DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 19701 Fairchild<br>Irvine, CA 92612<br>(949) 608-2900 Fax:(949) 608-4417<br>Industry Information: www.fda.gov/oc/industry | 07/13/2009 - 07/24/2009 |
| | FEI NUMBER<br>2027158 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

**TO:** Jeffrey D. Herzfeld, Sr. Vice President and General Manager

| FIRM NAME | STREET ADDRESS |
|---|---|
| Teva Parenteral Medicines INC | 19 Hughes |
| CITY, STATE, ZIP CODE, COUNTRY | TYPE ESTABLISHMENT INSPECTED |
| Irvine, CA 92618 | Manufacturer |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## QUALITY SYSTEM

### OBSERVATION 1

The quality control unit lacks responsibility to approve and reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products.

Specifically,

A. The ANDA submits for the "Validation of Aseptic Operations (Sterile Media Fills) are performed "To minimize the bioburden levels during the manufacturing process, strict aseptic manufacturing procedures are followed." "Aseptic media fill runs are performed in order to confirm the established aseptic manufacturing procedures used by the company." "Process simulation runs (media fill runs) are performed (b) (4) (at a minimum) to requalify the total aseptic manufacturing operations for the filling process" to support of the "Sterility Assurance Validation" for the "Validation of Aseptic Fill and Terminal Sterilization Processes for Small Volume Parenteral Products". However, the company has not performed media fills since the original 1998 ANDA submission.

B. The company has not submitted, for example, a Post Approval Change or a Change (b) (4) for the ANDA that addresses the cessation of aseptic media fills and/or provides the scientific rationale with respect to the cessation and impact on the "Sterility Assurance Validation" for the finished product.

C. The company has not submitted, for example, a Post Approval Change or a (b) (4) for the ANDA regarding the use of a (b) (4) for the (b) (4) steam sterilization process with less than a (b) (4) spore population.

D. MIR 09-003, 01/20/09 concerns an (b) (4) results for bacterial endotoxin from three vials of Finished Product lot # (b) (4) with positive gel-clot in dilutions (b) (4) The MIR was reviewed and signed by the Quality Unit on 3/6/09 submits the impact on the product and corrective action as follows. "There is no impact to the products" and concerning the product test results, "Based on the above results, there is no corrective action taken." In addition, "Note: QA reviewed the batch record to determine if the manufacturing

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process could have contributed to the high endotoxin. No area was identified" 2/06/09. However, the source and cause of the (b) (4) bacterial endotoxin contamination remains to be unknown.

E. MIR 09-015, 06/10/09 concerns the pooled sample from customer complaint vials of finished product lot (b) (4) revealed an endotoxin concentration of (b) (4) EU/mg. The MIR was reviewed and signed by the Quality Unit on 7/6/09 submits the corrective action as follows. "Since the root cause is unknown, no corrective action can be implemented". However, the source and cause of the (b) (4) bacterial endotoxin contamination remains to be unknown.

## OBSERVATION 2

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

Specifically, there is no assurance that (b) (4) mg/ml (b) (4) ml is free of bacterial endotoxin. For example,

A. Lot (b) (4) failed bacterial endotoxin test on 7/15/2009 on retain samples. This lot met pre-shipment and post-shipment release and (b) (4) units were released for distribution on 2/18/2009.

B. Lot (b) (4) failed bacterial endotoxin test on 7/15/2009. This lot met pre-shipment and post-shipment release and (b) (4) units were released for distribution on 2/26/2009.

## OBSERVATION 3

In-process materials are not tested for quality and purity and approved or rejected by the quality control unit during the production process.

Specifically,

A. Following the (b) (4) Process, the non-sterile bulk solution is sampled to determine the level of bioburden. However, the Quality Unit has not taken into consideration obtaining samples of the non-sterile bulk solution to determine the presence, and levels of, bacterial endotoxin prior to the aseptic filling process.

B. The "end-of-run" samples (i.e., (b) (4) are sampled to determine the level of bioburden. However, the Quality Unit has not taken into consideration obtaining samples of the "end-of-run" aseptically filled vials to determine the presence, and levels of, bacterial endotoxin prior to the (b) (4) process.

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## OBSERVATION 4

Acceptance criteria for the sampling and testing conducted by the quality control unit is not adequate to assure that batches of drug products meet appropriate statistical quality control criteria as a condition for their approval and release.

Specifically, finished product sampling of (b) (4) mg/ml (b) (4) ml is not representative of the batch produced. For example, the firm's sampling plan for LAL and Particulate Matter requires (b) (4) units to be pulled. Out of those (b) (4) units pulled, (b) (4) units are pulled for LAL bacterial endotoxin testing per SOP # QML-1022 titled "Bacterial Endotoxins Test." The following (b) (4) ml batches were produced:

1. Lot (b) (4) units
2. Lot units
3. Lot units
4. Lot units

## OBSERVATION 5

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, Operational Deviation Report was not performed in accordance with SOP QPC-1010 which states that "If you can find NO assignable cause, state what is not the root cause (i.e. what has been eliminated as possibilities)." The Operational Investigation Report PR ID 81190, dated 10/25/2008, had no assignable root cause for the chipped vial of (b) (4) ml lot (b) (4) and had not eliminated other possibilities. This Operational Investigational Report was closed 10/29/2008. ~~The firm produced the following (b) (4) from 06/16/08 to~~ 08/22/08:

20mL

BTN 07/24/09

(b) (4) 1 ml

## OBSERVATION 6

Investigations of an unexplained discrepancy did not extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.

Specifically, the firm initiated investigation reports # 83109, 84180, 84184, 84224, and 88497 in November 2008 and January 2009 in response to "water found inside the vials during (b) (4) filling process". These (b) (4) mL vials with water were discovered as they were exiting the depyrogenation tunnel and prior to the filling machine on Line (b) (4) in Building (b) (4)

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There was no consideration to include 50mL or 100mL Propofol products that are manufactured on the same filling line which also may have been affected.

## OBSERVATION 7

The responsibilities and procedures applicable to the quality control unit are not in writing.

Specifically, there is no established written procedure to describe the review and approval of work orders performed for routine and on demand maintenance and repair of production equipment. For example, routine and on demand work orders for preventive maintenance and repair of (b) (4) Machine on 01/12/09 for batch (b) (4) is not reviewed by the QA unit.

## OBSERVATION 8

Drug product production and control records, are not reviewed by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically, during the manufacturing of (b) (4) drug product, the production department clean room fill operators utilize SOP PF-1009, Att. 1 "Production Department Information Log and Production Notes Down Time/Mechanical Issue" to document pump draw back settings, filtration rates, line speeds, and other information that the Production Department may utilize for building a product run history. This record is reviewed by QA during in-process record review. However, this documentation is not submitted or included in the production batch record. The "Production Notes Down Time/Mechanical Issues" for lot (b) (4) dated 1/12/09 documents for example, "Bad Crimps" at varied intervals during the capping operations. However, the production batch records do not describe the same level of details as noted in the "Production Notes", which only note "capper delay".

## FACILITITES AND EQUIPMENT SYSTEM

## OBSERVATION 9

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its intended use.

Specifically,

A. The June 2008 revalidations of the (b) (4) topper washer document number RV08-035 establishes "The objective of this revalidation was to demonstrate the ability of the (b) (4) Stopper Washer (b) (4) to reduce endotoxin and detergent residue and to

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monitor bioburden and particulate matter (PM) levels on the stoppers per SOP QOV-1118/Revison 4." The revalidation for Cycle (b) (4) and Cycle (b) (4) consists of "detergent with no siliconization" and "non-detergent with no siliconization", respectively. The cycles did not include an evaluation with silicon to demonstrate a bacterial endotoxin reduction to achieve "a minimum (b) (4) log reduction meeting the acceptance criterion". In addition,

1. The November 2008 revalidation for (b) (4) Stopper Washer (b) (4) referenced in document number RV08-056, establish that Cycle (b) (4) and (b) (4) consisted of a "detergent cycle with siliconization" and "non-detergent with no siliconization", respectively. However, for Cycle (b) (4) the "(b) (4) (b) (4) " The cycles did not include an evaluation with silicon to demonstrate a bacterial endotoxin reduction to achieve "a minimum (b) (4) log reduction meeting the acceptance criterion".

2. Despite the review and final approval by the Directors of Validation, Microbiology, Component Preparation and Quality Systems of the aforementioned 2008 (b) (4) Stopper revalidations, Cycle (b) (4) is not a validated cycle.

B. The Final Report No. SC99005: Concurrent Validation of (b) (4) /ml, (Preserved with (b) (4) Process, sign off date May 25, 2000 submits "(b) (4) (b) (4)

C. The (b) (4) is used to terminally sterilize the (b) (4) finished products. The ANDA submits that the steam sterilization validation will include the use of *Bacillus coagulans* biological indicators (BI) with "a minimum of a (b) (4) spores". However, in August 2004 (b) (4) uns), 2005 (b) (4) uns), 2007 (b) (4) uns) and in 2008 (b) (4) runs) the (b) (4) used for (b) (4) l vials consists of a (b) (4) pore population. (Please note that the steam sterilization cycle is not designed/intended to reduce the levels of bacterial endotoxin). In addition,

1. During the (b) (4) utoclave will generate an alarm message that signals any aberrant events that may occur during routine steam sterilization process. Examples of some alarms include "chamber pressure lack", external steam lack, phase time excess, sterilization temperature lack, circulation (b) (4) alarm, and sterilization time suspended. (Please note that these are examples of alarms and they are not intended to be an all inclusive list of (b) (4) alarms). As described by the Production Supervisor for Sterilization & Lyophilization the alarms are assessed, for example, before a deviation report is generated, request for maintenance, or decisions are made that no corrective measures are needed in response to the alarm events. However, there is no established written procedure to describe the manner with which the assessment and triage of the steam sterilization processing alarms are performed.

2. The (b) (4) evalidation of the empty chamber temperature uniformity uses (b) (4) to monitor the temperature of the autoclave interior. The establish procedures Revalidation of (b) (4) Autoclave – Terminal Sterilization #QOV-1041 describe how the (b) (4) re positioned and secured to the equipments

interior. However, the procedure does not address the manner with which the (b) (4) temperature probe is secured to assure that the temperature monitoring probe does not contact any metallic surfaces.

D. Utility (b) (4) micron filters used for nitrogen flush was not replaced with approved nitrogen filtration unit in accordance with SOP PGP-1007 titled "Utility Filters for Production Equipment, dated 3/10/09." The (b) (4) failed bubble point at less than (b) (4) psi final integrity testing on 6/20/2008 at drop # (b) (4) and was replaced with unapproved (b) (4) filter (b) (4) on 6/16/2008 which also failed final integrity testing on 8/22/2008. This nitrogen filter supplies nitrogen to the (b) (4) during the processing of (b) (4) From 06/16/08 to 08/22/08, the firm produced the following numbers of propofo (b) (4) g/ml lots

(b) (4)

## OBSERVATION 10

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Specifically, the firm's investigations into (High Efficiency Particulate Air) HEPA filter failure in aseptic filling rooms were incomplete. For example:

A. During periodic certification in December 2008, the following HEPA Filters failed leak testing:

| Location – Building (b) (4) | Classification | Filter Number | Leak Failure Result (Spec ≤ (b) (4) |
|---|---|---|---|
| (b) (4) | (b) (4) | (b) (4) | (b) (4) |

These HEPA filters in Building (b) (4) Line (b) (4) Filling room were "located in a critical area where the filling and stoppering process of (b) (4) drug production is performed" and "within the barrier shield over or near the stoppering equipment." The HEPA filter in Line (b) (4) compounding is "located in a critical area where the actual compounding process is being performed." The HEPA filters were subsequently replaced. Out-of-Tolerance HEPA Reports were generated. However, the firm failed to perform a root cause evaluation to determine an assignable root cause for the leak failures.

B. During periodic certification in May 2009, HEPA Filter# (b) (4) failed leak testing with a failure result of (b) (4) (spec= (b) (4) This filter is located in Building (b) (4) Room (b) (4) Component Prep in a non-critical area. This filter was recently replaced during the previous periodic certification in December 2008. An Out-of-Tolerance HEPA Report was

generated. However, the firm failed to perform a root cause evaluation to determine why the filter failed leak testing after (b) (4) months.

## OBSERVATION 11

Equipment and utensils are not cleaned and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

A. There are a number of existing conditions and practices concerning the evaluation and determination for the presence of bacterial endotoxin in the manufacturing facility and manufacturing operations. For example,

C. Washed and depyrogenated vial stoppers are off loaded from th(b) (4)ash equipment with the use of a stainless steel so-called "carrier cart" prior to the vial stoppers being placed inside poly bags for steam sterilization. The "carrier cart" is cleaned with 70% IPA. However, the 70% IPA is not intended to reduce the presence of bacterial endotoxin. There is no record to document that the "carrier cart" is periodically cleaned and sanitized.

D. The washed and depyrogenated vial stoppers are not routinely sampled to determine the level of bacterial endotoxin presence prior to steam sterilization. The silicone oil used for the vial stoppers is not sampled to determine the level of bacterial endotoxin. (Please note that the steam sterilization is not designed or intended to reduce the levels of bacterial endotoxin.)

E. An approximate(b) (4)iter stainless steel "stock pot" is used to manually transfer approximately (b) (4)iters of bulk solution from the bottom of the(b) (4)iter stainless steel mixing jacketed vessel to the top of the tank following the(b) (4) Process. There is no record to document that the stainless steel "stock pot" is periodically cleaned and sanitized prior to use.

B. There are a number of microbiology investigative reports (MIR) that report bacterial endotoxin recovery in various Water For Injection and Reverse Osmosis water ports. For example,

MIR 08-042, 5/28/08, WFI port(b) (4)
MIR 08-061, 7/10/08, WFI port
MIR 08-075, 10/14/08, WFI po
MIR 08-083, 12/4/08, WFI port
MIR 08-044, 5/19/08, RO port
MIR 08-081, 12/1/08, RO port
MIR 09-001, 01/20/09, RO port
MIR 09-010, 5/26/09, RO port

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The corrective actions taken to address the removal of bacterial endotoxin from the WFI and RO sample ports are to "flush for (b) (4) minutes" and to wash via the (b) (4) washer respectively. However, there is no data to validate that a "flush for 20 minutes" or washing the sampling ports in the (b) (4) washer can remove or reduce the presence of bacterial endotoxin.

C. The firm has not performed fogging validation study to support SOP # BMS-1001 titled "Sterile Area (b) (4) Procedure"

D. The firm's cleaning validation study, VAL285-1, Compounding Vessels and Associated Equipment in the (b) (4) Compounding Area using the (b) (4) CIP (Clean-in-Place) system, approved 10/20/00 was inadequate in that the firm failed to show that the process demonstrates that after cleaning, the equipment microbial bioburden and endotoxin levels meet predetermined acceptable limits. The firm utilized tailings of previously produced (b) (4) batches to "soil" the equipment. There was no known initial bioburden or bacterial endotoxin levels present in these tailings or solutions used in the soiling of the equipment. There was no other activity to show that the cleaning detergent, CP-3155, utilized by the CIP system is effective in the reduction of microbial bioburden and bacterial endotoxin to predetermined acceptable limits.

## OBSERVATION 12

Records are not kept for the cleaning and sanitizing of equipment.

Specifically, the Annual Evaluation of Antimicrobial Efficacy of routine Sanitizers against Cleanroom and Bioburden isolates, Microbiology Report MR 09-032, approval date of 02/24/09 establishes the following. "There are several cleaning solutions which have been qualified for use in Teva Parenteral Medicines in Irvine to sanitize the classified areas. The evaluation of the effectiveness of the cleaning and sanitization agents used to clean the facility and the sanitization agents used by personnel to sanitize their gloves prior to entering the manufacturing area have been qualified and are challenged annually using the test tube study." The report concludes an efficacy of the varied sanitizers via "a contact time of (b) (4) minutes". However, there are no records to document that the manufacturing areas and production equipment are exposed to the sanitization solutions for "a contact time of (b) (4) minutes".

## OBSERVATION 13

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, the Surface Adhering Microorganisms, Microbiological Sampling Buildin(b) (4) #QML-1403; Monitoring of Air Particle Counts in environmentally Controlled Areas in Building (b) (4) #QML-1105, and the Microbiological Monitoring of Air - Building (b) (4) Use of (b) (4) Sampler) #QML-1301 standard procedures establish a (b) (4) frequency of the (b) (4) sampling performed for the (b) (4) manufacturing areas that include the manufacturing room [illegible], which is used for capping of the

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finished product vials. (b) (4) ml lots of (b) (4) finished product referenced in consumer complaints did not include (b) (4) mpling for the (b) (4) manufacturing capping area during there respective dates of manufacture.

**LABORATORY SYSTEM**

**OBSERVATION 14**

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically, the firm's SOP No. QML-1022 titled "Bacterial Endotoxin Test" is deficient in that:

1. There is no requirement for vortexing the finished product via (b) (4) prior to sample preparation.
2. The firm did not follow USP <85> for Bacterial Endotoxin testing in checking pH by mixing a portion of the sample prep with lysate first before adjusting the pH of the sample prep solution.
3. There is no assurance that the heat block is protected from vibration during testing of bacterial endotoxin via the gel clot test method.

**PRODUCTION SYSTEM**

**OBSERVATION 15**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and written.

Specifically, the Surface Sampling of Personnel standard procedure #QML-1224 establishes "A monitoring program for personnel working in the sterile environment is necessary to maintain the proper environmental conditions for filling aseptic products." And, "The objective of this procedure is to maintain personnel surface levels within acceptable microbial levels to assure minimal probability for product contamination." However, the procedure is silent with respect t (b) (4) mpling for personnel working in the (b) (4) apping area room (b) (4) There is no (b) (4) ampling of personnel during the capping of (b) (4) nished products prior to steam sterilization process.

**RAW MATERIALS SYSTEM**

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## OBSERVATION 16

Each lot of a component liable to objectionable microbiological contamination is deficiently subjected to microbiological tests before use.

Specifically, not all of the raw materials used in the manufacture of (b) (4) inished products are periodically tested to determine the presence and levels of bacterial endotoxin. For example, the (b) (4) (b) (4) are not sampled to determine that they do not provide a source of bacterial endotoxin.

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