Mr. Alonza Cruse

District Director

U.S. Food and Drug Administration

19701 Fairchild

Los Angeles, CA 92612-2506

Re: Custom Compounding Centers, LLC
Inspection and 483 Response
FEI 3009855773

Dear Mr. Cruse,

This submission is a response to Custom Compounding Centers, LLC's ("CCC" or "we") August 27th, 2014 FDA inspection.

Custom Compounding Centers, LLC

9/18/2014

On behalf of Custom Compounding Centers, LLC ("CCC"), I authorize the United States Food and Drug Administration (FDA) to publicly disclose the information in the attached letter responding to the FDA's Form 483 observations for Custom Compounding Centers, LLC issued 08/28/2014, excluding attachments/exhibits, on the FDA's website.

It has been our pleasure to work with the district in the interest of patient safety as we make additional modifications to our system. We believe that we have been diligent in our response to the issued Form 483 dated 08-28-2014. If the responses contained herein are not considered adequate to meet the requirements necessary for our stated position under section 503(a) of the Federal Food Drug and Cosmetic Act, and then please let us know at your earliest opportunity. It is our intention, with the assistance of the District, to comply fully with USP 797 Guidelines and all applicable state and federal laws regulations and guidelines (**PLEASE SEE EXHIBIT A**).

OBSERVATION 1

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

Specifically, Environmental Monitoring of the firm's ISO 5 and ISO 7 Cleanroom Environments used to produce sterile drug products does not represent actual production, for example:

a) Lack of active monitoring of differential pressures. There is no monitoring of the cleanroom pressure differentials during aseptic process of drug products. Within the firm's sole cleanroom, the ISO 5 area is separated from the ISO 7 area only by flexible plastic curtain strips.

There is no manner in which to measure pressure differentials for these areas. Further, there is no system to detect loss of air supply to HEPA filters during processing.

b) Lack of active non-viable particulate air monitoring - ISO 5 and ISO 7. There is no active monitoring of the nonviable air particulates during aseptic processing of drug products in the ISO 5 or ISO 7 areas of the cleanroom.

There is only semi-annual non-viable particulate monitoring conducted by an outside contractor.

Response to Observation 1, item a): "the ISO 5 area is separated from the ISO 7 area only by flexible plastic curtain strips."

We appreciate the district's observations indicating the need for additional monitoring during aseptic processing

CCC appreciates the district's concern regarding the separation of the ISO 5 and ISO 7 areas by plastic strips. To ensure that there is no incursion of less controlled air into the ISO 5 area during processing, CCC employed an outside clean room design/certification consultant (Controlled Environmental Regulatory Testing Services) to demonstrate proper separation of air flow between ISO 5 processing and adjacent ISO 7 environments.

Please find attached "Smoke Study Video dated July 31, 2014" with attached (smoke study video and cover page conducted by consultant Controlled Environmental Regulatory Testing Services **PLEASE SEE EXHIBIT B)** demonstrating and stating "the airflow in the ISO 5 workstation is mostly laminar, with no turbulence or up drafts as the smoke moves over the table. The smoke has good downward flow as it moves over the table and half is pulled into the wall returns and the other half moves towards the pharmacy technician. The product sees first air at all times."

Please find attached "Smoke Study Video dated April 25, 2014" with attached (smoke study video conducted by consultant Controlled Environmental Regulatory Testing Services – **PLEASE SEE EXHIBIT B**) demonstrating and stating "that there is no incursion of less controlled air into the ISO 5 area during processing"

We believe that CCC is in compliance with USP 797: Viable and Nonviable Environmental Sampling (ES) Testing, "Pressure Differential Monitoring"..... that states that "a pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area." A magnehelic gauge is currently in use to monitor pressures. **(PLEASE SEE EXHIBIT C-1 – PRESSURE DIFFERENTIAL MONITORING USP 797)**

Additional Action by CCC:

In addition CCC will install wall mounted magnehelic continuous recording gauges between the ISO 7 and ISO 8 controlled areas and the ISO 8 and the non-controlled area and continue to monitor differential pressures **(PLEASE SEE EXHIBIT C – PRESSURE DIFFERENTIAL MONITORING LOG)** Proper operation and training will be conducted with affected employees and their understanding will be documented and provided upon request.

Timeline: Completion by 10-20-2014

Response to Observation 1, item b):

We believe that CCC is in compliance with USP 797: Viable and Nonviable Environmental Sampling (ES) Testing, "Environmental Particle Testing Program" – Engineering Control Performance Verification that states "Certification procedures such as those outlined Certification Guide for Sterile Compounding Facilities (CAG-003-2006) shall be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated or altered or major service to the facility is performed." And Total Particle Count (same reference) Certification is within established guidelines shall be performed no less than every 6 months ....." **(PLEASE SEE EXHIBIT B-1 CLEAN ROOM CERTIFICATION)** Clean Room Certification Report dated April 25, 2014 performed by consultant Controlled Environmental Testing Services)

CCC currently monitors pressures between the ISO 7 buffer area and ISO 8 processing areas and the ISO 8 and the general environment outside the compounding areas on a daily basis (each shift) **(PLEASE SEE EXHIBIT C – PRESSURE DIFFERENTIAL MONITORING LOG**) copies of magnehelic pressure gauge measurements between the ISO 7 buffer area and ISO 8 areas and the ISO 8 area and the general outside environment for the months of June 2014 through August 2014)

Additional Action by CCC:

In addition CCC will install wall mounted magnehelic continuous recording gauges between the ISO 7 and ISO 8 controlled areas and the ISO 8 and the non-controlled area and continue to monitor differential pressures. Proper operation and training will be conducted with affected employees and their understanding will be documented and provided upon request.

Timeline: Completion Date 10-20-2014

Additional Action by CCC:

Additionally, CCC will add non-viable particulate monitoring equipment to enable detection of loss or interruption of HEPA filtered air during aseptic processing, increasing the environmental monitoring capability control in the ISO 7 and ISO 5 environments. This additional equipment will provide constant monitoring of the aseptic processing area for non-viable particulate matter during processing. Proper operation and training will be conducted with affected employees and their understanding will be documented and provided upon request.

Timeline: **Completion Date 10-20-2014**

OBSERVATION 2

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

Specifically, there is no release testing performed to assess the presence of bacterial endotoxin in finished drug products aseptically processed and not terminally sterilized. Drug products are produced from non-sterile API by the firm; sterilization is by O.22μ filtration aseptically processed.

The firm does not conduct an endotoxin analysis on each aseptically processed drug product.

Response to Observation 2

CCC currently compounds single individual patient specific prescriptions. CCC does not compound "batches". CCC does not prepare high-risk level CSP's in groups of more than 25 identical individual single dose packages.

We believe that our current practice is in compliance with current ***USP 797*** **(PLEASE SEE EXHIBIT D – BACTERIAL AND ENDOTOXIN TESTING)** that states "All high-risk level CSPs.....that are prepared in groups of more than 25 identical individual single dose packages (e.g. ampules, bags, syringes, vials) or in MDVs for administration to multiple patients or that are exposed longer than 12 hours at 2-8 degrees and longer than 6 hours at warmer than 8 degrees before they are sterilized shall be tested to ensure that they do not contain excessive bacterial endotoxins.

Additional Action by CCC:

CCC is consulting with Associates of Cape Cod to establish a protocol for endotoxin testing for drugs used in the compounding of each individual patient prescription. Considerations include the maximum dose of the drug administered, route of administration, allowable endotoxin limit calculations and steps to mitigate any inhibitory properties of the drug.

Currently, CCC considers the endotoxin content of each compounded prescription as specified in the Certificate of Analysis for each lot of each particular drug to assure that an adult patient (specified as 70kg) receives less than the USP allowable EU per dose in an individual prescription for a continuous pump controlled intra spinal infusion. **(PLEASE SEE EXHIBIT E – Certificate of Analysis Morphine Sulfate , USP)**

Timeline: **Completion Date 10-20-2014**

FDA OBSERVATION 3

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, there is no release testing performed to assure the potency of each active ingredient for each batch. The firm does not conduct potency testing on aseptically processed drug products.

Furthermore, there is no second verification on the weighing out of the active ingredient raw materials during formulation.

Response to Observation 3

CCC currently compounds single individual patient specific prescriptions. CCC does not compound identical compounds for more than one patient or "batches".

CCC has conducted potency testing for several representative compounded individual solutions to determine process accuracy **(PLEASE SEE EXHIBIT F).** These test results represent typical individual patient specific prescription concentrations tested at different time intervals compounded routinely by CCC **(Also SEE EXHIBIT F)** measuring potency of lot CC 21463 Fentanyl Citrate at time points day 1, day 45 and day 90). Although each individual prescription compounded is distinct from one another, the compounding process for each prescription is the same; therefore we believe that a random sample testing approach to demonstrate process accuracy (potency) is appropriate.

A second individual accordance with USP 797 Guidelines currently verifies that correct volumes of correct ingredients are measured to make each compounded sterile prescription.

We believe that this is in compliance with ***USP 797*** **(PLEASE SEE EXHIBIT D – Compounding Accuracy Checks)** that states "Preferably, a person other than the compounded can verify that correct volumes of correct ingredients were measured to make each CSP."

Additional Action by CCC:

A printer that records the weight of each component of an individual prescription will be added to each balance used. Proper operation and training will be conducted with affected employees and their understanding will be documented and provided upon request.

Timeline: **Completion Date 10-20-2014**

Schedule for Updates and Conclusion:

We intend to submit updates informing the District of progress on our planned activities on October 10, 2014 and October 20, 2014. By that time we anticipate that all commitments to planned activities will be complete. If the District would like any additional information before those dates, please let us know.

We again appreciate the observations that the District provided regarding our compounding operation and hope it agrees that with the proposed steps we are taking and that Custom Compounding Centers, LLC should be allowed to continue to provide high-quality compounded prescription drugs to the patients and practitioners who rely on them.

Sincerely,

Paul R. Wheeler, Pharm.D.
President and Pharmacist in Charge
Custom Compounding Centers, LLC

/Exhibits

Cc: Ms. Jessica Mu, FDA, Los Angeles District