DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313) 393-8139 Industry Information: www.fda.gov/oc/industry	02/12/2015 - 02/23/2015* FEI NUMBER 3011357279

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: William C. Drake, President

FIRM NAME	STREET ADDRESS
Tri-Med, Inc. dba Advanced Care Infusion-Shelby	50860 Corporate Dr Suite 100
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Shelby Township, MI 48315-3123	Producer of Sterile Drug Products

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 I OBSERVED:

OBSERVATION 1

Written records of investigations into unexplained discrepancies do not always include the conclusions and follow-up.

Specifically,

For each of the discrepancies and out-of-specification results below, there was inadequate investigation in that no immediate remediation and/or appropriate corrective actions were taken to address the issue.

i. (b) (4) active viable air sampling performed in your facility on 7/9/14 included the following results
   a. (b) (4) air samples in the ISO 7 buffer room resulted in notations for "Fungus Present" by the contract testing laboratory. No speciation for any fungi was provided and the presence of fungi was not included in the numerical cfu count for these samples.
   b. (b) (4) air samples in the ISO 7 buffer room exceeded the limit of NMT (b) (4) with a result of 12 cfu/m^3.
   c. (b) (4) air samples in the ISO 7 buffer room recovered *Raoultella planticola*, a gram-negative rod bacterium.
   d. (b) (4) air samples in the ISO 8 ante room recovered *Acinetobacter lwoffii*, a gram-negative cocco-bacillary rod, and *Pseudomonas stutzeri*, an environmental bacterium.
ii. A resample of active viable air monitoring performed in the ISO 7 buffer room on 8/19/14 exceeded the limit (b) (4) cfu/m^3 with a result of 14 cfu/m^3.

Aseptically processed drug products affected include:
- TPN 3:1 1125mL product produced on 8/19/~~15~~14

OBSERVATION 2

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

Specifically,

AMENDMENT 3

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	Jeffrey D. Meng, Investigator	02/23/2015

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A. Adequate aseptic process simulations (media fills) have not been performed under representative worst case aseptic processing conditions to assure the sterility of drug products. To date, media fills conducted by operators utilize the (b) (4) which primarily consists of (b) (4) Examples of aseptic processing operations at your firm that are not reflected in this media fill include:

i. During production of Morphine 15mg/mL + Bupivicaine 10.5mg/mL in 40 mL syringe on 2/5/15, the work order indicates that (b) (4) which requires multiple sterile manipulations and connections.

ii. During production of TPN bags on 2/4/15, the work order indicates that (b) (4) requiring multiple manipulations and connections in the ISO 5 area.

B. Aseptic practices and techniques observed at your facility during the processing of sterile drug products are inadequate in that:

i. Full sanitization of all items entering the ISO 5 hood was not performed. On 2/12/15, a cap from the container with non-sterile powder was placed on the ISO 5 hood surface without being fully sanitized.

ii. The operator was observed to rest gloved hand on ISO 5 work surface and subsequently performed aseptic manipulations without additional hand sanitization.

iii. During periodic cleaning of the ISO 5 hood with sterile (b) (4), the operator used bare hands to operate the spray bottle and use the non-sterile wipe to clean and sanitize the hood surface. Each sterile (b) (4) spray bottle is dedicated to and always stored in each ISO 5 hood.

iv. During aseptic processing, the operator was observed to contact this spray bottle and perform aseptic manipulations without resanitization.

v. On 2/12/15, the operator was observed to have bare hands in the ISO 5 hood to done the sterile gloves and to then contact objects in the ISO 7 buffer room environment when transfering items into the ISO 5 hood without resanitizing the sterile gloves upon all reentries into the ISO 5 space.

C. No (b) (4) (b) (4), such as (b) (4) (b) (4) is performed for the (b) (4) used to sterilize aseptically processed products formulated using non-sterile ingredients. During each (b) (4) are used including (b) (4) For example, Morphine 15mg/mL + Bupivicaine 10.5mg/mL in 40 mL syringe on 2/5/15.

D. No documentation was provided to support that air pattern analyses, such as smoke studies, were performed in the ISO 5 laminar hoods under dynamic conditions.

Aseptically processed drug products generally affected include:
- TPN 3:1 1125mL product produced on 8/19/~~15~~14
- TPN 3:1 1125mL bag produced on 2/4/15
- Morphine 15mg/mL and Bupivicaine 10.5mg/mL in 40 mL syringe produced on 2/5/15

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OBSERVATION 3

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically,

The cleaning and sanitization activities performed in the aseptic processing areas are not adequate.

i. Only sterile (b) (4) is used to clean the ISO 5 hoods and no sporicidal agent is used on these surfaces or equipment.
ii. Non-sterile wipes are used to clean the ISO 5 surfaces. These wipes are stored exposed to the ISO 7 environment before use and do not appear to be fully saturated with IPA when used.
iii. There is no assurance that an adequate concentration (b) (4) is used to periodically clean the floors, walls, and ceiling of the ISO 7 buffer and ISO 8 ante room. The bottle of (b) (4) states "Not for sanitization or disinfection" and does not state a percent concentration to allow for proper dilution.

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- TPN 3:1 1125mL bag produced on 2/4/15
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OBSERVATION 4

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

Specifically,

A. The active viable environmental monitoring (EM) program at your facility is inadequate in that:
   i. Active viable EM is not performed during every drug production shift in the critical areas. Active viable air samples are taken in the ISO 5 laminar hoods, ISO 7 buffer room, and ISO 8 ante room approximately every (b) (4) Sterile drug processing activities typically occur (b) (4)
   ii. Active viable EM is not always representative of dynamic conditions in that the samples are typically taken when no routine activities are occuring.
   iii. There is inadequate assurance that active viable EM includes media and incubation parameters validated to recover fungus and mold species.

B. The non-viable particulate (NVP) EM program at your facility is inadequate in that:
   i. NVP monitoring is not performed routinely during every drug production shift in the critical areas. NVP samples are taken in the ISO 5 laminar hoods, ISO 7 buffer room, and ISO 8 ante room approximately every (b) (4)

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ii. There is no documentation stating the volume of air sampled for discrete NVP monitoring.
iii. NVP monitoring is not always representative of dynamic conditions in that samples are typically taken when no routine activities are occuring.

C. The viable surface sampling program at your facility is inadequate in that:
i. Critical surfaces such as the ISO 5 laminar hoods are not monitored during each drug production shift. Currently, a single surface sample is taken from each ISO 5 laminar hood every (b) (4)
ii. The surface samples of the ISO 5 area do not evaluate the impact of drug processing activities in that the sample was observed to be taken immediately after cleaning and sanitization of the equipment.

D. The passive air samples taken using the (b) (4) are inadequate in that:
i. Passive air samples of each ISO 5 laminar hood are taken every (b) (4) No routine activities occur in the hood during the sampling period. Additionally this sample was observed to be taken immediately after the hood was cleaned on 2/13/15.
ii. There is no documented rationale to support the method and placement of passive air samples taken in the ISO 7 buffer room. A sample is taken from a (b) (4) Historical data from 2014 to present notes zero growth for all samples in the ISO 7 area.

E. The personnel monitoring performed at your facility is inadequate in that monitoring of each operator's gloves is not performed for each sterile drug processing shift. Personnel glove monitoring of each operator is typically performed every (b) (4)

F. There is no routine monitoring of pressure differentials between the ISO 7 buffer room, ISO 8 ante room, and uncontrolled building areas. Room pressure differentials are only monitored and recorded approximately every (b) (4) as part of a contractor's certification.

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OBSERVATION 5

Aseptic processing areas are deficient in that floors, walls, and ceilings are not smooth and/or hard surfaces that are easily cleanable.

Specifically,

Aseptic processing areas are deficient in that the floors, walls, and ceilings do not consist of smooth surfaces that are easily

AMENDMENT 3

cleanable. The ISO 7 buffer room containing the ISO 5 laminar flow hoods has the following:

i. Two of the walls consist of (b) (4) with many small pits and crevices.
ii. The flooring consists of (b) (4) with seams around every square foot.
iii. The ceiling tiles are not all fully sealed and small gaps were observed into several light fixtures. Observation of the utility area on top of the ISO 7 and ISO 8 areas noted gaps into the cleanroom light fixtures from the unclassified space.

OBSERVATION 6

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

Specifically,

A. There is an inadequate positive pressure differential between areas of differing air quality classifications. The most recent results recorded on 1/12/15 noted a differential of 0.0043" w.c. between the ISO 7 and ISO 8 rooms and a differential of 0.0081" w.c. between the ISO 8 and unclassified area.

B. The HVAC system for the ISO 7 and ISO 8 rooms does not facilitate an adequate number of air changes per hour. Testing performed on 1/12/15 noted that the ISO 7 buffer room has 7.49 air changes per hour and the ISO 8 ante room has 4.03 air changes per hour.

C. The terminal HEPA filters supplying air to the ISO 7 buffer and ISO 8 ante rooms were installed approximately 12/3/14 and have not been functionally tested for leaks post-installation. Prior to 12/3/14, there was no terminal HEPA filtration of air supplied to the buffer and ante rooms.

OBSERVATION 7

Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

Specifically,

A. The gowning of personnel performing aseptic operations is inadequate in that:
   i. The gowns, facemasks, and hairnets worn during aseptic processing are not sterile.
   ii. The current gowning method for aseptic processing consists of the gown, facemask, hairnet, shoe covers, and sterile gloves which leaves exposed skin around the neck, cheeks and forehead.
   iii. The gown is not an enclosed outfit and is similar to a smock that ends above the knees and with a tied opening down the center of the back. This exposes clothing worn outside and in the unclassified areas of the building to the ISO 7 buffer room environment.

B. Gowning worn in the ISO 7 buffer room is not dedicated to the ISO 7 space or disposed of prior to reentry. Multiple instances were observed where the gowned operator exited the ISO 7 buffer room, performed activities or interacted with personnel in the ISO 8 ante room, and reentered the ISO 7 buffer room to commence additional aseptic operations. Only new sterile gloves were worn in these instances.

C. There is no protective gowning required to enter the ISO 8 ante room from the building's uncontrolled areas. For example, personnel wearing street clothes and shoes were observed to enter the ISO 8 ante room and perform activities.

D. Gloves are not always worn in the ISO 7 buffer room, exposing the skin of the hands to the room environment and equipment. This was observed during multiple activities including during cleaning of the room and during transfer of the transport cart near the ISO 5 laminar hoods. Additionally, the operator was observed in multiple instances to clean the ISO 5 laminar hood surfaces with bare hands using a non-sterile wipe sprayed with the sterile (b) (4) bottle which remains within the ISO 5 hood and is also utilized during aseptic processing.

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- TPN 3:1 1125mL bag produced on 2/4/15
- Morphine 15mg/mL and Bupivicaine 10.5mg/mL in 40 mL syringe produced on 2/5/15

OBSERVATION 8

Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.

Specifically,

A. Not all lots of sterile product aseptically processed are tested for sterility. For example, lots produced from the combination of commercially sourced sterile raw materials, including Methylprednisolone 1gm/100mL prepared on 2/4/15 and TPN formulas prepared on 2/4/15.

B. Your in-house sterility test using the (b) (4) which is performed on all drug products aseptically processed from non-sterile powders, including Morphine and Bupivacaine solution on 2/5/15, is not scientifically valid. Deficiencies include, but not limited to:
   i. No fluid thioglycollate media (FTM) or equivalent is used to detect anaerobic bacteria.
   ii. No method suitability testing has been performed using the required organisms in the presence of product.
   iii. No growth promotion testing was performed.

C. No endotoxin testing is performed for any aseptically processed sterile drugs produced at your facility.

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OBSERVATION 9

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically,

No potency testing is performed for any of the drug products produced.

OBSERVATION 10

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically,

Not all assigned BUDs for sterile drug products processed at your facility are supported by stability testing data. For example, Morphine 15mg/mL and Bupivacaine 10.5mg/mL with normal saline in a 40 mL syringe was aseptically processed on 2/5/15 from non-sterile powders. The dose delivery date of 2/10/15 notes when this preservative free product is injected into an implanted intrathecal pump for continuous infusion over an extended period with intended delivery lasting through date of 4/28/15 and drug stable through date of 5/6/15.

OBSERVATION 11

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

Specifically,

The majority of procedures governing aseptic processing operations at your facility are either not written, inadequate, or not followed. Routine activities, which are not always documented, may be modified through verbal discussions. For example:

i. Cleaning procedures do not specify all cleaning frequencies, agents, dilution instructions, and techniques to be used. (b) (4) cleaning of the ceiling initiated since 9/1/14 is not documented.
ii. There is no procedure stating the specific requirements and conditions to adequately validate aseptic processes via media fills.
iii. There is no procedure stating the requirements and conditions for environmental and personnel monitoring as well as the

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specifications or resulting actions and follow-up.

*** DATES OF INSPECTION:**
02/12/2015(Thu), 02/13/2015(Fri), 02/16/2015(Mon), 02/23/2015(Mon)

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