TO: US FDA Detroit District (DET-DO)
ATTN: Art Czabaniuk, Detroit District Director, DET-DO
Jeffrey D. Meng, Investigator, DET-DO
300 River Place, Suite 5900
Detroit, MI 48207

Date: 3/12/2015

RE: Posting of FDA Form 483 Response

FEI: 3011357279, Tri-Med, Inc. dba Advanced Care Infusion-Shelby

EI: 2/12/2015 - 2/23/2015

Dear Sir:

Please accept this letter as an authorization to post on the US FDA Internet Website, Tri Med, Inc; D/B/A Advanced Care Infusion - Shelby's response to the FDA Form 483 Notice of Observations, dated 2/23/2015, as submitted to DET-DO, unredacted. We understand this response will be posted under the FDA Form 483 Notice of Observations for Tri Med, Inc., D/B/A Advanced Care Infusion - Shelby, issued on 2/23/2015 by Investigator Meng (DET-DO).

Thank you,

William C. Drake, Pharm.D.
President
Tri Med, Inc., D/B/A Advanced Care Infusion - Shelby
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Shelby Township, MI 48315
(586) 323-8280

Hard copy to:
US FDA, Detroit District Office
ATTN: Art Czabaniuk, Detroit District Office
300 River Place, Suite 5900
Detroit, MI 48207

CC electronic copy to:
US FDA, Detroit District office
ATTN: Jeffrey D. Meng, DET-DO Investigator
300 River Place, Suite 5900
Detroit, MI 48207

Tri-Med, Inc. D/B/A Advanced Care Infusion – Shelby, is a Home Infusion Provider, and has been licensed in the State of Michigan as a pharmacy for over 27 years. We provide Home Infusion Therapy services to patients in the home setting, based on individually prescribed therapies and medication orders by physicians. We have been accredited by either JCAHO or ACHC since 1991.

On February 12, 2015, FDA Inspector Jeff Meng arrived at Advanced Care Infusion's pharmacy, accompanied by two State of Michigan Pharmacy Inspectors. Staff at Advanced Care Infusion was advised that this was a "no notice, random inspection", and was not based on any complaints or reported problems.

Although Advanced Care Infusion is licensed as a pharmacy, Mr. Meng appeared to be utilizing what seemed to be standards and polices that are applied to large pharmaceutical manufacturers of injectable medication, not an infusion pharmacy operation. In addition to ACHC accreditation standards, our pharmacy follows USP 797 Standards. However, as far as we understand, we are not required to follow Good Manufacturing Practices (GMP) that are applied to Pharmaceutical Manufacturers.

We also would like it noted that Tri-Med, Inc. D/B/A Advanced Care Infusion-Shelby, the staff, managers, and corporate owners, cooperated to the fullest extent requested. We provided all documents requested by Mr. Meng that were available to us at the time of the inspection, and during follow up.

We look forward to further clarification by the FDA, and finalization of draft polices recently released by the FDA, pertaining to compounding pharmacies and infusion therapy pharmacies. Advanced Care Infusion will work to implement polices and compliance with those requirements.

The following list of observations, and our corresponding responses, are based on those made by Mr. Meng, while applying what we believe are GMP standards for Manufacturers to our pharmacy.

We appreciate this opportunity to respond to the following observations.

OBSERVATION 1

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.

Observation 1 response:

We believe that Advanced Care Infusion did in fact take corrective action in response to this issue. Re-testing of the environment did occur, as there were significant concerns regarding the contracted company's technician who had performed the initial sampling. A Performance Improvement Plan was written and completed. As part of this plan, Advanced Care Infusion did make improvements to more efficiently and completely perform cleaning processes. In addition, action was taken to increase the overall air quality in the controlled environment by significantly increasing the quality of the air supply.

Advanced Care Infusion will review the air sampling process, draft a procedure to more clearly define what testing shall be done for our facility, including frequency and conditions under which these tests are performed, and also include requirements for time frame for review of results of air sampling reports. Detail will be included to address action to be taken in the event that unacceptable air samples are reported.

Plan: Written procedure to be completed by 4/15/2015, and expanded scope of air testing to occur with subsequent scheduled sampling.

OBSERVATION 2

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.
B. Aseptic practices and techniques observed at your facility during the processing of sterile drug products are inadequate…
C. No sterile filter integrity testing, such as bubble point testing, is performed for the sterile filters used to sterilize aseptically processed products formulated using non-sterile ingredients.
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.

Observation 2 response:

A. Advanced Care Infusion will review process and revise current procedures for process simulation testing, expanding methods of testing operators performing high risk manipulations. Consideration of worst case aseptic processing conditions will be included in the formulation of procedures, as well as include follow up procedures in the event of positive results. Revised testing process will

be representative of processes performed when compounding from non-sterile powder as well as complex TPN manipulations.

Plan: Written procedures to be completed by 4/30/2015, testing of appropriate personnel to be completed by 7/31/2015.

B. Advanced Care Infusion will re-train personnel operating in the ISO 5 environment on the matter of maintaining sterility of the ISO 5 environment when introducing objects and/or themselves into the area. In addition, hands will be gloved at all times in the buffer area. This topic has already been discussed with personnel. Procedures will be written to specifically address the movement of items from one classified environment to another environment with stricter classification. Personnel will also be observed on an ongoing basis and also formally documented as reviewed annually with employees' performance evaluation/skills review.

Plan: Procedures to be written and reviewed with personnel by 3/31/2015, annual reviews done based upon employee date of hire.

C. Advanced Care Infusion will research methods for filter integrity testing and implement method best suited for our practice.

Plan: Complete research by 4/15/2015, and written procedures and filter integrity testing to be implemented by 5/15/2015.

D. Advanced Care Infusion will review air sampling process, draft a procedure to more clearly define what testing shall be done for our facility, including frequency and conditions under which these tests are performed.

Plan: Written procedure to be completed by 4/15/2015, and expanded scope of air testing to occur with subsequent scheduled sampling.

OBSERVATION 3

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

Observation 3 response:

Advanced Care Infusion will review and further proceduralize the processes for cleaning of the ISO 5 laminar flow hoods, as well as the buffer room and ante room. Details will be included related to methods and frequency of cleaning, sanitizing agents to be used, dilution instructions and techniques needed to achieve proper sanitization, rotation of these products and frequency of this rotation, noting specifically the inclusion of sporicidal agent on all surfaces in stated rotation.

Plan: Written procedures to be completed and actively being practiced by 3/31/2015.

OBSERVATION 4

A. The active viable environmental monitoring (EM) program at your facility is inadequate…
B. The non-viable particulate (NVP) EM program at your facility is inadequate…
C. The viable surface sampling program at our facility is inadequate…
D. The passive air samples taken…are inadequate…
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 6 months.
F. There is no routine monitoring of pressure differentials between the ISO7 buffer room, the ISO 8 ante room, and uncontrolled building areas.

Observation 4 response:

A. And B.

Advanced Care Infusion is a pharmacy that prepares doses pursuant to a valid prescription for an individual patient; we are not a drug manufacturer. While noting that our procedures for testing are presently under review and revision (see Observation 1 response above), Advanced Care Infusion policy meets USP <797> guidelines, which recommend that certification procedures shall be performed "no less than every 6 months". Advanced Care Infusion will review, research, and revise air sampling processes, draft a procedure to more clearly define what testing shall be done for our facility, including frequency and conditions under which these tests are performed.

Plan: Written procedure to be completed by 4/15/2015, and expanded scope of air testing to occur with subsequent scheduled sampling.

C. Advanced Care Infusion will research, review, and revise procedures for viable surface sampling, including timing and methods used for this testing. Consideration will be given specifically to sampling at the conclusion of work processes.
D. Advanced Care Infusion will research, review, and revise procedures for passive air sampling, including timing and methods used for this testing. Alternate testing methods to be utilized in order to capture more meaningful sample data.

Plan: Written procedure to be completed by 4/30/2015, and expanded scope of environmental testing to occur with subsequent scheduled sampling.

E. Advanced Care Infusion is a pharmacy that prepares doses pursuant to a valid prescription for an individual patient; we are not a drug manufacturer. As such, Advanced Care Infusion policy meets USP <797> guidelines, which recommend that "all compounding personnel shall have their aseptic technique and related practice competency evaluated initially during the *Media-Fill Test Procedure* and subsequent annual or semi-annual *Media-Fill Test Procedures*". Therefore, we believe that we are in compliance with the

guidelines recommended for a compounding pharmacy. In the interest of maintaining an abundance of caution, Advanced Care Infusion will evaluate our processes, and revise personnel monitoring plan accordingly.

Plan: Review current procedures by 4/15/2015, and personnel monitoring to occur per procedure on an ongoing basis, with documentation of same to be formally documented per procedure.

F. Advanced Care Infusion will evaluate the need to implement methods of achieving room pressure differential monitoring in order to meet current standards for compounding pharmacies.

Plan: Research and obtain necessary information from contractors and other sources by 5/15/2015, review and revise procedures, documenting plan for environmental monitoring by 6/15/2015, and implement agreed-upon upgrades by 8/15/2015

OBSERVATION 5

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

Observation 5 response:

Advanced Care Infusion will research upgrades to the environment which may be implemented to achieve greater compliance with USP <797> standards with regard to design of ISO 7 environment. Sealing of surfaces will be integral focus of this investigation.

Plan: Research and obtain necessary information and bids for contract work as needed in order to upgrade environment by 5/31/2015. Necessary improvements will be completed by 8/31/2015.

OBSERVATION 6

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

Observation 6 response:

Advanced Care Infusion has demonstrated that the air supply in our classified environments is filtered through HEPA filters, and also provides positive pressure differential. Advanced Care Infusion will further evaluate improvements to the air supply system that should be made in order to meet current standards for compounding pharmacies, and will research various options and features which may be implemented in order to achieve greater compliance.

Plan: Research and obtain necessary information from contractors and other sources by 5/15/2015, implement agreed-upon upgrades by 8/15/2015.

OBSERVATION 7

A. The gowning of personnel performing aseptic operation is inadequate…
B. Gowning worn in the ISO 7 buffer room is not dedicated to the ISO 7 space or disposed of prior to reentry.
C. There is no protective gowning required to enter the ISO 8 ante room from the building's uncontrolled areas.
D. Gloves are not always worn in the ISO 7 buffer room, exposing the skin of the hands to the room environment and equipment.

Observation 7 response:

A. Advanced Care Infusion will research various types of gowns, facemasks, shoe covers, and hair covers for use during the processes surrounding aseptic drug preparation.

Plan: Procedure to be revised by 4/30/2015.

B. Advanced Care Infusion recognizes the need to minimize the interaction between buffer room and ante rooms, and will educate personnel to ensure that every precaution is taken to allow for compounding personnel to maintain inside the buffer room continuously. Additional personnel to maintain supportive processes in ante room and unclassified areas, obviating need for compounding technician to leave buffer room until all aseptic processes are complete. Each entry into buffer room shall commence with fresh garb, including gloves, at all times. This topic has already been discussed with personnel. Procedures will be written to specifically address the movement of items from one classified environment to another environment with stricter classification. Personnel will also be observed on an ongoing basis and also formally documented as reviewed annually with employees' performance evaluation.

Plan: Procedures to be written and reviewed with personnel by 3/31/2015, annual reviews done based upon employee date of hire.

C. Advanced Care Infusion recognizes the need to minimize the interaction between the ante room and unclassified environment, and will educate personnel to ensure that every precaution is taken to further minimize unnecessary traffic into this area. Specific consideration will be given to increasing the level of garb as personnel moves into classified environment. Procedures will be written to specifically address the requirements of garbing when moving into the ante room.

Plan: Procedures to be written by 3/31/2015, implement increased garb as soon as necessary items are available.

D. Advanced Care Infusion recognizes the need to minimize the potential for any contaminant to enter the ISO 7 environment. Gloves are to be worn at all

times in the ISO 7 environment, and additional aseptic training has already occurred with personnel. Procedures will be written to specifically address the garb needed in each environment. Personnel will also be observed on an ongoing basis and also formally documented as reviewed annually with employees' performance evaluation.

Plan: Procedures to be written and reviewed with personnel by 3/31/2015, annual reviews done based upon employee date of hire.

OBSERVATION 8

A. Not all lots of sterile product aseptically processed are tested for sterility.
B. Your in-house sterility test....is not scientifically valid.
C. No endotoxin testing is performed for an aseptically processed sterile drugs produced at your facility.

Observation 8 response:

A. Advanced Care Infusion is a pharmacy that prepares doses pursuant to a valid prescription for an individual patient; we are not a drug manufacturer. While noting that our procedures for testing are presently under review and revision (see B. below), Advanced Care Infusion policy exceeds USP <797> guidelines, in that it is our practice to perform a sterility test on every single high-risk level CSP that is prepared. USP <797> guidelines state that this only needs to be done under certain conditions (i.e., groups of 25 or more packages, multiple dose vials, longer than 6 hours before sterilization).

Plan: See response to B. below with regard to sterility testing methods. USP <797> does not address testing of low- and medium-risk CSPs.

B. Advanced Care Infusion recognizes the importance of improving testing processes.

Plan: Research expanded tests, to specifically include but not necessarily be limited to: testing for anaerobic bacteria, method suitability testing, and growth promotion testing. Complete research by 5/15/2015, and write new processes for scope of new testing by 6/15/2015, with testing being processes being fully instituted by 7/15/2015.

C. Advanced Care Infusion is a pharmacy that prepares doses pursuant to a valid prescription for an individual patient; we are not a drug manufacturer. Therefore we are in compliance with USP <797> guidelines in our policies and procedures with respect to "Bacterial Endotoxin (Pyrogen) Testing".

Plan: We do not feel that there is any action needed; Advanced Care Infusion, as a pharmacy, is in compliance with USP <797> guidelines.

OBSERVATION 9

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

Observation 9 response:
Advanced Care Infusion is a pharmacy that prepares doses pursuant to a valid prescription for an individual patient. We are in compliance with USP <797> guidelines in our policies and procedures with respect to "Identity and Strength Verification of Ingredients".

Plan: We do not feel that there is any action needed; Advanced Care Infusion, as a pharmacy, is in compliance with USP <797> guidelines.

OBSERVATION 10
There is no written testing program designed to assess the stability characteristics of drug products.

Observation 10 response: Advanced Care Infusion is a pharmacy that prepares doses pursuant to a valid prescription for an individual patient. We are in compliance with USP <797> guidelines in our policies and procedures with respect to "STORAGE AND BEYOND-USE DATING". Further, within this section of USP <797>, it is stated, "Beyond-use dates for CSPs are rarely based on preparation-specific assay results, which are used with the Arrhenius equation to determine expiration dates (see *General Notices and Requirements*) for manufactured products." Advanced Care Infusion compounds preparations for one patient at a time, never in "batches", and does not prepare "manufactured products."

Plan: We do not feel that there is any action needed; Advanced Care Infusion, as a pharmacy, is in compliance with USP <797> guidelines.

OBSERVATION 11
The majority of procedures governing aseptic processing operations at your facility are either not written, inadequate, or not followed.

Observation 11 response:
See responses to Observation 3, Observation 2A, and Observations 1 and 4A through 4F, above, which have previously addressed Advanced Care Infusion's response and plan of action for items i., ii., and iii., respectively.