ADVANCED COMPOUNDING SOLUTIONS
A New England Life Care Company

08 September 2017

To: FDA New England District Office

Mr. Joseph Matrisciano Jr, District Director

One Montvale Avenue

Stoneham, MA 02180

Re: Posting of FDA Form 483

FEI: 3010371376

Dates of Inspection: 2 August 2017 through 22 August 2017

Dear Mr. Matrisciano,

Please accept this letter as our authorization to post, on the US FDA internet website, Advanced Compounding Services' response to the FDA form 483 Notice of Observations, dated 22 Aug 2017, as submitted to the New England District Office, un-redacted and without attachments. We understand this response will be posted under the FDA Form 483 Notices of Observations for Advanced Compounding Solutions, Issued on 22 August 2017, by investigators Robert J. Martin and Erik W. Koester.

Please do not hesitate to contact me should you have any questions, comments or concerns. I can be reached either by email at HPatel@nelifecare.org or by telephone at 1-844-649-6352.

Sincerely,

Hina Patel, RPh
Director
Advanced Compounding Solutions
4 Constitution Way, Suite L
Woburn, MA 01801

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**Hardcopy to:**

New England District Office
ATTN: Mr. Joseph Matrisciano Jr, District Director
One Montvale Avenue
Stoneham, MA 02180

CC electronic copy to:
New England District Office
ATTN: Joseph Matrisciano Jr, District Director
One Montvale Avenue
Stoneham, MA 02180

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Below, please find responses to Form FDA 483 Inspectional Observations, issued on 22 August 2017 by US FDA Investigators Robert J Martin and Erik W Koester at Advanced Compounding Solutions, 4 Constitution Way, Suite L Woburn MA 01801:

**OBSERVATION 1**

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

Specifically,

From June 22, 2017 to July 24, 2017 the firm failed to conduct potency testing for Phenylephrine drug products (40mcg/mL, 80mcg/mL and 100mcg/mL) prefilled syringes. The Quality Unit had released (16) batches without potency testing of which the firm has distributed (4) batches (approximately 1,100 prefilled syringes) to client hospitals.

**RESPONSE TO OBSERVATION 1:**

All affected (16) batches were tested for potency and all lots passed. Certificates are on file and available for review. The 4 batches in question that were shipped (Lot # 20170710-3F051D, Lot # 20170718-412054, Lot # 20170706-71F2D3 and Lot # 20170706-2B060D) were amongst the lots that were tested for potency: certificates are on file and available for review.

**TIMELINE FOR OBSERVATION 1**

Completed 21 August 2017

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**OBSERVATION 2**

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

Specifically,

a. The firm does not perform active air sampling for viable and non-viable particulates within the ISO 5 Laminar Flow Hood during aseptic operations. The firm will only conduct active air sampling along with surface sampling post aseptic operations. Furthermore, the placement of the settle plate which is used for passive sampling in the ISO 5 Laminar Flow Hood during aseptic operations is not located near the majority of aseptic manipulations but located directly under the wall mounted laptop which is used for the electronic batch records.
b. The firm does not monitor differential pressure of the ISO 5 Laminar Flow Hoods during sterile to sterile operations but will only take one reading at the beginning of operations. The firm uses four ISO 5 Laminar Flow Hoods to produce sterile products on a routine basis. Since June 22, 2017 the firm has produced (87) lots of sterile products of which two including Phenylephrine 40mcg/mL and Phenylephrine 100mcg/mL have been commercially distributed to Massachusetts hospitals/medical centers.

**RESPONSE TO OBSERVATION 2a**

The firm's Environmental Monitoring (EM) program procedure, PP 03-01, shall be edited to include active sampling for both viable and non-viable particulates once those procedures have been established. The testing shall be performed in the vicinity of aseptic manipulations. The firm is in the process of scoping the materials and equipment needed to satisfy viable and non-viable particulate testing requirements.

**TIMELINE FOR OBSERVATION 2a**

**Estimated** Completion date of 30 Nov 2017

**RESPONSE TO OBSERVATION 2b**

The manufacturer of the firm's ISO 5 Laminar Flow hoods has provided us with a method to provide real time monitoring based on air pressure differential across the PEC HEPA filter. The firm has committed to install the necessary equipment.

**TIMELINE FOR OBSERVATION 2b**

Estimated completion date December 15th 2017

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**OBSERVATION 3**

Equipment for adequate control over air pressure and micro-organisms is not provided when appropriate for the manufacture, processing, packing or holding of drug product.

Specifically,

The requalification's of the four Baker ISO 5 Laminar low Hoods were inadequate in that the static and dynamic smokes studies conducted did not demonstrate the actual setup and aseptic operations within the Laminar Flow Hoods as used by the firm during routine sterile to sterile operations. For example, static and dynamic smoke studies were conducted with a smoke stick and in some areas did not show unidirectional air flow. Additionally, routine set up conditions were not captured in these studies.

**RESPONSE TO OBSERVATION 3**

The firm's contracted Third Party (Air Systems technologies) shall document results on video tape. Advanced Compounding Solutions shall be requesting Air Systems Technologies to change applicable procedures to provide more specific details. For instance, actual setup and aseptic operations within the Laminar Flow Hoods during sterile to sterile operations in static and dynamic conditions, and around the methodology of conducting and videotaping the smoke test to assure more complete documentation. In the future, when dispositioning a smoke study the video tape shall demonstrate that the study was complete and that acceptance criteria are supported by the video tape.

Advanced Compounding Solutions has reviewed the data associated with these existing smoke studies and made recommendations for smoke studies to be re-performed and completed by Air Systems Technologies.

Air Systems Technologies will complete a new smoke study under static and dynamic conditions within our PECs. The dynamic conditions will be representative of the production processes. The results of the smoke studies will be available upon request.

**TIMELINE FOR OBSERVATION 3**

Estimated Completion date 15 December 2017

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**OBSERVATION 4**

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically,

The firm's aseptic process simulations (media fills) were inadequate in that the media fills were not representative of all critical process procedures and were not done at an appropriate scale to demonstrate commercial sterile operations. For example:

Aseptic media fills conducted under Qualification Procedure (PP# 03-07.02) indicates that operators will fill a mini-bag by adding 20 portions to the partially filled bag and then fill (10) syringes to qualify for aseptic simulations however, the average batch size of commercial sterile products are (500) to (600) syringes. The firm had no documented justification for the simulation size. This simulation only represents approximately 2% of routine fills and was not representative of all sterile to sterile operations. This method was used to qualify operators (b) (6) on June 1, 2017 and (b) (6) on July 13, 2017.

**RESPONSE TO OBSERVATION 4**

The firm will revise the media fill program accordingly to include the following elements:

1) Media fill SOP to be written/revised to include the media fill study to be representative of the average batch size of commercial Compounded Sterile Preparations.
2) Allocation of sterile preparation using different types of final container closures, which will include syringes and bags. The new media-fill program will include filling syringes and bags with reconstituted powdered tryptic soy broth.
3) Consideration of the worst case conditions for exposure of sterile preparations to the aseptic environment, including but not limited to employee breaks, removal and reintroduction of pool bags into and out of the LFH, and stress events such as spills within the LFH during compounding.
4) Various manipulations that are made during preparation of sterile compounded preparations.

**TIMELINE FOR OBSERVATION 4:**

Revision of Media-Fill Standard Operating Procedure (SOP) completed on 05 September 2017; estimated target date for completion of media-fill program for all currently employed compounding technicians: 05 November 2017.

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**OBSERVATION 5**

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

Specifically,

On August 4, 2017 we observed the following:

- Operator (b) (6) was conducting sterile to sterile operations for Neostigmine 1mg/mL, 3mL lot number 20170804-6FF7DF and it was observed that (b) (6) movements within the LFH were not slow and deliberate.
- Operato (b) (6) was conducting sterile to sterile operations for Phenylephrine 80mcg/mL, 10mL lot number 20170804-53D817 and it was observed that (b) (6) movements were not slow and deliberate. Furthermore throughout the sterile to sterile operation (b) (6) had several instances in which the top of her head went into the LFH along with parts of her shoulders.
- Operato (b) (6) was conducting sterile to sterile for Neostigmine 1mg/mL, 3mL lot number 20170804-420BC5 and it was noted tha (b) (6) movements were not slow and deliberate. Furthermore throughout the sterile to sterile operation (b) (6) had several instances in which her shoulders had entered the LHF.
- On August 3, 2017 we observed that personnel movements were not consistent with sterile operations in that operators dressed in sterile gowning were moving between the ISO 7 Ante Room (used for sterile gowning) to the ISO 8 Gowning Room while conducting cleaning operations instead of moving from clean area to dirty area in a single direction.

**RESPONSE TO OBSERVATION 5**

The firm will update the Laminar Flow Hood Operation and Maintenance policy, PP 05-33 as well as the competency assessment sterile aseptic technique, PP 05-01B. Updates are to include slow and deliberate movement while compounding and how to position oneself in the hood while working or cleaning, for example operating in the hood without introducing other than one's hands and forearms. Staff retraining will also be conducted to ensure adherence to updated policies.

**TIMELINE FOR OBSERVATION 5**

Completion September 30 2017

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**OBSERVATION 6**

Each component is not tested for conformity with all appropriate written specifications for purity, strength, and quality.

Specifically,

The firm's process for evaluating incoming raw material and drug products are inadequate in that the firm's procedure requires that incoming sterile and pathogenic free materials are evaluated via the Certificate of Analysis and incoming drug products also require that the potency, sterility and pathogenicity is confirmed via Certificate of Analysis however the firm does not always receive a Certificate of Analysis even though the incoming receipt forms have Certificates of Analysis reviewed. For example the following was noted:

The firm received 750 units of Ephedrine Sulfate 50mg/mL (Lot# 00020A) on 05/05/2017, 25 units of Phenylephrine HCL 10mg/mL (Lot# 10015A) on 07/06/2017, 48 units of Phenylephrine HCL 10mg/mL (Lot# 00011A) on 06/12/2017, 4020 units of Neostigmine Methylsulfate 1mg/mL (Lot# 10187A) on 07/06/2017, and 640 units of CP3000 Pinnacle 3000mL EVA Mixing Containers (Lot# 17A26) received on 05/22/2017. Each of the aforementioned lots was received without a specific accompanying Certificate of Analysis detailing the results of the testing including: potency, sterility, and endotoxins.

**RESPONSE FOR OBSERVATION 6**

All five cited COAs have been obtained and all meet the standard set forth in the 483.
All ACS team members have been re-trained regarding PP 10-08.02, receiving and inspection of incoming items regarding obtaining only a Certificate of Analysis that indicates the sterility, pathogenicity and potency for all incoming active pharmaceutical ingredients (API) and pathogenicity and sterility for all incoming sterile material. The existing policy will also be updated to detail the requirements for a valid certificate of analysis. The firm's warehouse manager is in the process of reviewing all receiving paperwork and contacting all manufacturers where a certificate of analysis was not received. Any product where we are not able to obtain a valid certificate of analysis will be rejected and sent back to the vendor. It the situation continues our service agreement with the vendor will be terminated.

**TIMELINE FOR OBSERVATION 6:**

Aforementioned cited 5 Certificates of Analysis were all received by 01 September 2017. Estimated target date for revising and training current employees on the ACS Receiving and Inspection of Incoming Items (PP 10-08): 05 October 2017.

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**OBSERVATION 7**

Procedures describing the handling of all written and oral complaints regarding a drug product are not written.

Specifically,

The firm's complaints procedure (PP# 04-01.01) was created in April of 2017; however, the procedure was not approved until August 7, 2017, which was during the current inspection. In addition, the complaints procedure lacks instructions for the processing of adverse drug events. Furthermore, the firm's adverse events procedure (PP# 04-07.01) lacks specific details including: timeframes for the submittal of adverse event information to the FDA, submittal of follow-up reports and description of the four data elements (Identifiable patient, Identifiable reporter, Suspect drug product and serious adverse event).

**RESPONSE FOR OBSERVATION 7**

Policies PP 04-01, Member Grievance and PP 04-07, Major Incident Response Plan will be updated in accordance with Adverse Event Reporting for Outsourcing Facilities under Section 503B of the Federal Food, Drug and Cosmetic Act, Guidance for Industry.

Policy, PP 04-01 will be updated to provide instructions on how to process an adverse drug event. Policy, PP 04-07 will be updated to include timeframes for the submittal of follow up reports and the description of the four data elements (identifiable patient, identifiable reporter, Suspect drug product and serious event)

**TIMELINE FOR OBSERVATION 7**

Completion date 30th September 2017