Inspections, Compliance, Enforcement, and Criminal Investigations

Teva Parenterals Medicines, Inc. 12/11/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration
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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

December 11, 2009

W/L 05-10

Dr Jeffrey D. Herzfeld
Senior Vice President and General Manager
Teva Parenteral Medicines, Inc.
19 Hughes
Irvine, CA 92618

Dear Dr. Herzfeld:

This is regarding our July 13 through July 24, 2009 inspection of your pharmaceutical manufacturing facility, Teva Parenteral Medicines, Inc., located at 19 Hughes, Irvine, California. The inspection identified significant violations of the Current Good Manufacturing Practice (CGMP) Regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations (CFR), Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of Section of 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacturing, processing, packing, or holding do not conform to or are operated or administered in conformity with, CGMP.

We have received your firm's responses of August 10, September 4 and 8, October 27 and 29; and November 13, 2009, and note these Responses lack sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited to:

1) Failure 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)].

For example, your firm has not tested each lot of raw materials used in the manufacture of Propofol Injectable Emulsion finished products to determine the presence and levels of bacterial endotoxin. Such raw materials include, but are not limited to, **(b)(4)**

Your firm's responses, dated August 10, September 4, and November 13, 2009, state that your firm will subject each lot of incoming raw material to full microbiological testing, including endotoxin testing. We will evaluate the implementation of this testing and verify that you are subjecting each lot of incoming raw materials to full microbiological testing during our next inspection.

2) Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, Whether or not the batch has already been distributed, or to extend the investigation to other batches of the same drug products or other products that may been associated with the same failure or discrepancy [21 CFR 211.192], For example:

A) Your firm's analysis of pooled samples from customer .complaint vials of finished product (Lot#**(b)(4)**) revealed an endotoxin concentration of **(b)(4)**. Your firm failed to identify a root cause and failed to implement a corrective action.

Your response, dated August 10, 2009, revised the final product release specification for endotoxin levels to **(b)(4)** in the Propofol Injectable Emulsion product. However, reducing the release specification for endotoxin levels may not alone mitigate the potential for adverse reactions for end users of the drug. It is a CGMP requirement that you implement adequate manufacturing practices and controls to prevent bacterial endotoxin contamination.

B) Your firm was unable to determine the cause of an out-of-trend level of bacterial endotoxin contamination found in three vials of finished product (Lot #**(b)(4)**) of Propofol Injectable Emulsion. No corrective action was taken in response to this finding at the time of manufacture, and your firm released the lot. Subsequently, samples of Lot #**(b)(4)** (the finished packaging designation for Lot #**(b)(4)**) of Propofol Injectable Emulsion, were collected **(b)(4)**, tested, and found to have bacterial endotoxin levels in excess of **(b)(4)**. This lot was recalled.

Your response, dated August 10, 2009, is inadequate. Your firm committed to an increased sampling plan and testing of in-process bulk emulsion and finished product. In addition, you proposed to change the finished product release specification for bacterial endotoxin to **(b)(4)**. You described a sample size in this response but did not include a scientific rationale for it in this response nor in the subsequent response of September 4, 2009.

C) Operational Investigation Reports # **(b)(4)** were initiated in November 2008 and January 2009 when **(b)(4)** vials in-process for filling with Propofol were found to contain water as they were exiting the depyrogenation tunnel. This deviation was discovered in the vials prior to their entering the filling machine on **(b)(4)** in **(b)(4)**. Also, these investigations did not include a review of the **(b)(4)** or **(b)(4)** Propofol products, which are manufactured on the same filling line.

Your response, dated August 10, 2009, is inadequate. As described in your revised standard operating procedure **(b)(4)** the implementation of **(b)(4)** requiring enhanced visual examinations for such discrepancies applies to subsequently runs only. Your response does not describe specific procedures for ensuring investigations are extended to other batches of the same drug product, or other potentially affected drug products, when unexplained discrepancies occur. Also, your response does not describe how these investigations will be documented.

Finally, your response does not address current lots in distribution that may have been impacted by the above deviation. You have not demonstrated that the water deviation was not present prior to November 2008, and particularly before you increased the number of visual examinations of vials following detection of the deviation.

D) Operational Investigation Report #**(b)(4)** was opened on **(b)(4)**, for a chipped lip vial found during the fill check. The investigation did not determine a root cause or include any explanation for ruling out or eliminating plausible causes. This report was subsequently closed on **(b)(4)**.

Your response, dated August 10, 2009, is inadequate because the corrective actions are not systemic. Your firm completed an investigation for this specific event and has re-trained personnel. However, your response does not address how your firm will assure all unexplained or significant discrepancies will be thoroughly reviewed.

3) Failure to establish adequate acceptance criteria for the sampling and testing conducted by the quality control unit to assure that batches of drug products meet appropriate statistical quality control criteria as a condition for their approval and release [21 CFR 211.165(d)].

For example, your firm's finished product sampling plan for **(b)(4)** and **(b)(4)** in Propofol Injectable Emulsion is not representative of the batch produced. A total of thirteen units are sampled per lot, with three tested for bacterial endotoxin and ten tested for bioburden. This sampling of thirteen units is irrespective of lot size, which may vary from **(b)(4)** to **(b)(4)** units (vials) per lot.

Your response, dated August 10, 2009, is inadequate. You do not reference a sampling plan that utilizes basic elements of statistical analysis or provide a scientific rationale for sampling that would vary the amount of samples taken according to the lot size. Your response does not define a confidence limit to ensure an accurate and representative sampling of the product.

4) Failure to test in-process materials for quality and purity as appropriate, at the commencement or completion of significant phases of the production process [21 CFR 21I.110(c)].

For example, your firm has not tested in-process non-sterile bulk solution after the **(b)(4)** process, as well as, end-of-run samples **(b)(4)** for the presence of bacterial endotoxin.

Your response, dated August 10, 2009, is inadequate. Although you committed to testing for bacterial endotoxin, you did not include the action limits to be established for bacterial endotoxin levels and specify a timeline when such testing will be implemented. Also, the proposed testing for bacterial endotoxin does not state the sample size or reference a statistically valid sampling plan used to determine the sample size.

5) Failure to test, through appropriate laboratory testing, each batch of drug product required to be free of objectionable microorganisms [21 CFR 211.165(b)].

For example, the bacterial endotoxin test methods used for the final release of Propofol Injectable Emulsion were not adequate to ensure detection of bacterial endotoxin as described below.

A) SOP **(b)(4)**, is deficient because there is no requirement for vortexing the finished product vials of Propofol Injectable Emulsion prior to sample preparation.

B) The pH was not checked by mixing a portion of the sample preparation with **(b)(4)** first before adjusting the pH of the sample preparation solution. Failure to do this may result in a pH in the sample-**(b)(4)** combined solution that is outside of the range specified by the reagent manufacturer.

C) There is no assurance that the **(b)(4)** is protected from vibration during testing of bacterial endotoxin via the **(b)(4)** test method.

Your response of August 10, 2009, is inadequate. Your response states that vibration absorbing material will be placed under the **(b)(4)**, but this has not been implemented. Your corrective actions regarding vortexing and pH adjustment appear to be adequate, and these will be evaluated at a future inspection.

Additionally, your response does not address possible similar deficiencies that may exist with respect to the laboratory release testing of other drug products your firm manufactures.

6) Failure to demonstrate equipment used in the manufacture, processing, packing, or holding of drug products is of appropriate design to facilitate operations for its intended use [21 CFR 211.63]. For example:

A) The validation of Cycles #2 and # 3 for the **(b)(4)** Washers #1 and #2 did not include an evaluation or validation with **(b)(4)**. Such an evaluation or validation is necessary to demonstrate that the acceptance criterion of "**(b)(4)**" in bacterial endotoxin is met. In addition, there was no other evidence provided, such as results from any ongoing sampling and testing of the stoppers for endotoxin.

The validation report referenced in your response of August 10 and September 4, 2009, appears to address the observation. We will verify the data associated with the report during a future inspection.

B) The study to support the chemical and microbiological stability of Propofol bulk emulsion was not based on sampling from the **(b)(4)** mixing vessel, but on samples drawn from a **(b)(4)** "pressure can."

Your response, dated August 10, 2009, included a protocol **(b)(4)** for hold time validation and also discussed your plans to perform additional

bulk hold testing during the week of August 10, 2009. The report of this validation was included in your September 4, 2009 response and appears to be adequate. However, your response lacks raw data to support the chemical and microbiological test result. We will evaluate this data during a future inspection.

C) **(b)(4)** were used to monitor the interior temperature of the autoclave when revalidating temperature uniformity in the **(b)(4)** Sterilizer empty chamber. Your revalidation procedure does not describe how the **(b)(4)** temperature probe is secured to avoid its contact with metallic surfaces.

Your response, dated August 10, 2009, appears to be adequate. Your response refers to an updated procedure #**(b)(4)** that include instructions for positioning the **(b)(4)** to prevent contact with metallic surfaces. We will review this procedure during a future inspection.

7) Failure to clean and sanitize equipment and utensils at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a)]. For example:

A) You did not demonstrate that the **(b)(4)** system was adequate to ensure that the microbial bioburden and endotoxin levels of equipment meet predetermined acceptable limits.

Your response, dated August 10, 2009, is inadequate. Your firm cites an FDA Guidance Document, *Guide to Inspections Validation and Cleaning Processes*. More specifically, you refer to a statement in this Guidance Document: **(b)(4)**

Your response fails to address the major deficiency in the use of the **(b)(4)** system. Specifically, you failed to demonstrate that after cleaning, the equipment microbial bioburden and endotoxin levels met predetermined acceptable levels. Your firm did not support your cleaning and sanitization procedures with data supporting the system's ability to effectively remove these contaminants. Your response provides reasons why the **(b)(4)** system did not need to be validated, rather than addressing the insufficiency of the data supporting the adequacy of your cleaning and sanitizing procedures.

B) Your corrective actions to remove bacterial endotoxin from the Water for Injection (WFI) ports are to "flush for **(b)(4)** minutes." Your corrective actions also include using the **(b)(4)** washer to wash the Reverse Osmosis (RO) ports. However, there is no data to validate that a "flush for **(b)(4)** minutes" or washing the sampling ports in the **(b)(4)** washer can remove or reduce the presence of bacterial endotoxin in a water system.

Your response, dated August 10, 2009, is inadequate. Described as verification activities, your firm used this evidence to show that both a **(b)(4)** minute flush and a **(b)(4)** wash has historically reduced bacterial endotoxin levels. However, you failed to provide any validation or other studies to support this contention. In addition, the recurring presence of bacterial endotoxin levels in water sampled from the WFI and RO ports in excess of the USP specification indicates that the WFI and RO water systems are not in a state of control.

C) You stated that the **(b)(4)** "carrier cart," used to off-load washed and depyrogenated vial stoppers from the **(b)(4)** wash equipment, is cleaned only with **(b)(4)**.

Your firm does not properly clean and sanitize the **(b)(4)** "carrier cart" used to off-load washed and depyrogenated vial stoppers from the **(b)(4)** wash equipment. Your use of **(b)(4)** to clean the "carrier Cart" is not a proper method for reducing the presence of bacterial endotoxin. Furthermore, you lack any documentation to show that the "cattier cart" is periodically cleaned.

Your response, dated August 10, 2009, is inadequate. Your firm stated that it will continue to use **(b)(4)** to clean these cattier carts with a contact time of **(b)(4)** minutes. Management has agreed that **(b)(4)** is not adequate to reduce the presence of bacterial endotoxin. In addition, you proposed to perform a study to evaluate the bioburden and endotoxin load of the stopper contact portion of the cart by the end of September 2009. You have yet to submit this information for review.

D) Your firm has not performed a fogging validation study to support SOP # **(b)(4)**. This SOP describes fogging procedures for **(b)(4)** and **(b)(4)** production areas, **(b)(4)** vestibule and testing suite, and equipment in the **(b)(4)** pass-throughs. Additionally, you do not follow the frequency of testing, which is stated in this SOP as being conducted "**(b)(4)**." Rather, the fogging sanitization is conducted on an "as needed" basis under the direction of the microbiology or filling departments.

Your response, dated August 10, 2009, is inadequate. You stated fogging is performed on a monthly basis in addition to your normal routine cleaning practice. You stated you will perform a study by September 30, 2009 to validate the efficacy of **(b)(4)** solution in reducing the microbial load of the **(b)(4)** areas. This response does not reference fogging validation for **(b)(4)** production areas, the **(b)(4)** vestibule and testing suite **(b)(4)** in Building **(b)(4)**, and equipment in the **(b)(4)** pass-throughs. Also, this response does not describe the type of fogging to be implemented in these other areas. Your supplemental response of September 4, 2009, includes a validation protocol for fogging only **(b)(4)** areas and does not address the use of fogging in the other classified areas.

8) Failure of the quality control unit to take responsibility to approve and reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products [21 CFR 211.22(c)]. For example:

Your firm has not submitted a Post Approval Change or a Change Being Effected-30 (CBE-30) for ANDA **(b)(4)** that addresses **(b)(4)**, nor have you provided the scientific rationale for the **(b)(4)** impact this may have on the "Sterility Assurance Validation" of the finished product.

Your firm's response, dated August 10, 2009, included a CBE-30 letter to the Center for Drug Evaluation and Research (CDER) dated July 28, 2009. This letter states you have discontinued **(b)(4)** because this line has been dedicated for terminally sterilized products. This letter is currently under consideration.

9) Failure to define the responsibilities and procedures applicable to the quality control unit in writing [21 CFR 211.22(d)].

There is no written procedure to describe the review and approval of work orders performed for routine, on-demand maintenance, and repair of production equipment by the quality control unit (QCD). For example, the **(b)(4)** was repaired for batch **(b)(4)**, without QCD review. In another example, a work order was issued for an alarm sounding on the **(b)(4)**, related to production lot# **(b)(4)**. There was no notation made in the production batch record to indicate that an alarm occurred during the **(b)(4)**. Since neither event was reviewed, the QCD may not be aware of the problems or issues related to production equipment.

Your response, dated August 10, 2009, is inadequate. You stated that maintenance managers are the most capable individuals to determine whether the repairs conducted have restored the equipment back to proper operating conditions. However, your response involves multiple departments and SOPs to review routine maintenance, on-demand maintenance, and repair of production equipment. It is unclear if these collective corrective actions have defined the quality control unit as the responsible party to review work orders, and ensure adequate

maintenance and repair of production equipment. We will evaluate and verify the adequacy and implementation of these corrective actions during a future inspection.

10) Failure to implement systems for maintaining equipment used to control aseptic conditions in aseptic processing areas [21 CFR 211.42(c)(10)(vi)].

For example, your firm has not adequately investigated the root cause for three **(b)(4)** filter failures located in Room **(b)(4)**.

Your response, dated August 10, 2009, is inadequate. Your firm submitted an updated procedure, **(b)(4)**. This version adds instructions to determine the location of the leak and for inspection of the physical damage. However, this version does not require determination of a root cause for such failures. This revised procedure does not include provisions to help prevent recurrences of similar failures in the future.

11) Failure to maintain records for the cleaning and sanitizing of equipment [21 CFR 211.67(c)]. For example:

A) Your firm has failed to maintain records to document that the manufacturing areas and production equipment are exposed to sanitization solutions for the contact time of **(b)(4)** minutes. This requirement is described in the procedure entitled **(b)(4)**

Your response, dated August 10, 2009, appears to be adequate. Your film has committed to record the start and stop contact times for the sanitizing solutions in equipment cleaning logs. We will evaluate the implementation of this corrective action during a future inspection.

B) There is no record to document that the **(b)(4)** "stock pot" is periodically cleaned and sanitized prior to use. This "stock pot" is used to manually transfer approximately **(b)(4)** of bulk solution from the bottom of the **(b)(4)** mixing jacketed vessel to the top of the tank following the **(b)(4)** Process.

Your response, dated August 10, 2009, is inadequate. Your film reports that you have revised SOP **(b)(4)**, to document and describe specific equipment cleaned. However, the adequacy of using **(b)(4)** to reduce the presence of bacterial endotoxin on this "stock pot" is not addressed.

12) Failure to maintain an adequate system for monitoring environmental conditions of the aseptic processing areas [21 CFR 211.42(c)(10)(iv)].

For example, your firm's SOP for monitoring surface adhering microorganisms, air particle counts, and the microbiological monitoring of air in **(b)(4)** are deficient. Specifically, you do not require Environmental Monitoring (EM) sampling for **(b)(4)** areas such as the **(b)(4)** Room **(b)(4)** and the **(b)(4)** Room **(b)(4)** during manufacturing operations.

Your responses, dated August 10, September 4, and November 13, 2009, provide revised procedures for EM and appear to be adequate. We will verify the implementation of these procedures during a future inspection.

13) Failure to establish written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)].

For example, your SOP **(b)(4)** does not address environmental monitoring of personnel working in the **(b)(4)** Room **(b)(4)**. In general, you do not require or document the sampling of the gloves and gowns of personnel working in **(b)(4)** areas.

Your response, dated August 10, 2009, appears to be adequate for the **(b)(4)** capping rooms. The revised SOP **(b)(4)**, includes sampling of the gloves and gowns of personnel working in the **(b)(4)** Room **(b)(4)** during the manufacture of each lot of Propofol Injectable Emulsion. However, your response is inadequate in that you have not addressed how EM sampling will be performed on personnel working in other **(b)(4)** areas.

The violations cited in this letter are not intended to be an all-inclusive statement of the violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and 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. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture Propofol Sterile Emulsion for Injection, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address:
Alonza Cruse, District Director
Food and Drug Administration
Los Angeles District Office
19701 Fairchild
Irvine, CA 92612

If you have any questions about the content of this letter, please contact Dr. William Vitale, Compliance Officer, at 949-608-2919.

Sincerely,
/S/
Alonza E. Cruse
District Director

Cc: California Department of Public Health
Food and Drug Branch
1500 Capitol Avenue, MS-7602
Sacramento, CA 95899-7413

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