avenue
Irvine, CA 92614

Dear Mr. Casas:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, B. Braun Medical, Inc., at 2525 McGaw Avenue, Irvine, from April 18 to May 11, 2016.

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

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding 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 June 1, 2016, response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Your firm failed to establish and follow adequate written responsibilities and procedures applicable to the quality control unit (21 CFR 211.22(d)).

During the inspection, we observed that your quality unit was not effectively exercising its responsibilities, particularly for investigating product defect complaints, manufacturing deviations, and adverse trends. Your written procedures (e.g., Corrective/Preventive Action Program Quality Procedure; Discrepancy Management System (DSMS) Quality Procedure) require that you take appropriate corrective action and preventive action (CAPA) to address root causes in a timely manner. However, in many instances, implementation of corrective actions was significantly delayed or the actions implemented were ineffective.

Field Alert Reports

While reviewing your field alerts, we determined the status of investigations relating to 76 field alert reports (FAR) that you filed for parenteral drugs produced on your partial additive bag (PAB), Excel, and Titan XL lines. Of these FAR, 44 were related to customer complaints regarding visible particulate matter and leaking intravenous (IV) bags.

While you opened investigations into these significant complaints, some investigations have been open for extended periods without resolution. Your failure to conduct prompt and thorough investigations, including ensuring CAPA effectiveness, prolonged patient exposure to potential hazards posed by defective products.

Leaking Titan XL bags

You launched the Titan XL bag line, containing 0.9 percent sodium chloride irrigation, in September 2013 and first received complaints for leaking units in October 2013. You further identified a trend for complaints of leaking units in November 2013. On January 1, 2014, you opened investigation CAPA 2014-003-CA. On February 26, 2014 you approved an investigation report which identified the most likely root cause for the leaking units to be failing port welds induced by handling during shipping.

A further investigation, documented in your report dated December 18, 2015, was conducted to simulate distribution and handling of your product. This investigation also identified lost integrity during shipment and distribution as the likely root cause of leaking units. In addition, you determined through your investigations that your initial shipping studies had not adequately simulated the distribution of your drug products from the manufacturing site to the end user.

However, our May 2016 inspection found that, approximately 28 months after the investigation was opened, you had not implemented corrective actions despite identifying an adverse trend and many FARs submitted to FDA regarding Titan IV bag leaks. Since our inspection, your firm has submitted several additional FAR regarding leaking Titan IV bags.

Leaking and Contaminated PAB

You identified negative packaging trends and corner leakage in your PAB on June 2, 2014. From August 4 through September 16, 2014, you received six consumer complaints regarding bag leakage and mold contamination. You did not initiate an investigation until January 14, 2015 (2015-001-CA). On July 27, 2015, you identified five apparent root causes and submitted a change control request to implement corrective actions.

By our 2016 inspection nine months later, you had not implemented corrective actions to fully address root causes. In addition, you initiated a FAR on December 10, 2015, for seven complaints about visible particulate matter and IV bag leaks in lot J5J706 of dextrose injection USP, which was made on a PAB line. Rather than open a new investigation, you incorporated these complaints into the 2015-001-CA investigation you opened almost a year earlier on January 14, 2015.

Also, your 2013 and 2014 annual product reviews had identified an increase in complaints about PAB filled with 0.9 percent sodium chloride injection. The majority of complaints concerned leaking bags and particulate matter.
At the time of our 2016 FDA's inspection, you had neither evaluated the state of control of your process, nor adequately implemented corrective actions to address repeated instances of leaking IV bags and visible particulate matter.

Execution of CAPA to Improve Leak Detection

As a result of investigation 2015-001-CA, your quality unit implemented a change to the PAB assembly process checks. You increased the in-process leak test pressure to improve the detection of PAB top-cap corner leaks. However, your quality unit failed to ensure the leak test was adequate to detect these leaks. You also did not update your written procedure for conducting water leak tests, nor did you ensure that your technicians documented the actual pressure used during leak tests.

Container-closure integrity is imperative to ensure sterility of parenteral drugs, and manufacturing operations should be designed to prevent visible particle contamination.

During our previous inspections in February 2014 and March 2015, we observed that your quality unit failed to ensure that adequate CAPA were implemented to control your processes and prevent the release of defective product.

2. Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR 211.68(a)).

You failed to adequately qualify your **(b)(4)** Pinhole Leak Detector Machine which you use during inspection of finished drug products manufactured on PAB Line **(b)(4)**.

You lacked adequate qualification studies to demonstrate that the equipment is capable of detecting pinholes leaks. Corner pinholes comprise a large proportion of defects seen in your rejected PAB products. Some of these pinholes are as small as 127 microns. However, you qualified your equipment to detect pinholes greater than or equal to **(b)(4)** microns, approximately four times as large as known defects in your bags.

You also failed to qualify the detector under circumstances comparable to those expected during routine production. For example, you did not use your smallest volume of drug filled in the largest container, which is the worst-case product. In addition, your detector settings, as recommended by your vendor, do not sufficiently account for variables including consistency of wall thickness and product conductivity for all seven products manufactured on PAB line **(b)(4)**.

During installation qualification you performed sensitivity acceptance testing to determine how frequently the leak detection machine would fail to detect leaking containers. You approved this qualification, although five of the **(b)(4)** products manufactured on the PAB **(b)(4)** line failed the sensitivity acceptance criteria for false acceptance rate (leaking containers accepted as good product) of less than **(b)(4)** percent. The false acceptance rates of the five products which failed the qualification test ranged from 0.33 to 1.33 percent. You disregarded these failures and continued equipment qualification activities. The qualification study was subsequently approved by your manufacturing, engineering, and QA groups on September 24, 2014.

During the February 2014 inspection, we observed deficiencies with elements of the validation of your in-process inspection methods.

Repeat violations at facility

In previous FDA inspections of your facility in 2013, 2014, and 2015, FDA cited the same or similar CGMP violations. FDA detailed these violations in a July 20, 2014, Untitled Letter to your facility, and again discussed them at a November 3, 2015, regulatory meeting with your firm at FDA headquarters.

You proposed specific remediation for these violations in your responses. Given the recurring nature of the violations, it is clear that your CAPA are not robust and sustainable. Remediation efforts have not been adequately implemented.

These repeated violations demonstrate a failure of your executive management to exercise proper oversight and control over the manufacture of drugs. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems, processes, and ultimately, products conform to FDA requirements.

We will determine the adequacy of the corrective actions and preventive actions that you committed to in your June 1, 2016, and subsequent responses during the next inspection.

CGMP consultant recommended

Because you failed to correct repeat violations, we strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. Your work with a qualified consultant should include, but not be limited to

- comprehensively evaluating the robustness of manufacturing design and control;
- reviewing adequacy of container-closure systems;
- enhancing investigations of individual complaints that report critical defects;

- evaluating your capability to identify, investigate, and effectively resolve manufacturing quality issues; and
- assessing your overall quality system, including CAPA, process performance and product quality monitoring, change management, and management review

Your use of a consultant does not relieve your obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

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.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at **drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov)**, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

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. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within 15 working days. 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 reasons for delay and your schedule for completion.

If you have questions regarding the contents of this letter, please contact Ms. Jessica Mu via email at **Jessica.Mu@fda.hhs.gov (mailto:Jessica.Mu@fda.hhs.gov)** or by phone at (949) 608-4477.

Please identify your response with FEI 2021236.

Send your reply to:

Kelly D. Sheppard
Director, Compliance Branch
Food and Drug Administration
Los Angeles District Office
19701 Fairchild
Irvine, CA 92612

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

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)