



October 1, 2014

Department of Health and Human Services
Food and Drug Administration
22215 26th Avenue SE, Suite 210
Bothell, WA 98021

*Via Fax (425) 302-0404
and Overnight Delivery*

Attn: Miriam R. Burbach, District Director
Heika R. Tait, Investigator
Anita Narula, Investigator

Re: FDA Disclosure of 483 Response

RECEIVED

OCT 02 2014

SEA-DO DD

Dear District Director Burbach and Investigators Tait and Narula,

On behalf of Oregon Compounding Centers, Inc. d/b/a Creative Compounds ("Creative Compounds"), I authorize the United States Food and Drug Administration ("FDA") to publicly disclose the information described below on FDA's web site, and include the information described below any time the FDA provides a copy of the Creative Compounds' 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 FDA harmless for any injury caused by FDA's sharing the information with the public.

Information to be disclosed: Creative Compounds' letter dated October 1, 2014, excluding all attachments, which responds to FDA's Form 483 dated September 12, 2014.

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 Creative Compounds and my full name, title, address, and telephone number are provided below for verification.

Sincerely,

Denise S. Burnham
President, Creative Compounds
8560 S.W. Salish Lane, Suite 100
Wilsonville, OR 97070
Phone: (503) 685-6111

8560 SW Salish Lane, Suite 100 ♦ Wilsonville, Oregon 97070
Tel (877) 585-6111 or (503) 685-6111 ♦ Fax (503) 570-2831
www.creative-compounds.com



October 1, 2014

Department of Health and Human Services
Food and Drug Administration
22215 26th Avenue SE, Suite 210
Bothell, WA 98021

*Via Fax (425) 302-0404
and Overnight Delivery*

Attn: Miriam R. Burbach, District Director
Heika R. Tait, Investigator
Anita Narula, Investigator

Re: Response to FDA 483 Issued Sept. 12, 2014 to Oregon Compounding Centers,
Inc. d/b/a Creative Compounds

Dear District Director Burbach and Investigators Tait and Narula,

The Food and Drug Administration ("FDA") conducted an inspection of Oregon Compounding Centers, Inc. d/b/a Creative Compounds ("Creative Compounds"), a pharmacy located at 8560 SW Salish Lane, Suite 100, Wilsonville, Oregon, in August, 2014. Upon the conclusion of its inspection, the FDA provided Creative Compounds with an FDA Form 483. On September 12, 2014, the FDA issued an amended Form 483 to correct mistakes made in the original 483. This letter is Creative Compounds' 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 the Creative Compounds' FDA Form 483 to anyone outside the FDA.

The FDA's observations noted 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, and further explained in the FDA's Industry Guidance on cGMPs for Sterile Drug Products Produced by Aseptic Processing. Creative Compounds does not engage in drug manufacturing. Creative Compounds is a pharmacy licensed by the Oregon State Board of Pharmacy as a Retail Drug Outlet with controlled substances, and is subject to its jurisdiction. Creative Compounds is also licensed by the Washington State Board of Pharmacy as a Non-Resident Pharmacy with controlled substances, and is also subject to its jurisdiction. Creative Compounds has been accredited by the Pharmacy Compounding Accreditation Board ("PCAB") for both sterile and non-sterile compounding since 2010. *See* Attachment 1. Creative Compounds engages in the practice of pharmacy by compounding patient-specific prescriptions for patients located in Oregon and Washington. Creative Compounds also prepares and dispenses compounded medications pursuant to Shared Pharmacy Services agreements, as allowed by the Oregon State Board of Pharmacy rule

8560 SW Salish Lane, Suite 100 ♦ Wilsonville, Oregon 97070
Tel (877) 585-6111 or (503) 685-6111 ♦ Fax (503) 570-2831
www.creative-compounds.com

855-045-0200(4) which states, in relevant part:

(4) Any compounding activity that is not pursuant to a valid prescription or an order to prepare for administration and for a specific patient is considered to be manufacturing, and any person engaged in manufacturing must be registered in accordance with OAR 855-060-0001, with the following exceptions:

(a) Compounding by a pharmacy located in Oregon for a practitioner or dispenser located in Oregon that is covered by a Shared Pharmacy Services agreement as defined in OAR 855-006-0005;

(b) Compounding in anticipation of a prescription drug order or an order to prepare for administration, based on a routine, regularly observed pattern;

Shared Pharmacy Services is defined at 855-006-0005(24) as:

a written agreement, that has been approved in writing by the board, that exists for the processing by a pharmacy of a request from another pharmacy or a practitioner licensed to prescribe the drug, to fill or refill a prescription or a drug order, or to perform processing functions including but not limited to:

(a) Dispensing;

(b) Drug utilization review;

(c) Claims adjudication;

(d) Refill authorizations;

(e) Compounding; and

(f) Therapeutic interventions.

As a licensed pharmacy, Creative Compounds is required to comply with applicable Oregon and Washington state laws and regulations governing pharmacy compounding, and with the applicable United States Pharmacopoeia chapters 795 and 797 on pharmacy compounding. The FDA's cGMPs for finished pharmaceuticals are not applicable to Creative Compounds pharmacy or compounded medications prepared there. 21 U.S.C. § 353a specifically exempts a compounding pharmacy from the cGMP 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.

Creative Compounds operates in compliance with the requirements of 21 U.S.C. §353a, applicable Oregon and Washington state laws and regulations governing pharmacy compounding, and with United States Pharmacopoeia chapters 795 and 797. Therefore, Creative Compounds 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 Creative Compounds is not protected by Section 353a for drugs prepared and dispensed under Shared Pharmacy Services agreements, we believe that such conduct is expressly authorized by the Oregon State 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. Especially if the pharmacy, like Creative Compounds, is only doing so in its home state, and is not dispensing drugs without a

patient-specific prescription in any other state. In a letter to the FDA dated June 27, 2014, members of the US 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, Creative Compounds challenges the FDA's observations on the grounds that the cGMPs are not applicable to its compounding pharmacy operations. Creative Compounds complies with all applicable state and federal laws. Creative Compounds also adheres to the USP 797 guidelines for compounding sterile drug products. Our pharmacy is dedicated to doing things right, and more importantly, toward ensuring that our sterile drugs are prepared in a safe and effective manner. In light of Creative Compounds' dedication toward self-improvement, if we determined that the FDA's observation amounts to a pharmacy "best practice" that, if adopted, would benefit the safety of our patients, we will adopt that best practice, implement it into our policies and procedures manual, and train our staff on the newly adopted best practices.

1. Observation 1: Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

A. Observation 1.A.1: Aseptic Techniques observed on 8/04-05/14 were inadequate for the manufacturing of sterile injectable drug products as follows:

1. On 08/04/14 an operator wearing non-sterile gloves placed the non-sterile components and supplies in the IOS 5 hood for producing Alprostadil/Lidocaine without disinfecting the items. After putting on sterile gloves, the operator entered the ISO 5 hood, touched all of the non-sterile materials, removing their packaging and discarded the packaging in the ISO 5 hood next to where Alprostadil/Lidocaine 20mcg/10mg/ml Lot 20140801@15 was being sterile filtered and filled into a 5ml vial. There was no disinfection of gloves, area or equipment is conducted during these activities.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. USP 797 guidelines state, "Routine application of 70% IPA (sterile) shall occur throughout the compounding day and whenever nonsterile surfaces are touched." Our policies and procedures require that all staff members comply with the USP 797

guidelines. Creative Compounds has re-trained its staff on proper sterility procedures.

A. Observation 1.A.2: Aseptic Techniques observed on 8/04-05/14 were inadequate for the manufacturing of sterile injectable drug products as follows:

2. On 08/04/14 during the filling of Alprostadil/Lidocaine 20mcg/10mg/ml vials, Lot 20140801@15 we observed the product leaking out of the syringe and filter. The operator had selected a filter incompatible with ethyl alcohol and went to the ISO 8 area to retrieve the correct filter. The operator did not perform any sanitization of gloves and did not disinfect the new filter prior to introducing the item into the ISO 5 hood.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. USP 797 guidelines state, "Routine application of 70% IPA (sterile) shall occur throughout the compounding day and whenever nonsterile surfaces are touched." Our policies and procedures require that all staff members comply with the USP 797 guidelines. Creative Compounds has re-trained its staff on proper sterility procedures.

A. Observation 1.A.3: Aseptic Techniques observed on 8/04-05/14 were inadequate for the manufacturing of sterile injectable drug products as follows:

3. The following issues were noted during the manufacturing of MSM 15% Injectable Lot 20140804@14 on 08/05/14 in the ISO 8 area and then moved to ISO 5 hood for the aseptic filling process.
 - a. The product was formulated in the ISO 8 prep room in a pre-sterilized beaker using non-sterile MSM powder.
 - b. During the mixing of MSM powder with sterile water for injection, the paperwork was observed lying on the top of the open beaker.
 - c. The operator used a syringe to check the pH of the formulated MSM 15% and poured the contents from the syringe back into the beaker after testing the pH.
 - d. In the ISO 8 area, the operator formulating MSM 15% injectable was wearing non-sterile gloves and grabbed the open beaker from the top. This operator handed over the beaker to another operator who placed the beaker in the ISO 5 hood without disinfecting it.

- e. During the aseptic filling of MSM 15% Injectable into 100 mL vials in the ISO 5 hood, the operator initially used a Repeater Pharmacy pump to fill vials using sterile single use tubing containing a 0.2 micron filter. After filling three vials, the product starting leaking from the tubing. The operator poured the contents of three vials back into the beaker containing the formulated drug product for the Lot 20140804@14.

RESPONSE: Creative Compounds prepares “High-Risk Level Compounded Sterile Products.” When compounding high-risk compounded sterile products (“CSPs”), there are two methods of sterilization: aseptic sterilization and terminal sterilization. In the FDA’s Industry Guidance on cGMPs for Sterile Drug Products Produced by Aseptic Processing, the FDA distinguishes between these two types of sterilization and explained that the FDA is significantly less concerned with terminal sterilization procedures because terminal sterilization is a much safer sterilization procedure. Here, Creative Compounds complied with the following conditions set forth by USP 797 for compounding high risk CSPs through terminal sterilization: “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.” Creative Compounds complied with the 797 requirements for terminally sterilizing high risk CSPs; thus, Creative Compounds is in compliance with applicable requirements.

A. Observation 1.A.4: Aseptic Techniques observed on 8/04-05/14 were inadequate for the manufacturing of sterile injectable drug products as follows:

4. On 8/5/14 during the repackaging of Avastin 1.25mg/ 0.05 mL, Lot 20140805@1 into single use syringes in the ISO 5 hood, the operator withdrew Avastin into a 0.3 mL syringe from an opened and uncapped 4 mL (25mg/mL) vial and dispensed any excess amount of the desired volume of 0.05 mL back into the 4 mL Avastin vial that was used to fill a batch of 80 syringes. No further sterility measures are performed on these repackaged syringes prior to their distribution.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. Our staff has been retrained on sterile procedures, including training on the use of a folded sterile wipe to expel any excess amounts.

A. Observation 1.A.5: Aseptic Techniques observed on 8/04-05/14 were inadequate for the manufacturing of sterile injectable drug products as follows:

5. Personnel were observed on 8/04-05/14 entering the ISO 8 prep room from the unclassified area without donning any gowning materials while performing production checks and interacting with gowned personnel.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. Creative Compounds is instituting a new policy and procedure for production performance checks where pharmacy technicians are required to bring sealed chemicals and paperwork out of the ISO 8 area and to the pharmacists for production performance checks, to be fully implemented by October 15, 2014.

- B. Observation 1.B: There is no data to support the continued sterility of 30, 50, and 100 mL vials that undergo in-house sterilization and depyrogenation. The vials are stored in the ISO 8 area on a shelf near the floor where people enter and exit the room wearing street clothes. The top of the vials are individually covered with aluminum foil from the sterilization cycle and stored for up to 90 days until the time of use.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. We have relocated the vials from a shelf near the floor to an upper shelf in the ISO 8 area. *See* Attachment 2. We will perform sterility testing on our 30ml, 50ml, and 100ml vials to ensure that these items maintain their sterility until the 90-day expiration date that is assigned. These sterility tests will be performed by December 31, 2014.

- C. Observation 1.C: There is no data to support continued sterility of stoppers that undergo in-house sterilization in the Tuttnauer Autoclave. The stoppers are stored in the ISO 8 area wrapped in autoclave paper in a bin on a shelf near the floor where people enter and exit the room wearing street clothes. The stoppers are labeled with a 90 day expiration date.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. We have relocated the stoppers from a shelf near the floor to an upper shelf in the ISO 8 area. *See* Attachment 3. We will perform sterility testing on the stoppers to ensure that these items maintain their sterility until the 90-day expiration date that is assigned. These sterility tests will be performed by December 31, 2014.

2. **Observation 2: Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.**

- A. Observation 2.A: SOP 7.007.31, The High Risk Process Simulation Testing, does not specify all aseptic filling operations performed in the ISO 5 hood. The simulation test observed on 08/06/14 only simulates filling a 30mL syringe with

an attached 0.2 μ filter and transferring the product to 6 pre-sterilized and pre-depyrogenated, stoppered and capped, 10 mL vials with 10 mL of media, as specified in your procedure. However, you also fill 1, 2, 5, 10, 30, 50 and 100 mL vial sizes and have batch sizes ranging from 1-320 units.

1. The 30, 50 and 100 mL vials are not pre-sterilized and undergo sterilization and depyrogenation in-house and no media fill simulations using this container/closure system.
2. You conduct syringe-to-syringe transfers and filling, however you have not conducted any media fill simulations using this filling process.
3. You fill pre-mixed bulk drug products from a beaker using a Repeater Pharmacy pump with tubing and syringe containing a 0.2 μ filter into open vials and you have not conducted any media fill simulations using this filling process.
4. You conduct vial-to-syringe filling and have not conducted any media fill simulations using this filling process.
5. You allow a maximum of three operators in the ISO 7 area that can perform aseptic processing in the ISO 5 hoods during production of sterile drug products. Your media fill simulations are for one operator at a time and no interventions or interruptions are simulated during your media fills.

RESPONSE: As a compounding pharmacy, Creative Compounds complies with the media fill guidelines for high-risk CSPs as required by USP 797 and outlined in "USP on Compounding-A Guide for the Compounding Practitioner," Current, with USP 37-NF 32 through the First Supplement, February 2014, p. 45

B. Observation 2.B: The moist heat sterilization process (autoclave) for stoppers or loading patterns and cycle times used for terminal sterilization of aseptically filled drug products is not validated. You stated you use a Biological Indicator with each load to confirm sterility.

1. You stated that you autoclave stoppers for 20 minutes at 20 PSI and 250F. This is not documented;
2. For drug products no cycle parameters are documented on the Logged Formulation Worksheets. For example: Sodium Phosphate 92/93mg/mL Injectable, Calcium Gluconate 10% Injectable and Glycerin 72% v/v are terminally sterilized and there is no documentation on the Logged Formulation Worksheets of any of the autoclave parameters used.

RESPONSE: Creative Compounds follows the USP 797 “Sterilization of High-Risk CSPs by Steam” guidelines and procedures. The guidelines state that all CSPs will be exposed to steam at 121 degrees Celsius under a pressure of about one (1) atmosphere or fifteen (15) pounds per square inch (“PSI”) for the duration verified by testing to achieve sterility of the items, which is typically twenty (20) to sixty (60) minutes for CSPs. An allowance is made for the time required for the material to reach 121 degrees Celsius before the sterilization exposure duration is timed. Furthermore, the guidance states that “the effectiveness of steam sterilization shall be verified using appropriate BIs of *Bacillus stearothermophilus* and other confirmation methods such as temperature-sensing devices.” We use BIs, as stated above, to ensure that terminal sterilization has occurred.

Going forward, we have ensured each logged formulation worksheet contains the autoclave processing information, and we are adopting policies and procedures requiring the documentation of the time, pressure and temperature on the autoclave log and verifying that the autoclave is set at a minimum of specified temperature (250 degrees Fahrenheit) and pressure (fifteen (15) to twenty (20) pounds PSI) for twenty (20) minutes. This will be fully implemented by October 31, 2014.

- C. Observation 2.C: The Millipore 0.2 μ filter used in the vacuum filtration unit does not undergo any pre or post-use filter integrity testing. You use the vacuum filtration unit to sterile filter lots that are larger than 300mL, which includes sterile injectable products such as MSM 15% and Ascorbic Acid (preserved and preservative free) 500 mg/mL.

RESPONSE: Creative Compounds contacted the Millipore manufacturer to obtain information on proper integrity testing for these filters, and is in the process of changing to a different filter that will facilitate integrity testing. Implementation of the new filters and policies and procedures for integrity testing of such filters will be implemented by December 1, 2014.

- D. Observation 2.D: There is a failure to validate the 0.2 μ filters used to manufacture sterile injectable drug products produced from non-sterile components which includes Alprostadil, Bevacizumab/Dexamethasone, Glutathione 100 mg/mL. In addition, no pre-filtration bioburden limits have been established in order to determine if it exceeds the maximum capability of the filter.

RESPONSE: As a compounding pharmacy, Creative Compounds verifies that all of its filters comply with the USP 797 high-risk CSPs filtration guidelines. The USP 797 “Sterilization of High-Risk Level CSPs by Filtration” guidelines state, “Sterile filters used to sterilize CSPs shall be pyrogen free and have a nominal pore size of 0.2 or 0.22 μ . 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 under conditions similar to those in which the CSPs will be sterilized.” Additionally, Creative Compounds also follows the USP 797 guidelines that require the following: “Filter units used to sterilize CSPs shall also be subjected to manufacturers’ recommended integrity test, such as the bubble point test.” Our compliance with USP 797 guidelines for filtration validation fulfills our regulatory obligations regarding filtration devices.

3. Observation 3: Written records are not made of investigations into the failure of any batch or any of its components to meet specifications.

Specifically, your firm did not investigate testing results that show drug products have failed to meet specifications for sterility. For example, Methylcobalamin 20 mg/mL Lot 20140219@1/1 failed sterility testing on 02/24/14 and Glutathione 100 mg/mL injectable (Preserved) Lot # 20140620@13 failed sterility testing on 06/25/14 and you have not performed any investigation or implemented any corrective actions regarding these failed results. You have not performed an impact assessment to other products produced in the ISO 5 hood during the same time frame.

RESPONSE: Both the Methylcobalamin and Glutathione sterility test failures related to negative results from the RDI rapid scan test. In both cases, we followed up with a 14-day sterility test which concluded that these samples had no bacterial or biological growth. Based on these results, Creative Compounds determined that any additional follow-up was unnecessary.

Additionally, Creative Compounds is implementing an Out of Specification SOP on or before October 15, 2014. The Out of Specification SOP will include a numbering system for logged formulations sheets to ensure that there will be improved production schedule tracking.

4. Observation 4: Each batch of drug product purporting to be sterile is not laboratory tested to determine conformance to such requirements.

A. Observation 4.A: Sterility testing is not always performed on each batch of finished sterile injectable drug product produced. For example, no sterility testing is performed on any batches that are terminally sterilized which includes: Calcium Gluconate 10% (Preservative Free) Injectable, Sodium Phosphate 92/93 mg/mL (Preservative Free) Injectable, and Selenium 200 mcg/mL (Preservative Free). Sterility testing is not performed on batches of injectable drug products that are stored frozen for up to 45 days followed by 3-day refrigerated conditions which includes AlprostadiL/Lidocaine 20mcg/10mg/mL.

RESPONSE: Creative Compounds performs sterility tests in compliance with the USP 797 guidelines for compounding pharmacies. USP 797 states that sterility test must be performed if the BUD of a high-risk product is extended more than twenty-four (24) hours stored at room temperature, three (3) days under refrigerated conditions, or forty-five (45) days under frozen conditions. Also, USP 797 states that no sterility test needs to be performed if the product is filtered with a 1.2 micron or smaller nominal pore size filter into vials that are then steam sterilized at 121 degrees Celsius at about one (1) atmosphere or fifteen (15) PSI for twenty (20) to sixty (60) minutes and the batch is twenty-five (25) units or less and has been verified with a biological indicator.

- B. Observation 4.B: Endotoxin is not always performed on all batches of sterile injectable finished products. From January 2013 to August 2014 only 13 lots of finished sterile drug products were tested for endotoxin. Additionally, no endotoxin testing is performed on any non-sterile ingredients used in the manufacture of these drug products.

RESPONSE: Creative Compounds is following USP 797 guidelines and is not required to test for endotoxin on sterile products obtained from a drug manufacturer, or on compounded products intended for ophthalmic, irrigation or inhalation use. Creative Compounds does test for endotoxins when it compounds high risk CSPs, in conformance with USP 797.

- C. Observation 4.C: All of your finished sterile drug product samples are tested for sterility by a contract laboratory using a Scan RDI rapid sterility test method. No method suitability testing for the sterility test method was performed to ensure that the specific drug product samples tested do not interfere with the test.

RESPONSE: USP 797 guidelines for compounding pharmacies specify that a “USP 71, equivalent or superior sterility testing” shall be performed on sterile compounded drugs. Scan RDI has been used by the pharmaceutical industry for many years. Scan RDI’s white paper, provided at the time of the inspection, documents that the Scan RDI rapid sterility test is, at a minimum, equivalent to USP 71 sterility testing.

5. **Observation 5: Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.**

Specifically, potency testing is performed on a skip-lot testing schedule that tests no more than 5% of any finished product lots. You do not test for potency of the final drug product after performing dilution steps as part of the manufacturing process for numerous sterile drug products. For example, the admixture process

for Mitomycin 0.2mg/mL and 0.3 mg/mL Injectable requires two complex dilution steps.

RESPONSE: Creative Compounds acknowledges the importance of safe and potent compounded medications. As a compounding pharmacy, we follow USP 797 which does not require, potency testing on all batches. Creative Compounds agrees to focus its potency testing program on more complex admixture processes. Creative Compounds has had a potency test performed on Mitomycin 0.3mg/ml Injectable, with test results of 100% potency. A copy of this test result is included as Attachment 4.

6. **Observation 6: Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform. Specifically,**

- A. The gowns worn by operators when working in the ISO 5 hood are not sterile and the surgical masks do not provide adequate coverage to the forehead, neck, or face. Your procedure SOP 7.011 "Gowning and Gloving" allows for re-use of the gown during the production day to re-enter the ISO 5 and ISO 7 areas. On 08/04-05/14 we observed the operator store the mask and hairnet used while producing sterile drugs in the sleeve of her gown and re-used these items throughout the day. Additionally, an operator was observed wearing her personal tinted eyeglasses during filling of Avastin lot 20140805@1, which were not disinfected.
- B. On 08/05/14 during the repackaging of Avastin Lot 20140805@1 in the ISO 5 hood the operator's wrists were exposed due to inadequate glove and gown cover.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. Creative Compounds has re-trained its staff to ensure that masks and hairnets are discarded after each use. Creative Compounds also purchased sterile coveralls that include wrist attachments to ensure that skin is not exposed in the ISO 5 hood. See Attachment 5. Even though USP 797 states that, "Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs", Creative Compounds is instructing all staff members that wear eyeglasses to use disinfected goggles over their glasses in the ISO 7 area.

7. **Observation 7: Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.**

Specifically, your firm aseptically fills drug products in the ISO 5 Hoods and the ISO 7 and ISO 8 processing and support rooms and the procedure, SOP 9.038, "Surface Sampling Plan" for monitoring the areas are deficient in that:

- A. Active air sampling for non-viable and viable monitoring is not performed each day in the ISO 5 hood when sterile drug products are produced. Instead, it is performed every six months under static conditions.
- B. Surface sampling for microbiological monitoring is not performed each day that a batch of sterile drug is filled. Instead it is conducted every 2 weeks in the ISO 5 hood and the ISO 7 and ISO 8 areas. Also the locations where samples are taken is not identified or documented.
- C. Personnel monitoring of the operator's fingertips is not performed each day that a batch of sterile drug is filled in the ISO 5 hood. Instead the current procedure is to perform personnel monitoring every two weeks.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. We follow USP 797 which states "Air Sampling shall be performed at least semiannually (*i.e.*, every six (6) months) as part of the re-certification of facilities and equipment." Creative Compounds has re-trained its staff to document the location of each surface sample on the sampling documentation sheet, which contains a diagram of the ISO 5, ISO 7, and ISO 8 areas.

Personnel monitoring is performed in compliance with USP 797 guidelines, which states that for high-risk CSPs, personnel finger sampling and sterile media fills should be performed on a semi-annual basis. According to the USP, surface sampling is to be done periodically according to risk level. Most USP experts recommend weekly surface sample monitoring. Creative Compounds' surface sample monitoring (which includes fingertips) is performed every two weeks. If Creative Compounds finds more than three (3) CFU in the ISO 5 area, more than five (5) CFU in the ISO 7 area, or more than one-hundred (100) CFU in the ISO 8 area, the bi-monthly monitoring is increased to weekly monitoring. We acknowledge that surface sampling on a weekly basis is a "best practice" that would be beneficial to our patients. Therefore, Creative Compounds has increased its surface sampling (including fingertips) to weekly intervals. If the same limits established above are breached, Creative Compounds will increase its weekly sampling to daily sampling until samples are below the levels we have established for seven (7) days, and then sampling will go back to being performed on a weekly basis.

- 8. **Observation 8: Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.**
 - A. Observation 8.A: The suitability and efficacy of disinfectants, cleaning agents and procedures have not been assessed to ensure potential contaminants are

adequately removed from the surfaces in the classified areas. Routine cleaning procedures for the ISO 5 hood include using 70% IPA as a disinfectant. Virustat DC Plus and Acidified Bleach are rotated quarterly as the cleaning agents. The concentration of the acidified bleach is not documented.

RESPONSE: Creative Compounds complies with USP 797 requirements for cleaning and disinfecting rooms and equipment. Creative Compounds understands the value of properly documenting the concentration of acidified bleach and its cleaning procedures and activity. Creative Compounds will better document these activities. Specifically, it will document the concentration of acidified bleach on the formula worksheet, as well as the ph of the acidified bleach to ensure that it is mixed appropriately to have sporicidal activity. Creative Compounds is implementing this effective October 1, 2014, which is when the next cleaning cycle of acidified bleach begins.

B. Observation 8.B: The wipes used to clean the ISO 5 hood and ISO7 and ISO 8 support rooms are non-sterile, non-woven and have not been established as non-shedding.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. USP 797 guidelines state that “All cleaning materials, such as wipers, sponges, and mops, shall be nonshedding, preferably composed of synthetic micro fibers, and 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.” We have changed to sterile, nonshedding wipes to clean the ISO 5 hood and ISO 7 area, and to a different brand of nonshedding wipes for the ISO 8 area. See Attachment 6.

9. **Observation 9: Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure. Specifically,**

A. No static and dynamic airflow pattern studies (smoke studies) have been performed in the ISO 5 hood or ISO 7 buffer room where sterile injectable drug products are prepared and filled.

B. There is no continuous monitoring of air pressure differentials from the ISO 7 room to the ISO 8 room. It was observed that opening the doors to the ISO 7/8 area affects the pressure differentials of these areas.

RESPONSE: Creative Compounds acknowledges the importance of a safe and sterile compounding environment. As a compounding pharmacy, we follow USP 797, which does not require smoke studies in the ISO 5 and ISO 7 areas. USP 797 requires that pressure differential monitoring be documented and

reviewed at least every work shift, with a minimum of once daily. Creative Compounds has one work shift per day, and so monitor the pressure differentials from ISO 7 and ISO 8 areas on a daily basis.

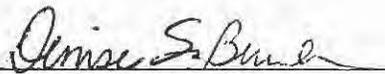
10. Observation 10: An adequate number of batches of each drug product are not tested to determine an appropriate expiration date.

Specifically, your firm does not have stability program or data to support Beyond Use Dates (BUD) assigned to sterile finished injectable drug products filled on site. No stability studies have been conducted to support assigned dates. For example: Glutathione 100 mg/mL, Preservative Free has a BUD of 90 days at refrigerated conditions. Glutathione 100 mg/mL, Preserved, has a BUD of 120 days at refrigerated conditions. Methylcobalamin 20 mg/mL Preservative Free has a BUD of 180 days at refrigerated conditions.

RESPONSE: The FDA's observation is referring to stability study requirements for drug product expiration dates. As a compounding pharmacy, we do not assign expiration dates, but rather determine Beyond Use Dates in accordance with USP 797. The BUD is determined by a review of scientific literature, testing done on our compounded products, and vendor BUD studies.

Through this response, Creative Compounds has sought to address all of the FDA inspector's observations and concerns. If the FDA requires additional information or communication from Creative Compounds, it is welcome to contact Denise S. Burnham, Creative Compounds' President, at (503) 685-6111.

Sincerely,



Denise S. Burnham
President, Creative Compounds
8560 S.W. Salish Lane, Suite 100
Wilsonville, OR 97070
Phone: (503) 685-6111