On behalf of the Wellness Center Pharmacy, Inc. dba Designer Drugs, I authorize the United States Food and Drug Administration (FDA) to publicly disclose the information described below on FDA’s website. 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 (0), 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 FDA harmless for any injury caused by FDA’s sharing the information with the public.

Information to be disclosed: Designer Drugs’ letter dated 06/17/2015 excluding attachments/exhibits, which responds to FDA’s Form 483 dated 05/28/2015.

Authorization is given to 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 Designer Drugs and my full name, title, address, telephone number, and facsimile number is set out for verification.

Randy Davis
7304 Jarnigan Road
Chattanooga, TN 37421
Phone 423.954.2585 / 888.935.2930
Fax 423.954.2460 / 855.846.0843
Brandon C. Heitmeier  
Investigator  
Department of Health and Human Services  
Food and Drug Administration  
404 BNA Drive, Building 200, Suite 500  
Nashville, TN 37217-2597

Re: Response to FDA Form 483 Issued May 28, 2015, to The Wellness Center Pharmacy, Inc. d/b/a Designer Drugs

Dear Mr. Heitmeier:

The Food and Drug Administration ("FDA") conducted an inspection of The Wellness Center Pharmacy, Inc. d/b/a Designer Drugs ("Designer Drugs"), a pharmacy located at 7304 Jarnigan Road, Chattanooga, Tennessee, between May 18 and May 28, 2015. Upon the conclusion of its inspection, the FDA provided Designer Drugs with an FDA Form 483. This letter is Designer Drugs' 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 Designer Drugs’ FDA Form 483 to anyone outside the FDA.

The FDA’s observations on the Form 483 are all requirements imposed on drug manufacturers under the current Good Manufacturing Practices ("cGMPs") for finished pharmaceuticals contained in 21 C.F.R. Part 211. Please note that Designer Drugs does not engage in drug manufacturing. We are a pharmacy licensed by the Tennessee Board of Pharmacy as a retail pharmacy and are subject to its jurisdiction. Furthermore, Designer Drugs is appropriately licensed in and complies with the laws of each state in which it dispenses medications.

Designer Drugs engages in the practice of pharmacy by compounding patient-specific prescriptions in compliance with the laws of Tennessee and any other state in which it dispenses medications. Prior to May 15, 2015, Designer Drugs also compounded commercially unavailable medications for office administration upon receipt of orders from licensed practitioners, as permitted by the Tennessee Pharmacy Practice Act of 1996. Specifically, Tenn. Code Ann. § 63-10-204 defines the “practice of pharmacy” to include the “[r]esponsibility for compounding and dispensing of prescription orders” and further defines “compounding” and “dispense,” in relevant part, as follows:
(6) "Compounding" means the preparation, mixing, assembling, packaging or labeling of a drug or device:

(A) As the result of a prescription order or initiative based on the prescriber-patient-pharmacist relationship in the course of professional practice;

(B) In anticipation of prescription orders based on routine, regularly observed prescribing patterns;

(C) For the purpose of, or as an incident to, research, teaching or chemical analysis and not for sale or dispensing;

(D) For use in a licensed prescribing practitioner’s office for administration to the prescribing practitioner’s patient or patients when the product is not commercially available upon receipt of an order from the prescriber; [or]

(E) For use in a health care facility for administration to a patient or patients receiving treatment or services provided by that facility when the product is not commercially available upon receipt of an order from an authorized licensed medical practitioner of the facility[.]

(14) "Dispense" means preparing, packaging, compounding or labeling for delivery and actual delivery of a prescription drug, nonprescription drug or device in the course of professional practice to a patient or the patient's agent, to include a licensed health care practitioner or a health care facility providing services or treatment to the patient or patients, by or pursuant to the lawful order of a prescriber[.]

As noted above, Designer Drugs previously compounded medications for administration in the offices of licensed Tennessee prescribing practitioners upon the receipt of orders from such prescribers. We believe that this practice was in full compliance with the Tennessee Pharmacy Practice Act of 1996. Nonetheless, Designer Drugs has been phasing out over the last couple of years compounding without a patient specific prescription; this activity ceased entirely as of May 15, 2015.

As a licensed pharmacy, Designer Drugs is required to comply with applicable state laws and regulations as well as applicable United States Pharmacopeia ("USP") chapters <795>
and <797> on pharmacy compounding. The FDA’s cGMPs for finished pharmaceuticals are not applicable to Designer Drugs or any compounded medications it prepares. 21 U.S.C. § 353a specifically exempts a compounding pharmacy from the cGMPs requirements imposed on a drug manufacturer by 21 U.S.C. § 351 (a)(2)(B). 21 U.S.C. § 353a states:

(a) In General.-- Sections 351 (a)(2)(B), 352 (f)(1), and 355 shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding--

(1) is by--

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2)

(A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between--

(i) the licensed pharmacist or licensed physician; and

(ii)

(I) such individual patient for whom the prescription order will be provided; or
(II) the physician or other licensed practitioner who will write such prescription order.

Designer Drugs operates in compliance with the requirements of 21 U.S.C. § 353a, applicable state laws and regulations governing pharmacy compounding and with USP chapters requirements. Therefore, Designer Drugs is exempt from complying with cGMPs applicable to drug manufacturers under 21 U.S.C. § 351(a)(2)(B).

To the extent that the FDA contends that Designer Drugs is not protected by Section 353a for drugs previously prepared for physician office use without a patient-specific prescription, we believe that such conduct is expressly authorized by the Tennessee Board of 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, Designer Drugs challenges the FDA’s observations on the grounds that the cGMPs are not applicable to its compounding pharmacy operations. Designer Drugs complies with all applicable state board of pharmacy regulations. Designer Drugs also adheres to USP chapter <797> guidelines for compounding sterile drug products. Therefore, we will respond to each observation as a pharmacy exempt from cGMPs and FDA registration requirements.

1. **Observation 1**: Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

   A. **Observation 1(a)**: Media fills performed for injectable drug products do not simulate the entire production process including but not limited to: all process steps and manipulations, and filtration performed under ISO 5 classified areas. Additionally, media fills do not include a challenge of worst case conditions.
including but not limited to: duration of aseptic processing and represented batch size.

Response: We acknowledge that, per USP chapter <797>, media fills are to be performed under conditions that closely simulate the most challenging or stressful conditions encountered during sterile compounding. USP chapter <797> does not otherwise specify procedural requirements for a media fill. Therefore, we believe that our current media fill practices are in compliance with applicable USP chapter <797> guidelines.

Corrective Action: Notwithstanding our present compliance, we have amended Standard Operating Procedure ("SOP") 9.100, Sterile Compounding Process Validation (Media Fills) and our media fill test logs to provide for two different methods of filling vials based on the batch size of the compounded medication. An annual test will be performed using 25 100ml vials to simulate production of our large batch; this is our worst case scenario. Another annual test will be performed using six 10ml vials to simulate production of our small batch; this is our typical scenario. A copy of the amended SOP 9.100 is provided as Attachment A. Copies of the amended media fill test logs for large and small batches are provided as Attachment B.

B. Observation 1(b): Integrity testing specifications set by your firm for the Supor 25 and 32 mm syringe filters (0.22µm) have not been verified by the manufacturer or otherwise validated. These filters are used as sterilizing filters in production of injectable drug products.

Response: We abide by the guidelines of USP chapter <797>, which require that filter units used in sterilizing compounded sterile preparations ("CSPs") be subject to manufacturers’ recommended integrity tests, such as the bubble point test. Our pressure specifications were validated using industry standards for comparable filters of the same size, porosity, and material or manufacturers’ guidelines when available. At the time of inspection, we had the industry standard guidelines for the Supor 25mm and 32mm 0.2micron syringe filters but lacked the manufacturer’s integrity test guidelines.

Corrective Action: The manufacturer’s recommended integrity test for Supor 25mm and 32mm 0.2micron have been retrieved, and we immediately revised our bubble point test requirements to reflect those recommendations. A copy of the updated bubble test requirements for Supor filters is provided as Attachment C. In addition, we have confirmed that the manufacturer’s recommended integrity
test documentation for all other filters is currently on file. Going forward, we will request and retain “brand-specific” guidelines for our filters.

C. Observation 1(c): Sterilization cycles using the Tuttnauer Tabletop Autoclave Model 2340 have not been validated for terminally sterilized finished drug products. Temperature mapping, heat penetration, and loading configurations have not been evaluated to ensure sterilization of finished drug products, equipment, and containers/closures.

Response: With regard to compounding equipment, USP chapter <797> requires that yearly maintenance, calibration, monitoring for proper function, and controlled procedures are to be established in SOPs and followed by the firm. Results are to be recorded and stored for the lifetime of the equipment. UPS chapter <797> does not dictate how such equipment should be tested and validated. Under our current policy, larger equipment, such as powder hoods and laminar airflow workbenches (“LAFH”), are routinely calibrated and validated twice yearly. We also manually calibrate and log results of our scales, refrigerators, freezers, and pH meters in accordance USP chapter <797>.

In February 2015, we became aware that all equipment required validation on a yearly basis. Upon knowledge of the deficiency, we contracted with a laboratory equipment repair, calibration, and maintenance company in Nashville, Tennessee, to validate our equipment in compliance with USP chapter <797> guidelines. Validation is currently scheduled to be completed by June 30, 2015. A list of the additional equipment to be certified annually is provided for your review under Attachment D.

In addition, USP chapter <797> does not specifically address load configuration and heat penetration requirements for compounding equipment. Instead, load configurations are considered based on the manufacturer’s recommendation. Configuration and proper heat penetration is validated by placing a Biological Indicator in every load in the “worst case” position. Lastly, the Mapping Validation is to be performed in a fully loaded configuration which will also evaluate load configuration as well as heat penetration.

Corrective Action: We have revised SOP 4.010, Compounding Equipment, to include a yearly inspection of equipment. SOP 4.010 is provided as Attachment E. Certification of our compounding equipment is expected to be completed by June 30, 2015. The Tuttnauer Tabletop Autoclave Model 2340, although certified and calibrated prior to its use, is a recent purchase for which a SOP has not yet been developed. We expect to have a new SOP concerning the
Tuttnauer Tabletop Autoclave Model 2340 developed and completed by June 30, 2015. In addition, we validated temperature mapping for the Tuttnauer 2340 Autoclave on June 5, 2015. A copy of the Temperature Mapping Log is provided as Attachment F.

D. Observation 1(d): Sterilization cycles using the All American Model 75X Electric Pressure Steam Sterilizer (serial number 0001199) have not been validated for terminally sterilized finished drug products. Temperature mapping, heat penetration, and loading configurations have not been evaluated to ensure sterilization of finished drug products, equipment, and container/closures. Additionally, the 75X steam sterilizer has not been qualified and no calibration/verification has been performed for the temperature and pressure instruments.

Response: With regard to compounding equipment, USP chapter <797> requires that yearly maintenance, calibration, monitoring for proper function, and controlled procedures are to be established in SOPs and followed by the firm. Results are to be recorded and stored for the lifetime of the equipment. UPS chapter <797> does not dictate how such equipment should be tested and validated. Under our current policy, larger equipment, such as powder hoods and laminar airflow workbenches (“LAFH”), are routinely calibrated and validated twice yearly. We also manually calibrate and log results of our scales, refrigerators, freezers, and pH meters in accordance USP chapter <797>.

In February 2015, we became aware that all equipment required validation on a yearly basis. Upon knowledge of the deficiency, we contracted with a laboratory equipment repair, calibration, and maintenance company in Nashville, Tennessee, to validate our equipment in compliance with USP chapter <797> guidelines. Validation is currently scheduled to be completed by June 30, 2015. A list of the additional equipment to be certified annually has been provided for your review under Attachment D.

In addition, USP chapter <797> does not specifically address load configuration and heat penetration requirements for compounding equipment. Instead, load configurations are considered based on the manufacturer’s recommendation. Configuration and proper heat penetration is validated by placing a Biological Indicator in every load in the “worst case” position. Lastly, the Mapping Validation is to be performed in a fully loaded configuration which will also evaluate load configuration as well as heat penetration.
Corrective Action: We have revised SOP 4.030, *Use, Verification and Maintenance of the All American 75X Autoclave*, to reflect a yearly inspection of the equipment and a twice yearly mapping validation. SOP 4.030 is provided as Attachment G. The All American Model 75X Electric Pressure Steam Sterilizer is expected to be certified and calibrated by June 30, 2015. We expect to complete mapping validation with Biological Indicators by that date as well.

E. *Observation 1(e):* Sterilization and depyrogenation cycles using the Yamato DK-43 dry heat oven have not been validated for sterilization and depyrogenation of containers, equipment, and powders used in drug products. Temperature mapping, heat penetration, and loading configurations have not been evaluated to ensure sterilization and depyrogenation of containers, closures, equipment, and drug components. Endotoxin challenges have only been performed for one cycle (glassware cycle), however your firm uses another cycle for powders which has not been challenged. Powders intended to be sterilized in this dry heat oven are then mixed into final injectable drug products without further sterilization. Additionally, the dry heat oven has not been qualified and no calibration/verification has been performed for the temperature and pressure instruments.

Response: With regard to compounding equipment, USP chapter <797> requires that yearly maintenance, calibration, monitoring for proper function, and controlled procedures are to be established in SOPs and followed by the firm. Results are to be recorded and stored for the lifetime of the equipment. UPS chapter <797> does not dictate how such equipment should be tested and validated. Under our current policy, larger equipment, such as powder hoods and laminar airflow workbenches (“LAFH”), are routinely calibrated and validated twice yearly. We also manually calibrate and log results of our scales, refrigerators, freezers, and pH meters in accordance USP chapter <797>.

In February 2015, we became aware that all equipment required validation on a yearly basis. Upon knowledge of the deficiency, we contracted with a laboratory equipment repair, calibration, and maintenance company in Nashville, Tennessee, to validate our equipment in compliance with USP chapter <797> guidelines. Validation is currently scheduled to be completed by June 30, 2015. A list of the additional equipment to be certified annually has been provided for your review under Attachment D.

In addition, USP chapter <797> does not specifically address load configuration and heat penetration requirements for compounding equipment. Instead, load configurations are considered based on the manufacturer’s recommendation.
Configuration and proper heat penetration is validated by placing a Biological Indicator in every load in the “worst case” position. Lastly, the Mapping Validation is to be performed in a fully loaded configuration which will also evaluate load configuration as well as heat penetration.

Lastly, USP chapter <797> states that endotoxin challenges should be performed twice a year. We are currently in compliance with USP chapter <797> with regard to endotoxin challenges. However, at time of the inspection, the investigator noted that our last three challenges were performed on the cycle for glassware but not the cycle for powder.

Corrective Action: We have reviewed SOPs 8.010, Sterilization and Depyrogenation, and 4.040, Use, Verification, and Maintenance of the Yamato DK-43 Dry-Heat Oven, to reflect a yearly inspection for the dry heat oven and a twice yearly temperature mapping (including both powder and glassware cycles) using BI indicator strips in each corner and in the center of the oven. Copies of SOP 8.010 and SOP 4.040 are provided as Attachment H and Attachment I, respectively. Equipment validation of the Yamato DK-43 dry heat oven is expected to be completed by June 30, 2015. In addition, a Mapping Validation Log, provided as Attachment J, has been created to record results.

In addition, we recognize the important role of endotoxin challenges in maintaining a safe and sterile compounding environment. Accordingly, as a “best practice,” we have modified our SOP 8.010 to require that endotoxin challenges include both temperatures/times for powders and glassware. We have modified our Pyro Test Log to reflect this change. A copy of the Pyro Test Log is provided as Attachment K. We have ordered the test kits to conduct our next endotoxin challenge and will perform this test based on powder time/temperature by June 30, 2015.

2. **Observation 2: Clothing of personnel engaged in the manufacturing, processing, and packing of drug products is not appropriate for the duties they perform.**

Specifically, polypropylene isolation barrier gowns, earloop masks, and bouffant caps used for aseptic processing in the Laminar Air Flow Hood (LAFH) (ISO 5 area) are not sterile. Additionally, gowning used for processing in the ISO 5 area does not provide for adequate coverage of the operator. The gowning does not cover the operator’s skin on the face and neck and it does not completely cover the operator’s clothing. Portions of the operator’s backside and lower legs are left uncovered by the isolation barrier gown.
Response: Based on USP chapter <795> for non-sterile compounders and USP chapter <797> for sterile compounders, our personnel were in appropriate garb for the duties performed. USP chapter <797> requires the use of dedicated shoes or shoe covers, sterile gloves, head and facial hair covers, face masks, and a non-shedding gown. Non-shedding gowns must have sleeves that fit snugly around the wrists and be enclosed at the neck. There is no requirement for sterile garb other than gloves for preventing exposure of all facial skin or for gowning that completely covers an operator’s clothing. Accordingly, we are in compliance with USP chapter <797>.

Corrective Action: Notwithstanding our current compliance with the garbing requirements of USP chapter <797>, we are considering alternative gowning options that provide greater coverage of skin and clothing.

3. **Observation 3:** Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

A. **Observation 3(a):** Sodium Hypochlorite 0.1% solution used to clean the LAFH (ISO 5 area) is not sterile. Additionally, the ISO 5 area is not periodically cleaned with a sporicide that has been demonstrated to be effective.

Response: USP chapter <797> does not require the use of sterile cleaners and disinfectants in the clean room. Per USP chapter <797>, cleaning and disinfecting agents are to be used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. The sodium hypochlorite observed by the inspector is listed in USP chapter <797> Appendix II as a recommended cleaner and as an appropriate sporicide. As our policies are currently in compliance with USP chapter <797> sterile cleaning requirements, we do not believe that additional corrective action is necessary for Observation 3(a).

B. **Observation 3(b):** Blue Shop Towels used for cleaning the LAFH (ISO 5 area) are not sterile.

Response: USP chapter <797> does not require the use of sterile towels to clean the LAFH (ISO 5 area). USP chapter <797> provides that all cleaning materials to be non-shedding, preferably composed of synthetic micro fibers, dedicated to use in the buffer or clean area, ante area, and segregated compounding areas and shall not be removed from these areas except for disposal. Please note that we do not use “Blue Shop Towels.” Instead, we use a wipe manufactured and sold specifically as a clean room product (see Attachment L). The wipe used is a lint-free, synthetic fiber as required by USP chapter <797>. 
Corrective Action: Although we are currently in compliance with USP chapter <797>, we have ordered a wipe that, although not sterile, is laundered and packaged in a clean room. The item purchased is specified to be for use in ISO 5-6 environments. (See Attachment L). On June 8, 2015, we implemented the use of the new wipes for cleaning the LAFH.

4. **Observation 4**: Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

   A. **Observation 4(a)**: Environmental monitoring of the LAFH (ISO 5 area) including surface, air, and personnel is not performed each day drug products are produced using the LAFH. Currently, surface and personnel monitoring is only performed every two weeks. Also, surface samples taken from the LAFH on 05/18/2015 were taken prior to production immediately after cleaning instead of after production activities. Additionally, non-viable particulate monitoring is only performed every six months during the certification of the LAFH and clean room.

   **Response**: Designer Drugs acknowledges the importance of a safe and sterile compounding environment. USP chapter <797> guidelines require nonviable particulate monitoring at least every six months, surface sampling on a periodic basis, and personnel sampling, initially, at least annually thereafter for low- and medium-risk level compounding, and every six months for high-risk level compounding. Our SOP 3.030, Environmental Monitoring of Clean Room, states that environmental sampling should be done after compounding and prior to cleaning. Our aseptic technician has been trained, validated in, and reminded of this technique. Accordingly, our current policy for viable air, surface, and personnel sampling meets and exceeds USP chapter <797> requirements.

   **Corrective Action**: Although we are currently in compliance with USP chapter <797> guidelines, we recognize that, as a precautionary measure, more stringent procedures may be a “best practice” to ensure a sterile compounding environment. Therefore, we have revised SOP 3.030 to reflect that the lab manager will provide the technician with needed touch plates and contact plates at the end of production activities, thereby eliminating the possibility of the test being performed prior to compounding. Also, settle plates have been added to the Environmental Monitoring Log to test air samples twice monthly. An amended copy of SOP 3.030 is provided as Attachment M. In addition, a copy of the Environmental Monitoring of Clean Room Facility log is enclosed as Attachment N.
B. Observation 4(b): The last qualification of the LAFH (Baker model EG-4252 and serial number E-4208) on 01/26/2015 did not include passive viable air sampling. It has been more than 6 months since passive viable air sampling in LAFH has been performed.

Response: The FDA's allegation that the last qualification of the LAFH (ISO 5 area) did not include passive viable air sampling is incorrect. On January 26, 2015, Southeastern Certification, Inc., a clean room compliance certification company, conducted passive viable air sampling tests in the ISO 5 area. A copy of the report was previously provided to the FDA and is also included in this response as Attachment O. The enclosed report indicates the testing location, the testing results, and the type of test.

Corrective Action: Documentation that the last qualification of the LAFH included passive viable air sampling has been provided to the FDA. Therefore, no additional corrective action is required for Observation 4(b).

C. Observation 4(c): Raw data for dynamic smoke studies performed in the LAFH (ISO 5 area) were not documented and retained.

Response: Designer Drugs acknowledges the importance of documenting and retaining testing information in order to ensure a safe and sterile compounding environment. USP chapter <797> guidelines require that smoke studies "demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions." USP chapter <797> does not require videotaping of smoke studies. Designer Drugs utilizes Southeastern Certification Inc., a clean room compliance certification company, to conduct smoke studies on a semiannual basis. Raw data from the dynamic smoke studies is based on visual observation that is subsequently documented during the certification process. Test results reflecting compliance with USP chapter <797> have been previously provided to the FDA.

Corrective Action: Data from previously conducted smoke studies performed in the LAFH (ISO 5 area) have been submitted to the FDA. A copy of the test results has been provided as Attachment O. Designer Drugs is currently in compliance with USP chapter <797>, and additional action is not required for Observation 4(c).

5. Observation 5: Equipment for adequate control over air pressure and microorganisms is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.
Specifically, the LAFH (ISO 5 areas) is not equipped with an air pressure gauge for monitoring pressure differentials. Also, air pressure differentials of the Buffer (IV) Room (ISO 7 area) and the Anteroom (ISO 8 area) are not continuously monitored during production of drug products. Currently, pressure differentials are only checked once a day. Additionally, the pressure reading of the Buffer (IV) Room was observed to be 0.03 inches of water immediately after the sterile filtration of Tri-Mix Lot # 05182015@15. Your firm’s pressure differential specification is 0.05 inches of water or greater.

Response: Designer Drugs acknowledges the importance of a safe and sterile compounding environment. USP chapter <797> does not require a pressure gauge for the LAFH (ISO 5 area) or that air pressure differentials between the buffer room and the ante room be continuously monitored during production of drug products. A continuous recording device is allowed, but is not required, as an alternative to visual monitoring. USP chapter <797> requires only that pressure differential monitoring be “reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device.” Designer Drugs currently has one work shift per day, and pressure differential monitoring is reviewed and documented during that work shift. Accordingly, pressure differentials in classified areas are monitored on a daily basis per USP requirements.

USP chapter <797> also requires that segregated buffer areas maintain a minimum differential positive pressure of 0.02 to 0.05 in water column. As a “best practice”, we strive to maintain this pressure at 0.05; however, the reading of 0.03 as observed by the FDA was within USP guidelines.

Corrective Action: Although we are currently in compliance with USP chapter <797> requirements for equipment and policies relating to pressure differential monitoring between the buffer room and the ante room, we have updated our Temperature, Humidity, and Pressure Monitoring of the Clean Room Facility log to reflect a range in which the pressure should fall. A copy of the updated log is provided as Attachment P. In addition, we will consider installing a pressure gauge in our LAFH (ISO 5 area) in order to better monitor airflow.

6. **Observation 6:** Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

A. **Observation 6(a):** The sterile prep area where drug components are weighed, dispensed, and mixed prior to aseptic mixing and filtration is not environmentally controlled. There are no physical barriers to separate the area from the non-sterile prep areas. The air system for the sterile prep area is shared with the rest
of the facility and is not appropriately filtered. The ceiling and floors in the sterile prep area are not constructed of readily cleanable materials. Additionally, access to the sterile prep area is not restricted. The area is equipped with a door which opens directly to the retail lobby and entry through this door is not restricted.

Response: The sterile prep area mentioned in this observation is designated an “ante area” or “pre-sterilization area” per USP chapter <797>. USP chapter <797> defines an ante area as an ISO Class 8 or better area where personnel hand hygiene and garbing procedures, staging of components, order entry, CSP labeling, and other high-particulate-generating activities are performed. The only specific requirements for this area is (1) that it be monitored by a twice yearly viable and nonviable sampling testing and (2) that “pre-sterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in no worse than an ISO class 8 environment.”

In January 2015, Southeastern Certification, Inc., a clean room compliance certification company, tested the pre-sterilization area and designated it an ISO class 8 environment. Accordingly, we perform twice monthly in-house environmental monitoring tests as required by USP chapter <797> for ISO 8 areas. In addition, daily, weekly, and monthly cleaning is performed and documented per USP chapter <797>.

The requirements listed in this observation, such as physical barriers, supply air filtration, floors and ceilings, and accessibility, are requirements designated for buffer areas, not ante areas.

Corrective Action: Although we currently are in compliance with USP chapter <797> ante room preparation, we will provide a line of demarcation restricting access to only those personnel who are properly garbed for ISO 8 areas. Please note that the door noted by the FDA is a mandatory emergency exit as required by the fire marshal. However, we will install new hardware to limit its use to an emergency exit door only. On the lobby side of the door, we will post a sign indicating “No Entry.” The exit side of the door will have a sign posted indicating “Emergency Exit Only.” We expect these best practices to be completed by June 30, 2015.

Please note that we plan to remodel our pre-sterilization area in order to be compliant with USP chapter <800> when it becomes finalized. However, as USP chapter <800> is still in review, we cannot begin an expensive remodel until its specific requirements are confirmed. We do anticipate that some of the
requirements will include permanent physical barriers, floor and ceiling changes, as well as air supply and return changes. In the meantime, with the assistance of the Tennessee Board of Pharmacy, we will be installing strip curtains to serve as a separation between the sterile prep area and the non-sterile area. We will also be changing the ceiling tiles to a readily cleanable material. The floor, while not “Buffer Room” compliant, is readily cleanable and meets with Ante-Room requirements. Air system, filtration, and flooring additions will be addressed when USP <800> is finalized, as they are currently compliant. We hope to have these changes in place by August 30, 2015, depending on the availability of the contractor. Accordingly, we understand that we will be making a significant investment in order to become fully compliant with the new requirements prompted by USP chapter <800>.

B. Observation 6(b): Hormone Replacement Pellets are prepared in a room, prior to terminal sterilization, which is not environmentally controlled. The air system for the sterile prep area is shared with the rest of the facility and is not appropriately filtered. The ceiling and floors in the sterile prep area are not constructed of readily cleanable materials. The room is equipped with a door which opens directly to a common hallway and entry through this door is not restricted.

Response: The room wherein Hormone Replacement Pellets are prepared is a newly renovated addition to our compounding lab. It has been in use as of March 2015. This room is treated as an ISO 8 area, where pre-sterilization activities, such as weighing and mixing for high-risk level CSPs, are performed. Accordingly, viable and nonviable air sampling testing is scheduled to be performed by Southeastern Certification, Inc., a clean room compliance certification company, during their June 2015 visit.

In addition, the FDA’s allegation that the area flooring is not constructed of readily cleanable materials is incorrect. The flooring noted by the inspectors is wide-sheet vinyl flooring with heat-welded seams. This is the same material utilized in our buffer room.

Corrective Action: We expect that viable and nonviable air sampling testing will be completed by Southeastern Certification by July 30, 2015.

We also plan, as a “best practice,” to replace the current ceiling tiles with a more readily cleanable material and to add a strip curtain separating the non-sterile area from the pre-sterilization area. We expect to have both items completed by August 30, 2015, or at the contractor’s earliest availability.
In addition, as stated in Observation 6(a), the door noted by the FDA is a mandatory emergency exit as required by fire marshal. However, we will install new hardware to limit its use to an emergency exit door only. On the lobby side of the door, we will post a sign indicating “No Entry.” The exit side of the door will have a sign posted indicating “Emergency Exit Only.” We expect these best practices to be completed by June 30, 2015.

Please note that we plan to remodel our pre-sterilization area in order to be compliant with USP chapter <800> when it becomes finalized. However, as USP chapter <800> is still in review, we cannot begin an expensive remodel until its specific requirements are confirmed. We do anticipate that some of the requirements will include permanent physical barriers as well as air supply and return changes. Accordingly, we understand that we will be making a significant investment in order to become fully compliant with the new requirements prompted by USP chapter <800>.

7. Observation 7: Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design and suitably located to facilitate operations for its cleaning and maintenance.

A. Observation 7(a): An office phone with handset is mounted to the wall in the Buffer (IV) Room (ISO 7 area).

Response: USP chapter <797> does not unilaterally prohibit the presence of office phones in the buffer area. In fact, USP chapter <797> permits in the buffer area the following items: furniture, equipment, supplies, and other materials required for the performance of the compounding activity. For items located in the buffer area, USP chapter <797> requires that the item first be cleaned and disinfected.

The wall phone in the buffer area is equipment necessary for the performance of the sterile compounding activity. In particular, the office phone allows the aseptic technician to communicate with personnel outside the clean room, thereby greatly reducing trips between the buffer room and ante room or the ante room and the general compounding area. This, in turn, reduces the risk of contamination. The wall phone is cleaned daily, weekly, and monthly as set forth in USP chapter <797> for all equipment in the buffer area and is located on the opposite wall from the LAFH. Likewise, the technician abides by USP chapter <797> requirements regarding frequent and repeated glove disinfection using sterile 70 percent IPA when the phone has been used.
Corrective Action: We are currently in compliance with the Tennessee Board of Pharmacy requirements for sterile compounding pharmacies and USP chapter <797>. Accordingly, we do not believe corrective action is required for Observation 7(a).

B. Observation 7(b): A chair located in the Buffer (IV) Room used by technicians during aseptic operations in the LAFH (ISO 5 area) is not constructed of materials that can be readily sanitized.

Response: USP chapter <797> requires that furniture in the buffer area be nonpermeable, nonshedding, cleanable, and resistant to disinfectants. The chair used in the buffer area was ordered from a clean room catalog and made of a vinyl material. Accordingly, the chair complied with USP chapter <797> requirements for buffer area furniture.

Corrective Action: While we believe we are in compliance with USP chapter <797> requirements, we acknowledge the FDA's concerns regarding the durability of the vinyl material. Accordingly, the vinyl chair was removed from the buffer room on May 19, 2015, and was replaced with a stool constructed of stainless steel.

C. Observation 7(c): There is no line of demarcation in the anteroom to separate the clean side from the dirty side. The anteroom is used for hand washing and gowning prior to entering the Buffer (IV) Room (ISO 7).

Response: USP chapter <797> does not require a line of demarcation separating a clean side and a dirty side in the ante room, but rather an order of garbing, hand washing, and gloving (proceeding from dirtiest to cleanest). However, our facility has a natural line of demarcation in that we have an enclosed ante room and an unenclosed segregated ante room. Both ante rooms are classified as an ISO 8 area. The doorway between these two areas is our natural demarcation line. On one side of the door is a “tacky mat” where the “dirtiest” donning (shoe covers, head and facial covers, face masks) occur. As the technician dons a shoe cover, he or she then steps into the enclosed portion of our ante room to don the second shoe cover. The remainder of the garbing and cleansing occurs in this area.

Corrective Action: We will add an additional line of demarcation in our enclosed ante room to denote where garbing is to occur and, beyond that line, where hand washing and gloving is to occur.
8 Observation 8: The calibration of instruments, apparatus, and gauges is not done at suitable intervals.

A. Observation 8(a): The Millipore pressure gauge identified as “Jan 2010 8978 8920” used to perform post filtration integrity testing of all sterilizing filters has not been calibrated.

Response: In February 2015, we became aware that all equipment required validation on a yearly basis. Upon knowledge of the deficiency, we contracted with a laboratory equipment repair, calibration, and maintenance company in Nashville, Tennessee, to validate our equipment in compliance with USP chapter <797> guidelines. However, the third-party company soon advised that it was unable to certify the Millipore pressure gauge due to its lack of qualified equipment for such a low PSI range.

Corrective Action: We will continue to contact vendors in order to locate a company able to perform the needed certification on the Millipore pressure gauge. We will arrange for an inspection to be performed as soon as the qualified company can be located and made available. In addition, we will record and retain equipment inspection reports for the life of the equipment. We expect to have the Millipore pressure gauge calibrated within 90 days from the date of this letter.

B. Observation 8(b): Thermometers used in the QL 140E and Boekel model 13200 incubators have not been calibrated. The QL 140E and Boekel model 13200 incubators are used for the incubation of environmental samples and finished drug product sterility and endotoxin samples.

Response: In February 2015, we became aware that all equipment required validation on a yearly basis. Upon knowledge of the deficiency, we contracted with a laboratory equipment repair, calibration, and maintenance company in Nashville, Tennessee, to validate our equipment in compliance with USP chapter <797> guidelines. Validation of our equipment is expected to be completed by June 30, 2015. The thermometers used in the QL 140E and Boekel model 13200 incubators have been included for certification and calibration by the third-party company. The list of the additional items to be certified annually has been provided as Attachment D.

Corrective Action: We expect the thermometers used in the QL 140E and Boekel model 13200 incubators to be certified by June 30, 2015. Certification reports will be recorded and retained for the life of the equipment.
9 Observation 9: Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically, sterility testing per your firm's procedure “9.110 Sterile Compounding Finished Preparation Testing” is only required on lots consisting of 25 or more units that are exposed longer than 12 hours at temperatures of 2-8 degrees Celsius and longer than six hours at warmer temperatures. Additionally, endotoxin testing is not performed on Hormone Replacement Pellets.

Response: As a compounding pharmacy, Designer Drugs complies with USP chapter <797>, which requires sterility and 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., ampuls, bags, syringes, vials) or in multiple-dose vials (MDVs) for administration to multiple patients or that have been 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 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 individual single-dose packages (e.g., ampuls, bags, syringes, vials) or in MDVs for administration to multiple patients or that have been exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° 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.”

Most of the Hormone Replacement Pellets are prepared in batches of 25 and are autoclaved; therefore, they are exempt from sterility or endotoxin testing. However, we randomly select these batches for in-house sterility testing as well as out-sourced sterility validation, as allowed by USP chapter <797> and in accordance with USP chapter <71>. In instances where batches greater than 25 were compounded, sterility testing, not endotoxin testing, was performed. These batches are also randomly selected for out-sourced sterility validation.
Corrective Action: Designer Drugs’ SOP 6.10, Total Quality Management, complies with the USP chapter <797> requirements for sterility and endotoxin testing. We have also been approved as a sterile compounding pharmacy by the Tennessee Board of Pharmacy, and our policies and procedures otherwise comply with Tennessee requirements for sterile compounding pharmacies.

Notwithstanding our compliance with the Tennessee Board of Pharmacy requirements for sterile compounding pharmacies and USP chapter <797>, we recognize that more stringent testing is a “best practice” that, if implemented, would benefit our patients. Accordingly, any future batches of Hormone Replacement Pellets will be compounded in batches of 25 or less. Random selection of sterility in-house testing and out-sourced validation will continue to be performed in accordance with USP chapters <797> and <71> guidelines. In the event batches of larger than 25 are compounded, we will perform sterility testing as well as endotoxin testing per USP chapter <85>.

10. **Observation 10:** Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

   Specifically, potency testing is not performed on every lot of sterile drug product produced by your firm. Potency testing is at the discretion of the Pharmacist-in-charge according to your firm’s procedure “9.110 Sterile Compounding Finished Preparation Testing.”

   **Response:** Designer Drugs acknowledges the importance of safe and potent compounded medications. As a sterile compounding pharmacy, we comply with USP chapter <797>, which does not require potency testing for every lot or otherwise specify when potency testing is required. Under our current policy, potency testing is performed on a regular basis, particularly when validating technician compounding procedure and when performing extended Beyond Use Dating ("BUD") studies.

   **Corrective Action:** Designer Drugs’ current policy meets and exceeds USP chapter <797> requirements with regard to potency testing. Accordingly, we do not believe additional action is required for Observation 10.

11. **Observation 11:** There is no written testing program designed to assess the stability characteristics of drug products.

   Specifically, stability testing performed to extend Beyond Use Dates (BUDs) of sterile drug products up to 270 days did not include sterility testing over the beyond use period.
Also, stability studies for preservative containing sterile products did not include testing of the antimicrobial effectiveness of the preservatives over the beyond use period.

Response: The FDA’s observation is referring to stability study requirements for drug product expiration dates, a process reserved for pharmaceutical manufacturers. As a compounding pharmacy, we do not assign expiration dates but rather determine BUDs for sterile products in accordance with USP chapter <797>. All sterile preparations are carefully reviewed to observe the recommended USP dating for BUDs. For high-risk sterile preparations, BUDs do not exceed 24 hours at controlled room temperature, three days under refrigerated conditions, and 45 days in a solid frozen state, in accordance with USP chapter <797>. To exceed these dates, we determine BUDs by a review of scientific literature, direct testing on our compounded products, and vendor-established BUD studies, in accordance with USP chapter <797>.

Corrective Action: We are currently in compliance with USP chapter <797> for sterile compounding pharmacies. Accordingly, we do not believe additional action is required for Observation 11. However, we acknowledge that more stringent testing is a “best practice” that, if implemented, would be beneficial to our patients. Accordingly, for future BUD studies, we will order stability testing to be conducted for the preservative, if one is used in the compound, as well as sterility testing at the beginning and end of the test. Copies of the Laboratory Reports from our recent orders for out-sourced BUD testing reflect the implementation of these “best practices” and are provided as Attachment Q.

12. **Observation 12:** Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

Specifically, temperatures of the QL 140E and Boekel model 13200 incubators are not continuously monitored or documented during incubation of environmental samples and finished drug product sterility and endotoxin samples.

Response: We acknowledge the importance of documentation for all data derived from tests, examinations, and assay in order to ensure a sterile compounding environment. While we currently maintain temperature monitoring logs for all other instruments, the thermometers of the QL 140E and Boekel model 13200 incubators were inadvertently overlooked.

Corrective Action: In accordance with USP chapter <797> guidelines, we have created a daily temperature monitoring log and have been recording and documenting temperatures of the QL 140E and Boekel model 13200 since June 1, 2015. Copies of the Incubator
Daily Monitoring Logs for the Boekel model 13200 and QL 140E incubators are provided as Attachment R.

13. **Observation 13:** Each component is not tested for conformity with all appropriate written specifications for purity, strength, and quality.

Specifically, compressed nitrogen used as a blanket/overlay gas in sterile filtered drug products is industrial grade nitrogen. No testing or certificate of analysis in lieu of testing was obtained prior to the use of this industrial grade nitrogen gas in sterile drug production.

**Response:** USP chapter <797> does not specifically impose requirements for the use of nitrogen as a blanket or an overlay gas. When utilized in this way, nitrogen is neither a container nor an ingredient. It is used only to displace oxygen in the vial in situations where a compound might lose stability if exposed to oxygen. Therefore, nitrogen is closely analogous to an “added substance” even though it does not become a part of the compound. USP guidelines on non-sterile ingredients and devices recommend that an added substance be an USP or National Formulary (“NF”) article. In the event that an item is not a USP or NF article, then it should be accompanied by a certificate of analysis to aid in judging the identity, quality, and purity in relation to its intended use. We acknowledge that the nitrogen observed by the FDA was not a USP or NF article and did not have a certificate of analysis. However, it has been our standard practice to filter the nitrogen prior to use in order to maintain quality and purity.

**Corrective Action:** The non-NF nitrogen tank was removed on May 19, 2015, and a replacement nitrogen tank that is a NF article was ordered on May 20, 2015. On June 3, 2015, the replacement nitrogen tank was received and placed in the clean room. All future nitrogen purchases will be NF articles.

**Conclusion**

With this response, Designer Drugs has sought to address all of the FDA inspectors’ observations and concerns. If the FDA requires additional information or communication from Designer Drugs, please contact me at (423) 954-2585.

Sincerely,

Randy Davis, Owner

Enclosures