Compounding
PHARMACY OF AMERICA

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6216 Highland Place Way
Suite 201
Knoxville, TN 37919

June 26th, 2015

Department of Health and Human Services
Food and Drug Administration
404 BNA Drive, Building 200, Suite 500
Nashville, TN 37217-2597

Attn: Patricia K. Schafer, District Director
Zada Giles, Investigator
Marvin Jones, Investigator

Re: FDA Disclosure of 483 Response

Dear District Director Schafer and Investigators:

On behalf of The Compounding Pharmacy of America, Inc. ("CPA"), I authorize the United States Food and Drug Administration (the "FDA") to publicly disclose the information described below on the FDA's web site and to include the information described below any time the FDA provides a copy of CPA's Form 483 to anyone outside of the FDA. I understand that the information that is disclosed may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. 1905, 21 U.S. C. 331(j), and 5 U.S.C. 552 (b)(4) that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I agree to hold the FDA harmless for any injury caused by the FDA's sharing the information with the public.

Information to be disclosed: CPA's letter dated June 26, 2015, excluding all attachments, which responds to the Form 483 issued by the FDA on May 21, 2015.

Authorization is given to the FDA to disclose the above-mentioned information, which may include confidential commercial or financial or trade secret information. As indicated by my signature, I am authorized to provide this consent on behalf of CPA and my full name, title, address, and telephone number are provided below for verification.

Sincerely,

Vincent Matthew Poteet, PharmD
President, The Compounding Pharmacy of America

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Via Fax (615) 366-7802 And Overnight Delivery

Attn: Patricia Schafer, District Director
Zada Giles, Investigator
Marvin Jones, Investigator

Re: Response to FDA 483 Issued 5/19/2015 to The Compounding Pharmacy of America, Inc. d/b/a The Compounding Pharmacy of America

Dear District Director Schafer and Investigators:

The United States Food and Drug Administration (the "FDA") conducted an inspection of The Compounding Pharmacy of America, Inc. d/b/a The Compounding Pharmacy of America ("CPA"), a pharmacy located at 6216 Highland Place Way, Suite 101A, Knoxville, Tennessee 37919, between May 12 and May 15, 2015. Upon the conclusion of its inspection, the FDA provided CPA with an FDA Form 483. This letter is CPA's response to the FDA Form 483 observations. We respectfully request that this response, excluding the attachments, be posted on the FDA's website with the Form 483 and be included every time the FDA provides a copy of CPA's FDA Form 483 to anyone outside the FDA.

The FDA's observations on the Form 483 are based primarily on requirements imposed on drug manufacturers under the Current Good Manufacturing Practices ("cGMPs") for finished pharmaceuticals contained in 21 C.F.R. Part 211, and further explained in the FDA's Industry Guidance on cGMPs for Sterile Drug Products Produced by Aseptic Processing. CPA does not engage in drug manufacturing. CPA is a pharmacy licensed by the Tennessee Board of Pharmacy as a retail pharmacy with controlled substances, and is subject to the rules, regulations and oversight of the Tennessee Board of Pharmacy. The Tennessee Board of Pharmacy adopted United States Pharmacopeia (USP) Chapter <797> on Sterile Compounding as its standard for operating a sterile pharmacy operation in the State of Tennessee.

CPA feels it is currently in compliance with the Tennessee Board of Pharmacy requirements for sterile compounding pharmacies and USP chapter <797>. We base this both on an exceptional inspection record conducted by the Tennessee Board of Pharmacy investigators as well as our internal quality assurance programs and Standard Operating Procedures (SOPs).

During the course of the FDA inspection which lead to this Form 483 being issued, it was brought to the attention of management of CPA that the FDA may consider CPA to fall under section 503b (Pharmacy Outsourcers) due to the fact that CPA had shipped products for office use across state lines to states that allow office use compounding. CPA began dispensing "office-use" products to physician offices, only in areas and states that we were licensed by those states and only in those states which themselves have "office-use" compounding laws themselves. CPA has produced non-patient specific drugs for use by doctors during the course of their practice in their clinic since the signing of Tennessee Senate Bill .582 in 2013 which was specific in its purpose to amend the language of Tennessee Code 63-10-204(4) to allow compounding pharmacies the ability to compound pharmaceuticals for use in licensed prescribing practitioner's office for administration to the patient when the pharmaceutical is not commercially available. A copy of this bill has been entered into evidence by your investigators. From our standpoint the language was very clear; we may dispense non-patient specific medications to licensed prescribers for office use while being a 503a pharmacy.

We further believe that Congress did not intend to allow the FDA to prohibit pharmacy compounding for office use in states where it is expressly allowed and regulated. In a letter to the FDA dated June 27, 2014, members of the U.S. Congress clarified its intent as follows:

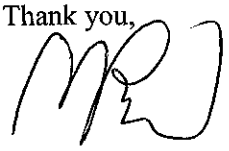
Pharmacies that produce small amounts of compounded products in advance of receiving a patient-specific prescription and practice within States where office use is authorized and regulated by State Boards of Pharmacy should not be the focus of FDA oversight. Expecting these small pharmacies that practice in accordance with State law to register as outsourcing facilities solely because products are intended for office use is unreasonable. As FDA prioritizes its resources in a way that best protects public health, we believe the focus should be on manufacturers, not small pharmacies providing safely-compounded products for the physicians and hospitals in their communities.

For these reasons, CPA challenges the FDA's observations on the grounds that the cGMPs are not applicable to its compounding pharmacy

operations. CPA complies with all applicable state and federal laws. CPA also adheres to the USP <797> guidelines for compounding sterile drug products. Our pharmacy is dedicated to ensuring that our sterile and non-sterile drugs are prepared in a safe and effective manner. In light of CPA's commitment to self-improvement, if the FDA's observations amount to pharmacy "best practices" that, if adopted, would benefit the safety of our patients, we have considered those practices for adoption as best practices in our policies and procedures manual and have trained our staff on any newly adopted best practices.

We only became aware of the FDA's interpretation that office-use compounding is not within our scope of practice as a 503a establishment during our inspection by the FDA. We had investigated the issue and assumed the letter of legislative intent gave us the ability under 503a to make office use products. Our intent was never to practice as a 503b outsourcer or manufacturer. In light of the FDA's opinion on "office-use" compounding and section 503b and our willingness to comply with the FDA's opinion on the subject, we immediately ceased the practice of "office use" compounding. CPA now requires a patient-specific prescription for all sterile and non-sterile compounded medications. However, to the extent that the FDA contends that CPA is not protected by Section 353a for patient-specific drugs prepared and dispensed to practitioners for administration, we believe that such conduct is expressly authorized by the Tennessee Board of Pharmacy.

Thank you,



Vincent Matthew Poteet, PharmD
President, The Compounding Pharmacy of America, Inc.

The following Observations were cited in our 483:
Observation 1

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

Specifically,

1. ***Microbial testing is not performed for each lot of drug product purporting to be sterile. Your firm's lots range in volume from 1 ml to 2400 ml. Furthermore, you have not validated your microbial testing method.***

   Response: CPA is in full compliance with the guidelines set forth in USP 71, USP 797, and USP 85 on microbial and sterility testing. Microbial testing was and is performed on each lot of drug product purporting to be sterile in accordance to USP standards. Please see Observation 7 in the FDA's Form 483, where CPA's microbial testing is referenced by the investigators. The microbial testing method CPA used was the direct inoculation method in USP <71> and was in compliance with USP Standards before the FDA inspection. CPA was in the process of switching from the direct inoculation method of sterility testing to membrane filtration testing, another accepted and preferred microbial testing method by USP. CPA has implemented a new microbial testing program, still in compliance with USP Standards Chapter <71>, using membrane filtration.

2. ***No endotoxin testing is performed on finished product and vials and stoppers are not de-pyrogenated before use. All drug products your firm makes are produced from non-sterile components.***

   Response: CPA is in full compliance with the guidelines set forth in USP 71, USP 797, and USP 85 on microbial, endotoxin, and sterility testing. As a compounding pharmacy, CPA complies with USP chapter <797> which requires endotoxin testing as follows:

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 multiple-dose vials (MDVs) for administration to multiple patients or that have been exposed longer than 12 hours at between 2-8 degrees C and longer than 6 hours at warmer than 8 degrees C before they are sterilized shall meet the sterility test before they are dispensed or administered.

.....

All high-risk level CSPs, except those for inhalation and ophthalmic administration, that are prepared in groups of more than 25 identical single dose packages (e.g. ampules, bags, syringes, vials) or in MDVs for administration to multiple patients or that have been exposed longer than 12 hours at 2-8 degrees C and longer than 6 hours at warmer than 8 degrees C before they are sterilized shall be tested to ensure that they do not contain excessive bacterial endotoxins.

Furthermore, USP chapter <797> guidelines state that:

Sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units.

Endotoxin testing is performed at CPA in compliance with the above USP Standards for sterility and endotoxin testing and the Tennessee Board of Pharmacy requirements for sterile compounding pharmacies. CPA does not prepare medications in batches of greater than 25 individual packages. However, Stoppers and vials are de-pyrogenated and a testing log is maintained, which is not required by USP Standards for CPA's compounding purposes. These documents were supplied to the FDA investigators.

Observation 2

Drug product containers and closures were not clean and sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Specifically, your firm does not de-pyrogenate any containers or closures used in the aseptic filling/terminal sterilization of drug products intended to be sterile.

Response: CPA is in full compliance with the guidelines set forth in USP 797 regarding de-pyrogenation of glassware. The section of USP 797 regarding the de-pyrogenation of glassware is as follows:

De-pyrogenation by Dry Heat
Dry heat de-pyrogenation shall be used to render glassware or containers such as vials free from pyrogens as well as viable microbes. A typical cycle would be 30 minutes at 250°. The description of the dry heat de-pyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility. The effectiveness of the dry heat de-pyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECVs to verify that the cycle is capable of achieving a 3-log reduction in endotoxin (Sterilization and Sterility Assurance of Compendial Articles <1211> and Bacterial Endotoxins Test <85>.

CPA was in full compliance with this portion of USP 797 at the time of the inspection. A copy of the Endotoxin Challenge Vial Log was supplied to the investigator at the time of the inspection and logged into evidence. The investigator suggested wrapping the glassware in aluminum foil prior to de-pyrogenation cycle and this suggestion, even though it is not explicitly stated to do so in the USP section referenced above, was adopted by CPA into its SOP on De-Pyrogenation. See SOP 8.046.1 Dry Heat Sterilization/De-pyrogenation and SOP 8.058 Dry Heat De-pyrogenation of Glassware and Metal ware.

Observation 3

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

Specifically,

1. ***Your firm has not validated your sterilization process for autoclaving glass vials to be used for drug products intended to be sterile.***

   Response: CPA is in full compliance with USP Standards for the sterilization process of glassware. USP Standards do not require

validation of the process of autoclaving glass vials to be used for drug products intended to be sterile. USP Standards recognize sterility by steam/pressure as a method to sterilize products. The section referencing sterilization by steam (autoclave method from USP is as follows:

The process of thermal sterilization employing saturated steam under pressure is carried out in a chamber called an autoclave. It is probably the most widely employed sterilization process. The basic principle of operation is that the air in the sterilizing chamber is displaced by the saturated steam, achieved by employing vents or traps. In order to displace air more effectively from the chamber and from within articles, the sterilization cycle may include air and steam evacuation stages. The design or choice of a cycle for given products or components depends on a number of factors, including the heat lability of the material, knowledge of heat penetration into the articles, and other factors described under the validation program (see
above). Apart from that description of sterilization cycle parameters, using a temperature of 121°, the F0 concept may be appropriate. The F0, at a particular temperature other than 121°, is the time (in minutes) required to provide the lethality equivalent to that provided at 121° for a stated time. Modern autoclaves generally operate with a control system that is significantly more responsive than the steam reduction valve of older units that have been in service for many years.

Additionally, the section on dry heat sterilization seems to preclude the use of dry heat sterilization except in instances where steam sterilization is untenable. Here is an excerpt from the Dry Heat Sterilization section in USP 797 elucidating this:

Dry heat sterilization is usually done as a batch process in an oven designed for sterilization. Heated filtered air shall be evenly distributed throughout the chamber by a blower device. The oven should be equipped with a system for controlling temperature and exposure period. Sterilization by dry heat requires higher temperatures and longer exposure times than does sterilization by steam. ***Dry heat shall be used only for those materials that cannot be sterilized by steam, when either the moisture would damage the material or the material is impermeable****. During sterilization,*

sufficient space shall be left between materials to allow for good circulation of the hot air. The description of dry heat sterilization conditions and duration for specific CSPs shall be included in written documentation in the compounding facility. The effectiveness of dry heat sterilization shall be verified using appropriate BIs of Bacillus subtilis (see Biological Indicators) and other confirmation methods such as temperature- sensing devices (see Sterilization and Sterility Assurance of Compendial Articles 1211 and Sterility Tests 71).

Despite the above guidance regarding the use of Dry Heat Sterilization and based solely on the recommendation of the investigators from the FDA, CPA has switched to Dry Heat Sterilization from Steam Sterilization for its vials that it sterilizes in-house, and to purchasing pre-sterilized vials from a third party company.

2. ***Your firm has not validated your filter sterilization process using a 0.2 micron filter to aseptically fill injectable drugs purporting to be sterile. Furthermore, the user manual for the filter that your firm is using states: "this filter is not intended for intrathecal drug administration." Your firm has been using this filter since 2012 to aseptically fill injectable drugs purporting to be sterile, including intrathecal solutions.***

CPA fully complies with the guidelines set forth in USP 797 regarding terminal sterilization of drug products via filtration. USP does not require the validation of filters used in aseptic processing. The section of USP regarding the sterilization of drug products via filtration is as follows:

STERILIZATION OF HIGH-RISK LEVEL CSPs BY FILTRATION Commercially available sterile filters shall be approved for human-use applications in sterilizing pharmaceutical fluids. Sterile filters used to sterilize CSPs shall be pyrogen- free and have a nominal pore size of 0.2 or 0.22 mm. They shall be certified by the manufacturer to retain at least 107 microorganisms of a strain of Brevundimonas (Pseudomonas) diminuta on each square centimeter of upstream filter surface area under conditions similar to those in which the CSPs will be sterilized (see High-Risk Conditions in High-Risk Level CSPs).

The filters CPA uses to aseptically sterilize injectable drugs, including intrathecal solutions, is used for preparation, not *administration* as the observation alleges. In fact, the same package insert states, in the "Indications" section under instructions for use:

Syringe Filters with Supor Membrane are designed for rapid filtration, high throughputs, low protein binding, and broad drug compatability. ***For drug preparation*** *and syringe bolus administration.*

We contacted a representative of B Braun by phone in their technical support department who further verified this product is in fact for final drug sterilization including intrathecal drugs.

The filter manufacturer, B Braun which is an FDA regulated facility, validated the sterilization process for the filter using the criteria from the excerpt above. Once again, the package insert states the filter is not to be used for intrathecal drug administration. CPA does not administer these medications, the physician does.

A copy of the package insert is included as an addendum for your review.

Each filter is tested for integrity via bubble point gauge to ensure integrity after the product has been sterilized. Copies of the filter integrity tests are then stapled to the original worksheet. Examples of these documents were provided to the FDA Investigators during inspection.

3. ***Your firm has not validated your process of de-pyrogenating glassware used in the mixing of drug products to be aseptically filled or terminally sterilized.***

CPA is in full compliance with USP 797 Standards for de-pyrogenating glassware used in the mixing of drug products to be aseptically filled or terminally sterilized. USP Standards do not require the validation of the process of de-pyrogenating glassware. The USP Standards for de-pyrogenating glassware are as follows:

De-pyrogenation by Dry Heat
Dry heat depyrogenation shall be used to render glassware or containers such as vials free from pyrogens as well as viable microbes. A typical cycle would be 30 minutes at 250°. The description of the dry heat de-pyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility. The effectiveness of the dry heat de-pyrogenation cycle shall be verified using endotoxin challenge vials (ECVs). The bacterial endotoxin test should be performed on the ECVs to verify that the cycle is capable of achieving a 3-log reduction in endotoxin (Sterilization and Sterility Assurance of Compendial Articles <1211> and Bacterial Endotoxins Test <85>).

These USP Standards are followed, are integrated into our policies. See SOP 8.046.1 Dry Heat Sterilization/De-pyrogenation and SOP 8.058 Dry Heat De-pyrogenation of Glassware and Metal ware. A manual log is kept of each de-pyrogenation cycle that is run which includes endotoxin challenge vial, temperature of oven, and total time of temperature exposure. The log was given to the investigators and entered into evidence.

During inspection, the FDA investigator recommended that we wrap our glassware in a double layer of aluminum foil before autoclaving as an additional safety measure. We agreed this would be beneficial and have updated our SOP (SOP 8.058 Dry Heat Depyrogenation of Glassware and Metal ware) and immediately instated this process.

4. ***Your firm's SOP 7.011 "Gowning and Gloving" states that the gloves will be disposed of upon leaving the Clean Room and a new pair donned to return. On 05/12/2015, we observed a technician leave the Clean Room to retrieve a syringe from the Ante Room. The firm's owner, who was not wearing gloves, had placed the syringe in the Ante Room for the technician without wiping down the syringe. The technician did not change gloves before beginning aseptic filling.***

5.

Response: This is true. This was not a representative example of how sterile processes at CPA are conducted. Our technician and owner were under tremendous scrutiny with four regulatory investigators watching their every move and they made a mistake. In response to

this mistake, CPA has fully re-trained all staff involved in the preparation of sterile products in our facility. This includes 30 hours of didactic training, including written examinations, hands-on observation by pharmacy leadership, and successful passage of a high risk media fill tests. CPA will vigilantly continue to test our aseptic compounding personnel using the most accepted methods currently available in order to evaluate their competency.

6. ***Your firm's SOP 8.012, "Compounding Sterile Solutions" states to produce all injectables in a Class 100 environments. On 05/12/2015, we observed Lidocaine 2% gel, lot # 05122015@6, Morphine 20 mg/ml Intrathecal Solution, lot# 05122015@15 and Methylcobalamin 1,000 mcg/ml injection, lot # 05122015@14 being compounded in the Lab Room, which is an unclassified room that does not have HEPA filtration.***

Response: CPA is in full compliance with USP 797 guidelines regarding sterile drug preparation. This observation is referring to CPA's pre-sterilization procedures in the production of high risk sterile preparations. These pre-sterilization procedures are performed in CPA's laboratory/pre-sterilization room. The guidelines for the air room and air quality for conducting pre-sterilization work in USP 797 are included in this excerpt from USP 797:

• *Pre-sterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 (USP <797> Table 1) environment.*

CPA is in full compliance with this guideline. CPAs laboratory/pre-sterilization area has been classified every 6 months since the company's founding in October 2012. The laboratory/pre-sterilization area has continually been classified as an ISO Class 7 room, which is an ISO Class better than what is required. On request, the owner of the third party certification company traveled to our site and re-calculated the numbers. There was a statistically insignificant calculation error in the company's calculation which determines the ISO designation. The room still classified as an ISO 7 room, however due to this insignificant calculation error in a third party report regarding the classification of CPA's pre-sterilization room, the FDA deemed the report invalid and "unclassified" the room. The calculation error did not affect the ISO classification of the pre-

sterilization room. CPA is in compliance with USP Standards, which state that pre-sterilization must be performed in an ISO Class 8 room or better.

7. ***Your firm's SOP 7.007.3, "Media Fill for High Risk Compounding" states that media-fill tests are to be performed semi-annually for each technician in an ISO class 5 area, however this does not simulate your firm's actual process because all drug products are produced in the Lab Room which is an unclassified area with no HEPA filtration.***

Response: CPA is in full compliance with the guidelines set forth in USP regarding media fill tests for staff members engaged in high risk compounding. CPA's "Media Fill for High Risk Compounding" *does* simulate CPA's actual process because CPA uses filtration to sterilize a non-sterile product in an ISO 5 environment. CPA is in compliance with USP 797 Standards, which requires terminal sterilization to be performed in an ISO 5 environment. The section of USP 797 regarding the classification of the activity known as "High Risk" compounding is as follows:

High-Risk Level CSPs
CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated.
High-Risk Conditions—
1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral), are incorporated or a nonsterile device is employed before terminal sterilization....
All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk level CSP solutions subjected to terminal sterilization are prefiltered by passing through a filter with a nominal pore size not larger than 1.2 mm preceding or during filling into their final containers to remove particulate matter. Sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.2-mm or 0.22-mm nominal pore size filter entirely within an ISO Class 5 (see Table 1) or superior air quality environment.
Examples of High-Risk Conditions—

1. Dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized....

Quality Assurance—Quality assurance procedures for high-risk level CSPs include all those for low-risk level CSPs. In addition, a media-fill test that represents high-risk level compounding is performed semiannually by each person authorized to compound high-risk level CSPs.

CPA's pre-sterilization activities are also in compliance with USP 797 Standards, which requires these activities to be performed in an ISO 8 Environment. Here is an excerpt from USP describing the conditions required for the space used for pre-sterilization activities:

• Pre-sterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8 (see Table 1) environment.

Again, our pre-sterilization area has consistently tested as an ISO 7 environment, which is a classification better than required.

The products are mixed in the laboratory/pre-sterilization room, and are sterilized in the buffer room. Due to an insignificant calculation error in a third party report regarding the classification of CPA's pre-sterilization room, the FDA deemed the report invalid. However, the calculation error technically did not affect the ISO classification of the pre-sterilization room.

8. ***Your firm's SOP 7.011 "Gowning and Gloving" does not have requirements for complete covering of the facial area. On 05/12/2015, we observed an employee aseptically filling Morphine 10 mg/ml Intrathecal Solution, lot #05122015@6, morpihine 20 mg/ml Intrathecal Solution, lot # 05122015@17 and Methylcobalamin 1,000 mcg/ml injection, lot 05122015@14 with exposed eyes and forehead.***

Response: CPA is in full compliance with USP 797 Standards regarding gowning and gloving. CPA's technicians garbed in compliance with USP 797 Standards, which do not require eyes or foreheads to be covered. Here is an excerpt from USP 797 regarding the garbing of personnel engaged in the act of sterile products

production NOTE: Most pertinent excerpts to this observation are in bold type:

Personnel Cleansing and Garbing
The careful cleansing of hands and arms and the correct donning of PPE by compounding personnel constitute the first major step in preventing microbial contamination in CSPs. Personnel shall also be thoroughly competent and highly motivated to perform flawless aseptic manipulations with ingredients, devices, and components of CSPs. Squamous cells are normally shed from the human body at a rate of 106 or more per hour, and those skin particles are laden with microorganisms.10, 11 When individuals are experiencing rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, as well as when they wear cosmetics, they shed these particles at even higher rates. Particles shed from compounding personnel pose an increased risk of microbial contamination of critical sites of CSPs. Therefore, compounding personnel with such conditions as mentioned above shall be excluded from working in ISO Class 5 (see Table 1) and ISO Class 7 (see Table 1) compounding areas until their conditions are remedied. Before entering the buffer area or segregated compounding area (see Low-Risk Level CSPs with 12-Hour or Less BUD), compounding personnel shall remove personal outer garments (e.g., bandannas, coats, hats, jackets, scarves, sweaters, vests); all cosmetics, because they shed flakes and particles; and all hand, wrist, and other visible jewelry or piercings (e.g., earrings, lip or eyebrow piercings) that can interfere with the effectiveness of PPE (e.g., fit of gloves and cuffs of sleeves). The wearing of artificial nails or extenders is prohibited while working in the sterile compounding environment. Natural nails shall be kept neat and trimmed.

Personnel shall don the following PPE in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face masks/eye shields. Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs.

After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, a hand cleansing procedure shall be

performed by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing. Hands and forearms shall be washed to the elbows for at least 30 seconds with soap (either nonantimicrobial or antimicrobial) and water while in the ante-area. The use of antimicrobial scrub brushes is not recommended because they can cause skin irritation and skin damage. Hands and forearms to the elbows will be completely dried using either lint-free disposable towels or an electronic hand dryer. After completion of hand washing, a non-shedding gown with sleeves that fit snugly around the wrists and enclosed at the neck is donned. Gowns designated for buffer area use shall be worn, and preferably they should be disposable. If reusable gowns are worn, they should be laundered appropriately for buffer area use. Once inside the buffer area or segregated compounding area (see Low-Risk Level CSPs with 12-Hour or Less BUD), and prior to donning sterile powder-free gloves, antiseptic hand cleansing shall be performed using a waterless alcohol-based surgical hand scrub with persistent activity12 following manufacturers' recommendations. Hands are allowed to dry thoroughly before donning sterile gloves.

As referenced above in USP 797, complete face protection is optional unless working with hazardous chemicals. At the time of the inspection, the staff observed was not working with hazardous chemicals.

9. ***Your firm's SOP 7.011, "Gowning and Gloving", states the technician will spray gloves with sterile IPA 70% when needed throughout the filling process and allow to dry. On 05/12/2015 a technician was observed spraying her gloves with sterile IPA 70% but not allowing the alcohol to dry before processing. The technician was aseptically filling Morphine 10 mg/ml Intrathecal Solution, lot # 05122015@6, Morphine 20 mg/ml Intrathecal Solution, lot #05122015@17 and Methylcobalamin 1,000 mcg/ml injection, lot # 05122015@14.***

Response: Neither CPA nor the FDA Investigator can definitively say whether the alcohol on the technician's gloves was completely dry or not. The technician believed the sterile IPA had in fact dried, and was the only person which was close enough to the gloves to make that

determination. However, in response to this observation, CPA has retrained all technicians with a comprehensive didactic sterile compounding course of 30 hours contact time,, and reiterated the importance of allowing the alcohol to fully dry.

10. ***Your firm's SOP 7.011 "Gowning and Gloving", states technicians will wash forearms and hands from the elbows down before gowning to enter the clean room. On 05/12/2015, we observed a technician washing only her hands and did not wash past the wrist before gowning and entering the clean room to aseptically fill Morphine 10 mg/ml Intrathecal Solution, lot# 05122015@6, , Morphine 20 mg/ml Intrathecal Solution, lot #05122015@17 and Methylcobalamin 1,000 mcg/ml injection, lot # 05122015@14.***

11. Response: CPA disagrees with this assessment. CPA management observed the technician during this process. The technician clearly washed up to her elbows. However, this did not include washing her actual elbows. CPA is in full compliance with the guidelines of USP 797 regarding the cleansing of hands and forearms prior to sterile products production. The excerpt from USP 797 regarding hand washing prior to sterile products production is as follows:

After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, a hand cleansing procedure shall be performed by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing. ***Hands and forearms shall be washed to the elbows*** *for at least 30 seconds with soap (either non-antimicrobial or antimicrobial) and water while in the ante-area.*

In response to this observation and out of an abundance of caution, CPA has retrained all technicians and pharmacists with a comprehensive didactic sterile compounding course of 30 hours contact time, emphasizing proper garbing and washing.

12. ***Your firm's SOP 4.004 "Incubator Temperature Monitoring" does not establish continuous monitoring or give procedures for investigating out of range temperatures. This incubator is used to incubate media fills, environmental monitoring samples, and finished product microbial testing. Temperature of the incubator is***

recorded once daily. During a record review for the past year of the temperature log it was noted the temperature went out of range approximately 30% of the time. No investigations were performed.

Response: CPA is in full compliance with the guidelines set forth by USP regarding the use and maintenance of the incubator. USP gives no direction on maintenance of the incubator or continuous monitoring. CPA developed an incubator maintenance program based upon common sense approach to a small incubator used in an extemporaneous compounding practice. The standard of practice for pharmacies engaged in compounding of this scale is once daily temperature monitoring. CPA believes that we were following the standard of practice with once daily temperature monitoring of the incubator.

The out of range temperature variance was a maximum of 1 degree Centigrade. Due to the subjectivity of reading the manual thermometer which was gauging the temperature, and the knowledge that 36 degrees Centigrade does not impede microbial growth in relation to 35 degrees Centigrade, the management determined this was an insignificant variance. CPA has since eliminated the small incubator from operations and replaced it with two larger, continuously monitored incubators.

13. ***Your firm does not perform positive or negative controls on media which is used for sterility testing on products and environmental monitoring.***

Response: CPA is in full compliance with USP 797 and 71 on the subject of sterility testing. Negative controls were performed on the media used at the time of the inspection. As part of our new sterility testing program, which was fully implemented in the weeks following the FDA inspection, CPA is performing a positive control on media (fluid thyoglycollate medium or FTM and soybean-casein digest medium or SCDM) used in our new membrane filtration procedures to ensure that the media lots can in fact provide growth in the presence of microbes. See SOP 9.022.1 Testing of Media. The 6 microorganisms described in USP <71> Growth Promotion Test of Aerobes, Anaerobes and Fungi are utilized.

14. ***Your firm does not perform growth promotion testing on media used for microbial testing.***

Response: This statement is inaccurate. See number 12 above. Procedures are based on USP <71> in which every lot of media is tested for growth promoting capability.

15. ***On 05/12/2015, we observed one of the firm's owners/pharmacists chewing gum in the Lab Room while Lidocaine 2% gel, lot #05122015@15, for intrathecal use was being produced.***

Response: CPA is in full compliance with the guidelines set forth by USP 797 regarding food in the critical work space. USP 797 says there is to be no gum in the ante and buffer rooms. The excerpt from USP 797 dealing with this issue is as follows:

13. Chewing gum, drinks, candy, or food items shall not be brought into the ***buffer area or ante-area****. Materials exposed in patient care and treatment areas shall never be introduced into areas where components and ingredients for CSPs are present.*

USP does not mention gum in the laboratory/pre-sterilization area, where the investigator alleges this observation occurred. It has always been a policy of CPA which goes above and beyond the USP 797 guidelines, no food, drinks, or gum is allowed in the pre-sterilization area under normal circumstances. The firm's owner does completely disagree with the timing of this observation, as the incident happened after all compounding had been voluntarily ceased by the firm in the pharmacy on the second day (05/13/2015) of the investigation.

16. ***On 05/12/2015, a technician was observed placing her hands between the product and air flow during processing. This obstruction could cause turbulent air flow around the product being aseptically filtered.***

Response: CPA fully complies with USP guidelines regarding sterile processing. USP 797 provides instruction for manipulation of products in the ISO 5 environment. CPA management observed the technician during the filtering process. This finding is inaccurate. The technician's hands remained on the barrel of the syringe while the syringe was positioned vertically. Air flow from the hood was coming at the syringe horizontally and fully meeting the critical transfer site where the syringes and filter connected for fluid transfer. Air flow to the critical site was never obstructed or blocked. USP <797> defines the critical site as follows:

Critical Site – A location that includes any component or fluid pathway surfaces (e.g., vial septa, injection ports, beakers) or openings (e.g., opened ampuls, needle hubs) exposed and at risk of direct contact with air (e.g., ambient room or HEPA filtered), moisture (e.g., oral and mucosal secretions), or touch contamination. Risk of microbial particulate contamination of the critical site increases with the size of the openings and exposure time.

Observation 4

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

Specifically,

1. ***No environmental monitoring is conducted in the Lab Room where weighing and mixing take place. The HVAC unit for this room is shared with other uncontrolled areas in the building and a supply vent is located directly above the space on the counter where compounding takes place. Weighing and mixing processes are not performed under a hood, the room is not classified, and does not have HEPA filtration.***
   Response: CPA is in full compliance with USP 797 guidelines regarding the production of sterile products. CPA engages in the production of High-Risk Classified compounds. High Risk compounds are compounds from which a sterile product is made from a non-sterile ingredient.. The section of USP 797 regarding the classification of the activity known as "High Risk" compounding is as follows:

   High-Risk Level CSPs
   CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated.
   High-Risk Conditions—
   1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral), are incorporated or a nonsterile device is employed before terminal sterilization....

All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk level CSP solutions subjected to terminal sterilization are pre-filtered by passing through a filter with a nominal pore size not larger than 1.2 mm preceding or during filling into their final containers to remove particulate matter. Sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.2-mm or 0.22-mm nominal pore size filter entirely within an ISO Class 5 (see Table 1) or superior air quality environment.
Examples of High-Risk Conditions—

1. ***Dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized....***

The activity performed in the laboratory area which the observation is incorrectly identifying as "production" is actually the pre-sterilization portion of high risk compounding. This step involves mixing non-sterile ingredients together in order to prepare it for terminal sterilization that is performed inside an ISO 5 environment at the Laminar Flow Work Bench inside the Buffer Room. As noted above, this is a non-sterile activity.
These pre-sterilization activities are also in compliance with USP 797 Standards, which requires these activities to be performed in an ISO 8 Environment. Here is an excerpt from USP describing the conditions required for the space used for pre-sterilization activities:

• Pre-sterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8environment.

Again, our pre-sterilization area has consistently tested as an ISO 7 environment, which is a classification better than required.

In regards to the "unclassified room" observation, a copy of all of the biannual certifications were supplied to the FDA Investigators at the time of the visit. The FDA Investigator requested a re-calculation of the numbers used to designate the room as an ISO 7 room. The owner of the certification company was summoned and the calculation re-done. There indeed was an insignificant calculation error in the report regarding the classification of CPA's pre-sterilization room. The room, after re-calculation, still certified as an ISO 7 room.

Nonetheless, the FDA used this error to deem the report invalid and invalidated the certification. Even though the calculation error did not affect the ISO classification of the pre-sterilization room, the FDA asserts that we were engaging in pre-sterilization work in an unclassified room. The employees and management of CPA used the room under the assurance that the room was classified as an ISO 7, and had taken every step possible to assure that the room was a classified room. At no point did we willingly use the room as an unclassified room.

After the FDA inspection, the room was re-certified and again achieved an ISO 7 classification. In the future and due to the third party certification company's calculation error, CPA will utilize another third party certification company for its biannual certifications.

Environmental monitoring is performed in the pre-sterilization area. Temperature and humidity are recorded daily. A copy of the temperature and humidity for the pre-sterilization room was supplied to the FDA Investigators at the time of inspection.

HEPA filtration system is not required by USP 797 for pre-sterilization area of high-risk compounds, only that the room classify as an ISO 8 as was previously stated. To reiterate, our pre-sterilization area exceeded the requirements set forth by USP 797.

There was no hood in the pre-sterilization area. Working inside a containment hood is not a requirement of USP Standards for pre-sterilization work. However, in response to this finding and in an effort to exceed USP Standards on pre-sterilization environment, an additional powder containment hood was placed in the room to be utilized for the weighing and mixing of powders. The air vent was moved two grid spaces and a deflector was placed on the vent at the suggestion of the FDA Investigators.

2. ***We observed the door to the Lab Room to remain open during weighing and mixing of non-sterile components to be used to produce drug products intended to be sterile. This door opens into a hallway that leads to the exit door and is adjacent to a door leading into the neighboring office.***

Response: CPA is in full compliance with USP 797 guidelines on facility design. The door was the original door in the original working configuration from the time of the official opening of CPA for business in October 2012. During that time, a minimum of 5 inspections from two different Tennessee Pharmacy Board Investigators as well as an inspection from the National Association of Boards of Pharmacy (NABP) failed to find any fault with either the constitution of the door (the door was wooden), or the position of the door during pre-sterilization work. In response to this finding, CPA took the recommendation of the FDA Investigator and has replaced the door with a self-closing steel door with 2 locks.

3. ***Your firm shares the building with an infusion office. The door into their office is adjacent to the door into your Lab Room. We observed employees from the infusion office coming into the Lab Room to retrieve product they have stored in your Lab Room.***

Response: CPA is in full compliance with USP 797 guidelines on facility design. CPA has always had a friendly relationship with our suitemate, which is an infusion office. CPA allowed the infusion office to store some of their medications in our facility to provide additional security during non-business hours. During the time which we were allowing the infusion suite to store their medications in our facility, a minimum of 5 inspections from two different Tennessee Pharmacy Board Investigators as well as an inspection from the National Association of Boards of Pharmacy (NABP) failed to find any fault with our storing of medications for the infusion suite. As a response to this observation, CPA no longer allows the other office to enter the laboratory and does not allow the infusion suite to store their medications in our facility. As referenced previously, CPA has replaced the door with a self-closing steel door, with double locks.

4. ***Viable air and personnel monitoring is not conducted for every production of injectable drug product. Currently your firm uses settling plates for viable air and finger-tip swabs for personnel monitoring only once per week and for only one technician.***

Response: CPA is in full compliance with USP guidelines regarding viable air sampling and personnel monitoring. USP <797> does not require viable air and personnel monitoring for every production of injectable drug product. USP <797> only requires viable air sampling

every 6 months, which is performed by an independent contractor for CPA. USP <797> requires semiannual gloved fingertip testing of sterile compounding employees. Additionally, CPA performs environmental surface sampling weekly as it is considered a best practice amongst USP experts, although USP <797> only states that the frequency of environmental surface sampling should be variable, but contains no specific requirements. CPA is in full compliance with USP <797> in this area.
The excerpt below from USP <797> describes air sampling frequency requirements:

Air Sampling Frequency and Process – Air sampling shall be performed at least semiannually (i.e., every 6 months) as part of the re-certification of facilities and equipment.

Observation 5

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

Specifically,

1. ***A review of your firm's Air Pressure Differential Log from the past year found the pressure from the Clean Room into the Ante Room and the Ante Room into the Lab Room to be equal in measurement. This indicates there is no positive pressure to direct air supply away from the clean room.***

Response: CPA is in full compliance with USP 797 guidelines regarding facility design. There is a fundamental misunderstanding of the way the pressure gauges system works by the FDA Investigators. The gauges that are referred to in this observation measure the pressure differential between two rooms, not an absolute pressure. For instance, the pressure gradient from the clean room/buffer room to the ante room is measured by a single independent gauge. That measurement was and is positive. A second and completely independently-operating gauge measures the air pressure from the ante room to the laboratory/pre-sterilization room. It was and is positive. The pressures are relative from room to room, not an absolute reading from the three rooms combined. A positive

measurement on gauge 1 and gauge 2 mean that both rooms are under positive pressure, regardless of whether both gauges are exhibiting identical positive pressures. The inspectors acknowledged this fact as they held their hands up around the door leading both from the buffer room to the ante- room and the ante room to the pre-sterilization area and were able to feel air blowing out. If one were to need to know the pressure difference between the buffer room and the pre-sterilization area, the pressures on both gauges would need to be added together.

2. ***Air pressure is not continuously monitored in the laminar flow hoods, Clean Room, or Ante Room.***

Response: CPA is in full compliance in regards to USP 797 guidelines regarding facility maintenance and monitoring. Continuous air pressure monitoring is not required in USP 797. Positive air pressure is monitored via the pressure gauges between the buffer room and ante-room and ante-room and pre-sterilization area in a continuous manner.

3. ***There is no HEPA filtration in the Lab room where components are weighed and mixed for producing drug products intended to be sterile. Weighing and mixing does not take place in an ISO classified area.***

Response: CPA is in full compliance with USP 797 guidelines in regards to facility design and maintenance.

The pre-sterilization room (the room in question) does not have a HEPA filter, as this is not required in USP 797. CPA is in full compliance with USP 797 guidelines regarding the production of sterile products. CPA engages in the production of High-Risk Classified compounds. High Risk compounds are compounds from which a sterile product is made from a non-sterile ingredient. The section of USP 797 regarding the classification of the activity known as "High Risk" compounding is as follows:

High-Risk Level CSPs
CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated.
High-Risk Conditions—

1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral), are incorporated or a nonsterile device is employed before terminal sterilization....
All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk level CSP solutions subjected to terminal sterilization are pre-filtered by passing through a filter with a nominal pore size not larger than 1.2 mm preceding or during filling into their final containers to remove particulate matter. Sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.2-mm or 0.22-mm nominal pore size filter entirely within an ISO Class 5 (USP <797> Table 1) or superior air quality environment.
Examples of High-Risk Conditions—
1. Dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized....
The activity performed in the laboratory area which the observation is incorrectly identifying as "production" is actually the pre-sterilization portion of high risk compounding. This step involves mixing non-sterile ingredients together in order to prepare it for terminal sterilization that is performed inside an ISO 5 environment at the Laminar Flow Work Bench inside the Buffer Room. As noted above, this is a non-sterile activity. These pre-sterilization activities are also in compliance with USP 797 Standards, which requires these activities to be performed in an ISO 8 Environment. Here is an excerpt from USP describing the conditions required for the space used for pre-sterilization activities:

• Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8environment.

Again, our pre-sterilization area has consistently tested as an ISO 7 environment, which is a classification better than required. A HEPA filtration system is not required by USP 797 for pre-sterilization of high-risk compounds, and our pre-sterilization area exceeded the requirements set forth by USP 797.

A copy of all of the biannual certifications was supplied to the FDA Investigators at the time of the visit. The FDA Investigator requested

a re-calculation of the numbers used to designate the room as an ISO 7 room. The owner of the certification company was summoned and the calculation re-done. There indeed was an insignificant calculation error in the report regarding the classification of CPA's pre-sterilization room. The room, after re-calculation, still certified as an ISO 7 room. Nonetheless, the FDA used this error to deem the report invalid and invalidated the certification. Even though the calculation error did not affect the ISO classification of the pre-sterilization room, the FDA asserts that we were engaging in pre-sterilization work in an unclassified room. The employees and management of CPA used the room under the assurance that the room was classified as an ISO 7, and had taken every step possible to assure that the room was a classified room. At no point did we willingly use the room as an unclassified room.

After the FDA inspection, the room was re-certified and again achieved an ISO 7 classification. In the future and due to the third party certification company's calculation error, CPA will utilize another third party certification company for its biannual certifications

4. ***Smoke studies for qualification of the ISO 5 area where injectable drug products are processed were not documented with diagram or video.***
Response: CPA is in full compliance with USP 797 guidelines regarding maintenance of Primary Engineering Controls. USP <797> requires smoke studies for ISO 5 areas, but does not require diagram or video documentation. Smoke studies are performed by an independent third party company. We notified the companies to address this issue, and on the re-certification of the ISO 5 area, which took place on 5/15/2015 a video documenting the smoke study was taken.

Observation 6

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

Specifically,

1. ***Your firm's daily cleaning of the Clean Room and Ante Room consists of wiping the walls and floors with a non-sterile Swiffer***

brand mop. On a monthly basis, your firm cleans with Lysol IC and Clorox Hydrogen Peroxide in the Clean Room and Ante Room. Your firm does not use any sporicide while cleaning and disinfecting a room for aseptic processing. Also, cleaning products used are not documented on cleaning logs.

Response: CPA is in full compliance with USP 797 guidelines regarding cleaning and disinfection of compounding areas. USP <797> only requires a non-shedding mop cloth, but not a sterile mop cloth. Sporicidin is used as a sporicidal agent, and many studies show hydrogen peroxide to have sporicidal properties if at a high enough concentration and if contacting surfaces for 10 minutes or more. CPA has updated their cleaning logs to include all instructions for cleaning on the logs, as well as what cleaner was made and how it was made. Please see SOP 5.001 Cleaning and Disinfection

2. ***You do not use a sporicide in your ISO 5 hood where aseptic filling takes place. The only product used to clean the ISO 5 hood is sterile 70% Isopropyl Alcohol.***
Response: CPA has updated their cleaning products to include Peridox RTU, which has sporicidal activity with 3 minutes of contact and is safe for stainless steel surfaces in clean room hoods.

3. ***On 05/12/15, we observed stacked, plastic baskets containing in-process drug product and aseptic filling equipment (pre-packaged syringes and filters). The technician took these stacked baskets into the Ante Room and did not wipe the baskets or materials down before entering. Once the technician completed gowning, she carried the baskets into the Clean Room for aseptic processing. The materials were wiped with a non-sterile, pre-wetted alcohol wipe before being placed in the ISO 5 hood. These wipes are in a re-sealable container via sticky flap located on the top.***

Response: CPA is in full compliance with USP 797 guidelines regarding introduction of materials into the buffer area. : USP <797> does not require wiping down baskets or materials before entering the ante room. USP <797> only requires wipe down of baskets and/or materials before entering the buffer room. This has been CPA's policy, but CPA has retrained all technicians on this issue. CPA emphasized the importance of wiping down all baskets and products

prior to placing items in bins, in the ante room, and in the clean room/buffer room. Please see the following excerpt directly from USP <797>:

Packaged compounding supplies and components, such as needles, syringes, tubing sets, and small and large-volume parenterals should be un-cartoned and wiped down with a disinfectant that does not leave a residue (e.g., sterile 70% IPA), when possible in an ante area of ISO Class 8 air quality, before being passed into the buffer areas. CPA has retrained all technicians. CPA emphasized the importance of wiping down all baskets and products prior to placing items in bins, in the ante room, and in the clean room/buffer room.

4. ***During the inspection, visible dirt and debris was observed on the return vent in the clean room and Swiffer mops used in the Clean Room and Ante Room were propped up against the walls in each room, with the mop end leaning against the wall. Also, it was noted the Clean Room, Ante Room, and Lab Room all had open trash receptacles.***

Response: CPA is in full compliance with USP 797 regarding buffer room and its components. There is no guideline in USP 797 that addresses whether mops should be hung on the wall or left propped against the wall. CPA has hung the mop on the wall. CPA purchased closed lids for all trash receptacles. CPA has cleaned the return vent in the clean room/buffer room, and has placed cleaning of the return vent.

5. ***The lighting in the Clean Room is not recessed into the ceiling and there is a visible gap between the light fixture and the ceiling that would allow for a build-up of dirt and debris.***

Response: We reached out for an opinion on this issue to Mike Vitullo, owner of Southeastern Certification, in order to have a knowlegable opinion on the subject of recessed lighting. The pertinent elements of his response are as follows:

Lighting is a two-fold issue. One is ease of cleaning when it is flush with the ceiling and the other is that all light fixture housings must be sealed and non-porous. This is the more important of the two issues for the following reasons: 1) Porous housings allow too much air to

escape into the interstitial space above the ceiling making the room not "as tight" as it should be. This often means that airflow has to be turned up to get the right pressure relationships between the rooms depending on how many light fixtures there are. They also contribute to vacillating static pressure regardless of how it is being measured, 2) Sometimes the space above the ceiling can be used as a return air plenum. If the HVAC system goes off and light housings are porous, dirty unfiltered air can be pushed through the housings and into the cleanroom by a space that has become more positive than the cleanroom when the HVAC system is out of service. That is the background rationale.

To my knowledge your light housings are non porous and there is a very small sealed hole where the Romex wiring comes through the ceiling to the light. It is a surface mounted sealed light inconvenient to clean. Sometimes, due to the proximity of the ceiling to ducting above or water lines or sprinkler lines, it is not possible to recess the lighting.

Recessed lighting is the better way to go for cleaning, but it is not the only way unless it is required. It is also the preferred way for manufacturing facilities. Hope that helps.

To address this finding, the light fixture has been caulked around to remove any cracks and crevices.

Observation 7

There is a failure to thoroughly review the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

Specifically,

A review of records from the past year found Sufentanil 50mcg/ml Intrathecal Solution, lot #01102014@24, Morphine 50 mg/ml Intrathecal Solution, lot #06252014@6, and Morphine 40 mg/ml + Fentanyl 2,000 mcg/ml Intrathecal solution, lot 08062014@19 all tested positive for microbial contamination. No investigations were performed and the lots were distributed.

Response: CPA retested this same lot by re-plating it. This second test charted zero growth and the initial test was surmised to be human error. There was only one medication produced from this specific lot number, and it had been

administered to the patient within 72 hours of making the lot. In response to this finding, CPA has updated its policy to include all of the necessary documentation related to quarantine and/or recall of contaminated products at the first sign of contamination. See SOP 1.054 Recalling Sterile and Non-Sterile Compounded Preparations and SOP 1.064 How to Handle a Product Recall.

Observation 8

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

Specifically,

1. ***Non-sterile gowns, face masks, and hair covers are used during the production of drug products intended to be sterile. These garments are stored in open containers in the Ante Room.***

2. Response: CPA is in full compliance with USP 797 guidelines regarding garbing and gowning. USP 797 does not require the gowns, face masks, or hair covers used during the production of sterile products to be sterile themselves. The portion of USP 797 regarding appropriate garb for the production of sterile products is as follows:

   Personnel shall don the following PPE in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face masks/eye shields. Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs.

   USP 797 requires non-shedding gowns, face masks, hair covers, shoe covers, and sterile gloves. CPA is in compliance with these guidelines.

3. ***On 05/12/15, we observed the processing of Morphine 10 mg/ml Intrathecal Solution, lot #05122015@6, Morphine 20 mg/ml Intrathecal Solution, lot #05122015@17 and Methylcobalamin 1,000 mcg/ml injection, lot #05122015@14, all purporting to be sterile. The technician's gown did not adequately cover the technician, leaving the collar of her shirt and her neck area***

exposed. Also, the technicians forehead and eyes were not covered and her hair was loose from her hair cover around the back of her neck.

Response: CPA is in full compliance with USP 797 guidelines regarding the production of sterile products. Full face covers are not a requirement by USP 797 guidelines. The excerpt pertaining to the components of garb to be donned before entering the ISO 7 Buffer Room from USP 797 are as follows:

Personnel shall don the following PPE in an order that proceeds from those activities considered the dirtiest to those considered the cleanest. Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face masks/eye shields. Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs.

At the time of the observation, the technician in question was not working with hazardous chemicals.

The technician's gown was not tightly fastened around the back. In response to this observation, CPS has changed to front-fastening, non-shedding gowns to replace the rear-tie gowns which could lead to the loos-fit observed by the investigators. Additionally, CPA has implemented and completed a full re-training program featuring 30 contact hours of training in sterile products preparation. A significant portion of this training deals with proper and appropriate garbing techniques and procedures.

4. ***On 05/12/15, we observed a technician mixing and filling Lidocaine 2% gel, lot #05122015@15, for intrathecal use, into glass vials to be autoclaved. The technician was wearing gloves, but not wearing any gowning or head/face covers over her street clothes. This process was taking place in the Lab Room, which is an unclassified room with no HEPA filtration.***

Response: CPA is in full compliance with USP 797 guidelines regarding the production of sterile products. CPA engages in the production of High-Risk Classified compounds. High Risk compounds are compounds from which a sterile product is made from a non-sterile ingredient. The section of USP 797

regarding the classification of the activity known as "High Risk" compounding is as follows:

High-Risk Level CSPs
CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated.
High-Risk Conditions—
1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g., oral), are incorporated or a nonsterile device is employed before terminal sterilization....
All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk level CSP solutions subjected to terminal sterilization are pre-filtered by passing through a filter with a nominal pore size not larger than 1.2 mm preceding or during filling into their final containers to remove particulate matter. Sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.2-mm or 0.22-mm nominal pore size filter entirely within an ISO Class 5 (see Table 1) or superior air quality environment.
Examples of High-Risk Conditions—
1. Dissolving nonsterile bulk drug and nutrient powders to make solutions that will be terminally sterilized....
The activity performed in the laboratory area which the observation is incorrectly identifying as "production" is actually the pre-sterilization portion of high risk compounding. This step involves mixing non-sterile ingredients together in order to prepare it for terminal sterilization that is performed inside an ISO 5 environment at the Laminar Flow Work Bench inside the Buffer Room. As noted above, this is a non-sterile activity. These pre-sterilization activities are also in compliance with USP 797 Standards, which requires these activities to be performed in an ISO 8 Environment. Here is an excerpt from USP describing the conditions required for the space used for pre-sterilization activities:

• Pre-sterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO Class 8environment.

Again, our pre-sterilization area has consistently tested as an ISO 7 environment, which is a classification better than required. A HEPA filtration system is not required by USP 797 for pre-sterilization of high-risk compounds, and our pre-sterilization area exceeded the requirements set forth by USP 797.

A copy of all of the biannual certifications were supplied to the FDA Investigators at the time of the visit. The FDA Investigator requested a re-calculation of the numbers used to designate the room as an ISO 7 room. The owner of the certification company was summoned and the calculation re-done. There indeed was an insignificant calculation error in the report regarding the classification of CPA's pre-sterilization room. The room, after re-calculation, still certified as an ISO 7 room. Nonetheless, the FDA used this error to deem the report invalid and invalidated the certification. Even though the calculation error did not affect the ISO classification of the pre-sterilization room, the FDA asserts that we were engaging in pre-sterilization work in an unclassified room. The employees and management of CPA used the room under the assurance that the room was classified as an ISO 7, and had taken every step possible to assure that the room was a classified room. At no point did we willingly use the room as an unclassified room.

After the FDA inspection, the room was re-certified and again achieved an ISO 7 classification. In the future and due to the third party certification company's calculation error, CPA will utilize another third party certification company for its biannual certifications.

Observation 9
Results of stability testing are not used in determining expiration dates.

Specifically,

Your firm has not conducted any stability testing. Expiration dates of 2-3 months are assigned to drug products intended to be sterile that do not contain preservatives. You have no data to support your product expiration dates.
Response: CPA is in full compliance with USP 71, 797, and 1163 Standards. All of CPA's beyond use dates are assigned in compliance with these standards. The Chapter on Assignment of Beyond-Use Dating in Pharmaceutical Compounding

reads as follows (Excerpt from USP 1163 on Documentation of Beyond Use Dating:

The purpose of documentation is to provide a record of all aspects of compounding operations and procedures that are described in this chapter, in á795ñ, and in á797ñ. Information on the compounding record should ideally be entered as the task is performed or as testing data is received. Compounding records should be reviewed for accuracy, completeness (as appropriate and approved by QA personnel, prior to dispensing. Additionally, beyond-use dating and sterility studies, where appropriate, should be documented by reference to at least one of the following:

- *Stability studies published in peer-reviewed literature,*
- *In-house or laboratory conducted stability and/or sterility studies,*
- *National compendia, or*
- ***An extrapolation of above based on professional judgment.***

CPA assigned beyond-use dating based on professional judgement extrapolated from peer-reviewed literature. At the time a brand new formula is introduced to CPA to be compounded, a literature search was performed and a beyond use dating was assigned based on that literature and the professional judgement of the pharmacist. Any compound for which none of the requirements listed in 1163 (listed above) could be found, beyond use dating was assigned at the strictest USP dating available for compounds not undergoing sterility testing (Example: 3, 9, or 14 days refrigerated based upon Risk Level of the preparation).

CPA now will have on-site documentation of the peer-reviewed stability studies which were the basis for determination of the beyond-use dating. Additionally, CPA has instituted a process to use third party stability studies for select products deemed to have questionable or non-existent peer-reviewed stability studies.

Observation 10

Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations related to aseptic processing of drug products.

Specifically,

1. ***Your firm's Clean Room contains two ISO 5 laminar flow hoods for aseptic filling; however, you only have one staging table for materials. When two technicians are filling in the Clean Room, they must share the table increasing the likelihood of a mix-up.***

Response: CPA is in full compliance with the guidelines set forth by USP 797 regarding sterile drug processing. Previously the table was segregated for each technician to work on one half of the table. In response to this finding, CPA has limited the amount of technicians allowed in the clean room/buffer room to only one technician at a time. This will continue until a new table(s) is purchased and the room is recertified.

2. ***In the Lab Room, several different products can be weighed and staged for mixing on the same counter top. For example, on 05/12/15, we observed pre-printed worksheets and labeling for different products on the counter where production takes place. There is no separation for these materials, which can lead to a mix-up of labeling or components. Also, multiple products can be taken into the Clean Room, simultaneously, for aseptic filling.***

   Response: CPA is in full compliance with the guidelines set forth by USP 797 regarding sterile drug processing. Each individual product is segregated into its own separate plastic bin. Each bin has the appropriate labels, worksheet, and materials in it for that particular lot of drug/prescription to be produced. Separation along these lines, while not specifically set forth in USP, has always been deemed adequate by Board of Pharmacy inspectors and pharmacy leadership teams at various practice sites which the leadership of CPA has experience. In fact, it is the standard across the industry.

3. ***On 05/12/15, 1 IV bag of 0.9% Sodium Chloride solution and 1 IV bag of Sterile Water for Injection were observed in the sink in the Ante Room. These bags had no additional labeling to determine if the firm had used them in processing or was going to use them, and no indication of what product these solutions would be used for.***
   Response: The bag of sodium chloride and the bag of sterile water were sitting in the sink to be wasted/disposed of. All CPA staff know that this denotes a bag which is not to be used in further aseptic processing.

Observation 11
There is no quality control unit.

Specifically,

Your firm has not established a quality control unit with the responsibility to approve or reject all components, containers, closures, packing material, labeling, and drug products. For example:

1. ***Containers and closures are not examined upon receipt to ensure they meet specifications for use.***

   Response: CPA is in full compliance with the guidelines set forth by USP 797, USP 71, and USP 1163 regarding quality assurance. Containers, components, closures, packing material, labeling and drug products are visually examined at the time of receipt. Unacceptable products, if they should be encountered, are rejected and returned to the source. An established quality control "unit" which documents these inspections is not required by the guidelines set forth in the referenced USP chapters. Additionally, CPA orders all containers and closures from FDA regulated facilities. FDA regulated products should meet CPA's requirements.

2. ***No finished product testing is performed on drug products intending to be sterile before release for distribution.***
   Response: CPA is in full compliance with the guidelines set forth by USP 797, USP 71, and USP 1163. Finished product testing prior to release of product is not a requirement in our USP <797> guidelines. It only absolutely requires sterility testing when wishing to extend the beyond-use-date beyond USP <797> limits. CPA does perform sterility testing (please see Observation 7). At the time of CPA was using a direct inoculation method, but was actively in the process of migrating to the use of membrane filtration testing method, which we currently use. Both the direct inoculation and membrane filtration methods of testing are compliant with the guidelines set forth in USP 71 and 797 regarding sterility testing of finished product.

3. ***Your firm has just recently established a complaint file. A review of your firm's Incident Report Forms found no investigations were performed for complaints to determine root cause. For example:***
   a. ***On 3/4/25, your firm received a complaint for Neurogenic XR + BAC + GAB cream being "sticky". No lot number was recorded on the Pharmacy Incident Report Form and you did not request that the product be returned for analysis. No investigation was performed and the corrective action was to remake the product and send the patient a new jar.***

b. ***On 03/06/15, your firm received a complaint for Anti-Inflammatory Plus 10 pain gel that had separated upon the patient receiving the product. No lot number was recorded on the Pharmacy Incident Report Form and you did not request that the product be returned for analysis. No investigation was performed and the corrective action was to remake the product and send the patient a new jar.***
Response: CPA is in full compliance with the guidelines set forth under USP 1163 and USP 797 regarding Quality Assurance in Pharmaceutical Compounding. CPA's SOP on Continuous Quality Improvement (See SOP 1.112 Performance Improvement Program - General and SOP 1.112.01Performance Improvement Program - Personnel Involvement) does not require recall of medication if the complaint is trivial in nature. If a complaint is received that is deemed a threat to individual or public safety, CPA has procedures in place for immediate recall of the drug product and all drug products associated with the lot number in question. (See SOP 1.054 Recalling Sterile and Non-Sterile Compounded Preparations and SOP 1.064 How to Handle a Product Recall.)

Observation 12
Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically,
Your firm has not established any hold times for processing drug products intended to be sterile.
Response: CPA is in full compliance with USP 797 and USP 1163- Quality Assurance in Pharmaceutical Products. The following section from USP 797 deals with release of finished product:

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 multiple-dose vials (MDVs) for administration to multiple patients or that are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized shall meet the sterility test (see Sterility Tests á71ñ) before they are dispensed or administered. The Membrane Filtration method is the method of choice where feasible (e.g., components are compatible with the membrane). A method not described in the USP may be used if verification results demonstrate that the alternative is at least as effective and reliable as the USP*

Membrane Filtration method or the USP Direct Inoculation of the Culture Medium method where the Membrane Filtration method is not feasible.

When high-risk level CSPs are dispensed before receiving the results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSPs when there is any evidence of microbial growth in the test specimens. *In addition, the patient and the physician of the patient to whom a potentially contaminated CSP was administered are notified of the potential risk. Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.*

CPA does not batch any product in groups of more than 25 individual packages. CPA has an on-going program requiring the daily observation of high-risk level CSPs (See SOP 9.021.03 Performing USP 71 Membrane Filtration Sterility Testing). A copy of the manual log documenting the daily observation of the sterility testing of high risk CSPs was provided to the FDA Investigators during the visit.

Observation 13

Routine calibration of equipment is not performed according to a written program designed to assure proper performance.

Specifically,

There are no records to demonstrate the following equipment has been calibrated for use:

1. ***The pressure gauge used for the filter integrity testing of the B. Braun 02.um filter used for aseptic filling.***
   Response: CPA is in full compliance with USP 797 and USP 1163. USP does not require the on-going calibration of the filter gauge used in testing the integrity of the 0.2 micron syringe filters. CPA is in compliance with USP guidelines on this matter. Furthermore, the filter gauge CPA uses for filter integrity testing was purchase already calibrated. The owner's manual for the filter integrity gauge is attached as exhibit (See Q.I. Medical, Inc – Integrity Test – Bubble Point Method and Reotemp Calibration Certificate). Nonetheless, out of an abundance of caution in response to this observation, CPA has purchased a new filter gauge, which is also calibrated.

2. ***The scale in the Lab Room used to weigh ingredients used in production of drug products.***

Response: CPA is in full compliance with the guidelines on analytical scale calibration outlined in USP 1176 and USP 797. All CPA analytical scales are internally calibrated daily. CPA also utilizes a third party vendor to calibrate all scales every 6 months. The investigators received a copy of the third party' scale calibration certificates for the previous 18 months, which were entered into evidence at the time of their visit. Please see that documentation.

3. ***The thermometer in the incubator used to test environmental samples and finished product.***

Response: CPA is in full compliance with USP 797. CPA utilized a manual mercury thermometer in the incubator used to test environmental samples and finished product. CPA was in the process of transitioning to two new and internally calibrated incubators and the retiring of the previous small incubator with manual thermometer. CPA has completed this transition and the small incubator with manual thermometer has been retired. The new incubators are in full compliance with USP 71, 797, and 1116 regarding quality assurance and microbial testing.

4. ***The thermometer used in the de-pyrogenation oven used for glassware.***

Response: CPA is in full compliance with the guidelines set forth under USP 1163 and USP 797 regarding Quality Assurance in Pharmaceutical Compounding. The dry heat oven utilized by CPA has an internal continuous thermometer monitor. Temperature is monitored and logged on the De-Pyrogenation Log, a copy of which was given to the FDA Investigators. In addition to the thermometer, secondary proof of appropriate temperature is attained by the use of Biological Indicators (BI) which activate when the appropriate temperature is reached in the oven. These indicators are used with each cycle of the oven, and a copy of the log was given to the FDA investigators upon their visit. After the visit by the FDA, and in order to provide another proof on the conformity and performance the de-pyrogenation process, routine inspection of the de-pyrogenation equipment has been scheduled as a continuous bi-annual service.

5. ***The thermometer in the autoclave used to sterilize glassware and terminally sterilize injectable drug products.***

Response: CPA is in full compliance with the guidelines set forth under USP 1163 and USP 797 regarding Quality Assurance in Pharmaceutical Compounding. The autoclave utilized by CPA has an internal continuous thermometer monitor. Temperature is monitored and logged on paper read-out, and, a copy of which was given to the FDA Investigators. In addition to the thermometer, secondary proof of appropriate temperature is attained by the use of Biological Indicators (BI) which activate when the appropriate temperature and pressure is reached in the autoclave. These indicators are used with each cycle of the oven, and a copy of the log was given to the FDA investigators upon their visit. After the visit by the FDA, and in order to provide another proof on the conformity and performance the autoclave process, routine inspection of the autoclave equipment has been scheduled as a continuous bi-annual service.

Observation 14

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each component and establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically,

1. ***Your firm accepts incoming lots of non-sterile raw materials and components based on the Certificate of Analysis (CoA). You do not conduct any additional testing on incoming lots of raw materials and components. Also, the CoA's you receive from your supplier do not include microbial testing.***

Response: CPA is in full compliance with USP 1163 and USP 797- Quality Assurance in Pharmaceutical Products. All raw materials CPA purchases are purchased from FDA regulated and inspected facilities. USP does not require CPA to conduct any additional testing on incoming lots of raw chemicals and components purchased from such facilities which include a Certificate of Analysis from the

chemical facility. All chemicals purchased by CPA include a Certificate of Analysis. CPA is in compliance with USP 797 Standards on the conformation and use of bulk chemical substances.

2. ***You have not qualified the reliability of your suppliers.***

Response: CPA is in full compliance with USP 797 and USP 1163 guidelines- Quality Assurance in Pharmaceutical Products. All of CPA's suppliers are FDA regulated facilities. USP does not require CPA to qualify the reliability of our chemical suppliers. Additionally, by using FDA regulated facilities, we believe that the onus on qualifying these facilities falls upon the FDA and that by these facilities being in operation, the FDA has approved of the quality of the products these chemical suppliers are introducing into the pharmacy marketplace.

Observation 15

Aseptic processing areas are deficient regarding temperature and humidity controls.

Specifically,

1. ***During a review of temperature and humidity logs from the past year (Jan. 2014-May 2015), it was found the temperature was out of range for the Lab room approximately 70% of the time, the Clean Room approximately 18% of the time, and the Ante Room approximately 98% of the time. No investigations were performed into these discrepancies.***

Response: These percentages are simply not accurate. While the temperatures were out of range a small percentage of the time, it was not nearly as often as referenced above. USP <797> does not require a documented investigative review when temperatures or humidity are out of range, but nonetheless a review of our logs in response to the FDA's findings revealed specific time sequences where an employee incorrectly logged temperature into the humidity column, and humidity into the temperature column. This skewed the time percentage that both values were out of range, when they were in fact in range. Employees logging ranges in the sterile lab have been retrained to understand how to properly and correctly document such values. Typically, the temperature and/or humidity are adjusted in the HVAC unit as needed on a daily basis. If temperature or humidity are

largely out of range or for extended periods of time our management is to contact maintenance to have the system professionally checked.

2. ***During a review of temperature and humidity logs from the past year (Jan. 2014-May 2015), it was found the humidity was out of range for the Lab Room approximately 13% of the time, the Clean Room approximately 63% of the time, and the Ante Room approximately 14% of the time. No investigations were performed into these discrepancies.***
Response: These percentages are simply not accurate. While the temperatures were out of range a small percentage of the time, it was not nearly as often as referenced above. USP <797> does not require a documented investigative review when temperatures or humidity are out of range, but nonetheless a review of our logs in response to the FDA's findings revealed specific time sequences where an employee incorrectly logged temperature into the humidity column, and humidity into the temperature column. This skewed the time percentage that both values were out of range, when they were in fact in range. Employees logging ranges in the sterile lab have been retrained to understand how to properly and correctly document such values. Typically, the temperature and/or humidity are adjusted in the HVAC unit as needed on a daily basis. If temperature or humidity are largely out of range or for extended periods of time our management is to contact maintenance to have the system professionally checked.

3. ***Temperature and humidity in aseptic processing areas are not continuously monitored. The gauge readings are only documented once daily.***
Response: CPA is in full compliance with USP 797. Temperature and humidity are monitored in the manner set forth in USP 797. The section regarding temperature and humidity in USP is as follows:

The entire compounding and storage area should be well lighted. Heating, ventilation, and air conditioning system shall be controlled to avoid decomposition and contamination of chemicals (see the General Notices and Requirements, Preservation, Packaging, Storage, and Labeling, Storage Temperature and Humidity; and the manufacturers' labeled storage conditions). ***Appropriate temperature and humidity monitoring should be maintained as required for certain components and compounded***

dosage forms. *All components, equipment, and containers shall be stored off the floor and in a manner to prevent contamination and permit inspection and cleaning of the compounding and storage area.*

Continuous temperature and humidity monitoring is not required in USP 797. Monitoring of temperature and humidity once daily is the pharmacy industry's standard. However, in response to this finding, CPA has taken steps to exceed the requirements set forth by USP on its refrigerated items and has integrated an alarm on an out-of-bounds reading into its alarm company.

Observation 16

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically,

1. ***Your firm's Logged Formula Worksheets do not contain a representative label from the product that was produced.***
   Response: CPA is in full compliance with USP 1163- Quality Assurance in Pharmaceutical Compounding guidelines. CPA's process does require a representative label from the product that was produced be placed on the Logged Formula Worksheet. CPA has retrained all technicians, and emphasized the importance of this requirement.

2. ***Your firm's Logged Formula Worksheets do not indicate which containers and closure were used or what container the product was filled into.***
   Response: CPA is in full compliance with USP 797 and 1163- Quality Assurance in Pharmaceutical Compounding guidelines. Pedigree of particular containers and closures which are used in the preparation of sterile compounded medications are not addressed and are not necessary in order to comply with USP 797 or 1163 on quality assurance. The type of container IS listed on logged formula worksheets. It is visible on page 1 at the top of the page under "Packaging". Examples of the Logged Formula Worksheet were given to the FDA Investigators and logged in as evidence.

3. ***Heating and mixing times during production are not documented in the Logged Formula Worksheets.***

Response: CPA is in full compliance with USP 797 guidelines regarding the production of sterile pharmaceutical products. Even though our Master Formulation Records used to compound mixtures generally have required heating and mixing times as applicable (i.e., autoclave for 30 minutes at 121°C and 15 PSI), mixing times are not absolute, and USP 797 provides both guidance and a charge to the compounding personnel to use the appropriate techniques for weighing, measuring, and mixing the product based on its physical characteristics. The actual heating times and other parameters of such devices are additionally recorded on the appropriate logs, such as autoclave or dry heat oven logs. The portion dealing with mixing the CSP from USP 797 is referenced below in the section "Master Formulation Record":

• *mixing instructions that should include:*
1. order of mixing
2. mixing temperatures or other environmental controls
3. duration of mixing
4. other factors pertinent to the replication of the preparation as compounded and the requirement simply states the solution must be mixed until it is fully dissolved.

CPA is in full compliance with these guidelines.