

To: US FDA San Francisco District Office (SAN-DO)  
ATTN: Ms. Lewis, District Director, SAN-DO  
Mr. Campbell, Compliance Officer, SAN-DO  
Ms. Rhyu, Consumer Safety Officer, SAN-DO  
1431 Harbor Bay Parkway  
Alameda, CA 94502

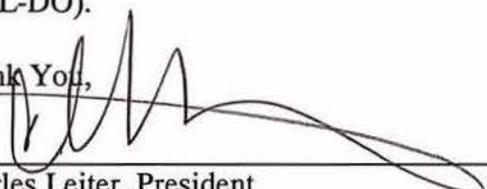
Re: Posting of FDA Form 483 Response

FEI: 3003434972, Leiter's Compounding Pharmacy  
EI: 10/22/13-11/05/13

Hello,

Please accept this letter as authorization to post on the US FDA Internet website Leiter's Compounding Pharmacy's response to the FDA Form 483 Notice of Observations, dated 11/25/13, as submitted to SAN-DO, unredacted but without attachments. We understand this response will be posted under the FDA Form 483 Notice of Observations for Leiter's Compounding Pharmacy, issued on 11/05/13, by CSO's Rhyu (SAN-DO) and Arista (DAL-DO).

Thank You,



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CC electronic copy to:  
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US FDA, Dallas District Office  
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4040 North Central Expressway, Ste. 900  
Dallas, TX 75204

11/25/13,

This letter is in response to the FDA Form 483. If this Form 483 appears on the FDA website, we respectfully request that this response, excluding the attached internal operating and testing procedures, be posted on the FDA's website alongside the Form 483 and be included as an additional attachment any time the FDA provides a copy of Leiter's Compounding Pharmacies' FDA Form 483 to anyone or any entity outside the FDA.

Responses to Form FDA 483 Inspectional Observations as issued on 11/05/13 by US FDA Investigators Jennifer Rhyu and Thomas Arista at Leiter's Compounding Pharmacy located at 1700 Park Ave, San Jose, CA 95126:

### **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) The "Sterile Compounding Personnel Qualification" document #2.030, version 1.0, dated 3-01-09 establishes that " All sterile compounding personnel must successfully complete three sterile compounding process validations according to SOP 9.110 Sterile Compounding Process Validation (Media Fills) before he or she can prepare parenterals." The aforementioned aseptic process validation media fill procedure establishes, "The purpose of this procedure is to establish requirements for sterile compounding process validations (media fills)"and documentation requirements for media fills to include but not limited to for example, "number of units incubated and

incubation time/temperature”; “number positive units at the conclusion of the incubation” and the media fill “results (pass/fail).”

**Observation 1.A. Response:**

We agree to perform media fills timely, ship media fills for private laboratory analysis within 24 hours of filling, and ship under appropriate conditions as finished product would be shipped to customers. Such as repackaged Bevacizumab shall be provided in light protective bags and under refrigerated conditions, both to customers and private testing laboratories.

**Time Line:** Appropriate media fills representing each operator’s typical aseptic operation are currently scheduled to be completed (in terms of analytical results received) by 12/31/13.

SOP 9.110 Aseptic Process Validation (Media Fills/Glove Sampling), version 2.0, can be found as **attachment 1**. Training records for this SOP can be found as **attachment 2**.

**Observation 1**

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

b) “Quality Assurance Program” document #9.010, version 1.0, dated 3-01-09 purpose “is to outline a quality assurance (QA) program at Leiter’s Pharmacy” define QA as “A state of control sufficient to result in a safe and effective product achieved by utilization of mechanisms for monitoring, evaluating, correcting and improving activities and operational systems.” And, it includes “Quality Process Controls” for “Media Fills – In regards to sterile compounding, media fills shall be performed.” The “Sterile Compounding Personnel Qualification” Document #2.030, version 1.0, dated 3-01-09, establishes that “Leiter’s Pharmacy shall require basic qualifications for each employee active in the process of sterile compounding.” Furthermore, “All sterile compounding personnel must successfully complete three sterile compounding process validations according to SOP 9.110 Sterile Compounding Process Validation (Media Fills) before he or she can prepare parenterals.” Despite the establishment of the aforementioned standard operating procedures, the table in Observation summarizes a number of deficiencies with respect to media fill records that are needed to support that personnel can adequately and successfully perform aseptic processing operations.

**Observation 1.B. Response:** See Observation 1.A. response.

**Observation 1**

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

c) The “Aseptic Processing Validation (Media Fills/Glove Sampling) document #9.110, version 1.0, dated 4-12-13, does not contain any language that authorizes and approves

that media filled vials are permitted to be refrigerated prior to shipment to the contract laboratory for incubation.

**Observation 1.C. Response:** See Observation 1.A. response.

### **Observation 1**

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

d) There is no record to document that the steam sterilizer has been subject to some form of equipment qualification and there is no record to document that the steam sterilization processes are appropriately validated.

**Observation 1.D. Response:** We agree to perform autoclave qualification for both autoclaves regarding full shelf load utilizing biological and chemical indicators placed throughout the load with the largest volume per unit we autoclave (100 ml per vial, 25 vials per load on one shelf).

We are also performing autoclave qualification with the largest load of our smallest vials per unit we autoclave (1 ml per vial, 125 vials per load on one shelf) with biological and chemical indicators placed throughout the load.

**Time Line:** Scheduled to be completed, in terms of analytical results received by 12/31/13.

### **Observation 1**

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

e) There are no sterilization records for the glass vial and liquid dropper that are used for some sterile ophthalmic solutions and/or for the plastic squirt bottles that are used for the sterile 70% isopropyl alcohol.

**Observation 1.E. Response:** We agree to maintain autoclave print-outs and attach to each Formula Worksheet for containers sterilized as we have for all finished product cycles, see **attachment 3** for five Formula Worksheets with the autoclave printout attached (copied).

We also commit to immediately discontinue the use of re-useable plastic bottles for containing sterile 70% IPA. Disposable containers of sterile 70% IPA have been purchased, see **attachment 4** for invoice of sterile 70% IPA purchased, dated 11/19/13.

**Time Line:** Implementing and maintaining autoclave print-outs completed. Purchasing of disposable sterile 70% IPA completed.

### **Observation 1**

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

f) There are no steam sterilization parameters (e.g., time, temperature, pressure) established for the two Tuttanes EZ-10 Autoclaves, that are used for the sterilization processes for various components (e.g., glass vials) and materials (e.g., plastic cleaning bottles), used for either the sterile drug products and used during the aseptic operations.

**Observation 1.F. Response:** Sterilization parameters are defined in the User Manual for the Operation & Maintenance Manual Electronic Tabletop Autoclaves, see **attachment 5**. These parameters are named with the following sterilization parameters:

1. Unwrapped instruments: Sterilization temperature of 273°F (134°C), for three minutes with no dry time.
2. Wrapped instruments and porous loads: Sterilization temperature of 273°F (134°C), for seven minutes with 30 minutes of dry time.
3. Glassware: Sterilization temperature of 250°F (121°C), for 30 minutes, with a slow exhaust of 15 to 20 minutes, and no dry time.

These parameters and cycle settings have not been modified. These sterilization parameters shall be explicitly defined in SOP 4.030 Use, Verification, and Maintenance of the Tuttnauer EZ10 Electronic Tabletop Autoclave.

**Time Line:** Defining sterilization parameters in SOP 4.030 Use, Verification, and Maintenance of the Tuttnauer EZ10 Electronic Tabletop Autoclave, along with appropriate Change Control, SOP review, and employee training shall be completed by 12/31/13.

### **Observation 1**

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

g) *Geobacillus stearothermophilus* ( $1.8 \times 10^5$ ) biological indicators (BI) is used to demonstrate the acceptability of a steam sterilization process. The BIs are subsequently incubated via a heat block with a recommended temperature of 55-60 °C for 24 hours. However, there is no temperature monitoring device (thermometer/temperature probe) to assure that the incubation temperature is achieved and there is no record to document the results of the BI challenge.

**Observation 1.G. Response:** We agree to calibrate the temperature probe utilized in the Biological Indicator heat block. We have purchased a calibrated temperature probe for the Biological Indicator heat block and put into use on 11/19/13, see **attachment 6** for a description of this probe, purchase invoice of the probe, and the calibration of the probe.

**Time Line:** Completed.

### **Observation 1**

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

h) The “Use and Maintenance of the Millex/Serivex Integrity Tester” document #4.210, version 1.0, dated 3-01-09 “establish requirements for the use and maintenance of the Millex/Sterivex Tester.” All aseptically filled drug products that are not terminally sterilized are subject to sterilization via the use of 0.22 micron filtration. The filters are integrity tested post use via a Bubble Point procedure. The Manager of Quality Control and Clinical Trials confirmed that the Bubble Point procedure is not part of the aforementioned 3/01/09 document and it has not been officially formalized as a standard operating procedure.

**Observation 1.H. Response:** We agree to formalize SOP 4.210 Use and Maintenance of the Millex/Sterivex Integrity Tester to include the bubble point procedure.

**Time Line:** Formalize the bubble point procedure in SOP 4.210 Use and Maintenance of the Millex/Sterivex Integrity Tester, to be completed by 12/31/13.

### **Observation 1**

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

i) There is no record to document that the Labconco lyophilizer has been subject to equipment qualification verification and there is no record to document that the freeze drying process for the Dapriprazole HCL 300mg has been appropriately validated.

**Observation 1.I. Response:** We agree to qualify the Labconco lyophilizer to represent the Dapriprazole HCL lyophilization process. We wish to note that no assignments for the Dapriprazole HCL lyophilization are currently scheduled with any assignments in the near future planned.

**Time Line:** Qualification to be completed by 12/31/13.

### **Observation 2**

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

Specifically, The Bevacizumab 2.5mg/0.1ml (1 cc syringe) Injection lot number 08282013@15 was Sterility Tested by the contract laboratory. The August 29, 2013 laboratory report documents the result as “Positive Aerobic at 5 days” with a confirmation of the microbial identification as *Cupriavidus metallidurans* (renamed from *Ralstonia metallidurans* a soil borne gram negative bacillus). The Director of Quality Assurance explained that the pharmacy technician has been retrained. However, no root cause analysis has been performed to determine the source(s) and/or personnel activities

that may have generated the microbial contamination to preclude the reoccurrence of the microbiological contamination.

**Observation 2. Response:** We agree to increase activities when any analytical failure is experienced to investigate associated activities. We do want to point out that every sterile batch is quarantined until acceptable results are received. Should a product batch fail analytical testing, that batch is destroyed and not dispensed. But we acknowledge additional investigative activities are to occur regardless if the batch is distributed or not.

Increased activities shall be updated in SOP 1.030 Deviations – OOS, including but not limited to:

1. Review the compounding record and shall verify that all components and quantities of materials are correct, that all steps were performed in the proper order, and that the second verification was performed. Verify the Beyond Use Date and finished product QC checks.
2. Review training records to verify operator qualification.
3. Review equipment qualification to verify current certification checks of the cleanroom, laminar airflow workbench (LAFW) or biological safety cabinet (BSC), product refrigerators/freezers, and automated compounding equipment.
4. Review environmental monitoring records to verify that the controlled environments (cleanroom, LAFW) were functioning properly.
5. Review complaints.
6. Review operators' history of product analytical testing and other product failures.

**Time Line:** SOP 1.030 Deviations – OOS update to be completed by 12/20/13. Investigative activities and documentation shall commence during the next investigation of a product failure.

### **Observation 3**

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

a) "Quality Assurance Program" document #9.010, version 1.0, dated 3-01-09 purpose "is to outline a quality assurance (QA) program at Leiter's Pharmacy" define QA as "A state of control sufficient to result in a safe and effective product achieved by utilization of mechanisms for monitoring, evaluating, correcting and improving activities and operational systems." And, it includes "Quality Process controls" for "Media Fills – In regards to sterile compounding, media fills shall be performed." The "Sterile Compounding Personnel Qualification" document #2.030, version 1.0, dated 3-01-09, establishes that "Leiter's Pharmacy shall require basic qualifications for each employee active in the process of sterile compounding." Furthermore, "All sterile compounding personnel must successfully complete three sterile compounding process validations according to SOP 9.110 Sterile Compounding Process Validation (Media Fills) before he

or she can prepare parenterals.” Despite the establishment of the aforementioned standard operating procedures, the table in Observation summarizes a number of deficiencies with respect to media fill records that are needed to support that personnel can adequately and successfully perform aseptic processing operations.

**Observation 3.A. Response:** See Observation 1.A. response.

### **Observation 3**

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

b) There are no airflow pattern evaluations (aka smoke studies performed of the ISO-5 clean room, ISO-5 cabinets, and/or the surrounding ISO-7 support areas e.g., personnel gowning and clean room entryway, preparations and material ante-room. Note: the ceiling HEPA filters provide vertical airflow that impact with two of the airflow cabinets' horizontal airflow, which have not been assessed.

**Observation 3.B. Response:** We agree to perform smoke studies to evaluate airflow patterns within the aseptic areas under dynamic conditions.

**Time Line:** This service is scheduled to begin 12/06/13 by Technical Safety Services, Inc. See **attachment 7** for the scheduling and proposal of contract work.

### **Observation 3**

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

c) The Director of Quality Assurance and the Manager of Quality Control and Clinical Trials confirmed that there is no established procedure regarding the clean room attire for personnel that perform aseptic filling operations. In addition, there is no established procedure to describe the acceptable manner with which personnel are required to don sterile clean room attire e.g., quality controls to preclude cross contamination onto the sterile attire.

**Observation 3.C. Response:** Cleanroom attire and procedures have always been a requirement for operators performing aseptic filling operations. We have taken this opportunity to increase documentation, gowning training, updating SOP and personnel monitoring for cleanroom attire including bringing in the outside contract services of Kimberly-Clark gowning instructor. Three on-site sessions have been completed to date, 10/10/13, 10/24/13, and 11/14/13.

**Time Line:** Three sessions of on-site instruction and observation have been completed by Kimberly-Clark, see **attachment 8** for Certificates provided by Kimberly-Clark for each operator on 10/10/13. See **attachment 9** for sign-in sheet of operators that participated in a second round of gowning procedures as performed by Kimberly-Clark on 10/24/13 in the anteroom. See **attachment 10** for Formula Worksheets generated for

the sampling of gowns via RODAC. These gown samples are currently being analyzed by a private laboratory.

Review, update, and employee training of SOP 9.100 Garb for Cleanroom shall be completed by 12/20/13.

### **Observation 3**

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

d) The “Environmental Monitoring of the Clean Room Facility” document #3.030, version 2.0 dated 7/08/13 establishes “The purpose of this procedure is to establish requirements for non-viable and viable environmental monitoring (EM) of the clean room facility”, which include personnel monitoring. However, there is no personnel monitoring performed for technicians who work within the ISO-5 clean room, ISO-5 cabinet and personnel who perform the aseptic operations.

**Observation 3.D. Response:** We agree to increase personnel monitoring performing aseptic operations beyond the USP requirement of bi-annually to quarterly. This personnel monitoring shall include glove and gown sampling for each operator.

**Time Line:** This increase in personnel monitoring shall commence during the on-site garbing instruction for gown sampling. RODAC samples of gowns were taken on 11/14/13 and sent for private laboratory analysis. These samples are in progress.

This increase in personnel monitoring shall commence during the next scheduled media fill process for glove sampling, currently scheduled to be completed by 12/31/13.

SOP 3.030 Environmental Monitoring of the Clean Room Facility shall be updated and employees trained for these current requirements by 12/20/13.

### **Observation 3**

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

e) The preceding observation regarding personnel monitoring documents that Leiter Compound Pharmacy is not adhering to the requirements established in their standard operating procedure.

**Observation 3.E. Response:** See Observation 3.D. response.

### **Observation 3**

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

f) Currently, the EM program consists of obtaining EM samples (RODAC and air viable samples at the end of the aseptic operations on Friday afternoon). The EM program does not include obtaining EM samples during the preceding four days of aseptic operations.

**Observation 3.F. Response:** We agree to increase EM to daily as opposed to weekly for surface sampling. We have taken this opportunity to incorporate and qualify the use of real time particle monitoring within the laminar hoods for each aseptic assignment, see **attachment 11** for the particle counter manual.

**Time Line:** SOP 3.030 Environmental Monitoring of the Clean Room Facility shall be updated, employees trained, and appropriate documentation generated for these current requirements by 12/20/13.

Daily surface samples shall be taken of the cleanroom laminar hoods beginning 12/20/13 to allow completion and implementation of above.

Four particle counters are currently being qualified for our intended use and evaluation of these units should be completed by 01/20/14.

### **Observation 3**

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

g) The “General Aseptic Technique” document #1.060, version 1.0, dated 3-01-09 establish the aseptic technique performed in the laminar airflow cabinet, that is, “Work shall always be performed approximately in the center of the work surface. When working in a horizontal LAFW, all work must be performed at a distance of no less than 6 inches from the front edge of the work surface.” Despite the establishment of the standard procedure for aseptic technique, the EM sampling consists of obtaining samples from the left and right hand side of the airflow cabinets and not from the work areas that personnel come in direct contact with.

**Observation 3.G. Response:** We agree to modify the surface samples of laminar hoods to redefine these samples be taken within the direct compounding area of the laminar hoods.

**Time Line:** Discussions with CCS, outside cleaning company and EM service, are currently in progress, see **attachment 12** for an e-mail coordinating this improvement. Completion and implementation to occur by 12/20/13.

Updates to these specific sampling locations, corresponding internal SOP 3.030 Environmental Monitoring of the Cleanroom Facility update, employee training, and appropriate documentation to occur by 12/20/13.

### **Observation 3**

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

h) The “Use, Verification and Maintenance of the Tuttnauer EZ10 Electronic Table Top Autoclave” document #4.030, version 1.0 dated 3-01-09 “establish requirements for the use, verification and maintenance of the Tuttnauer EZ10 Electronic Table Top Autoclave”. However, the standard operating procedure is silent with respect to the use of BIs for the steam sterilization process.

**Observation 3.H. Response:** We agree to include the use of biological indicators (BIs) for each sterilization cycle and document this use on each Formula Worksheet as was provided to the US FDA Investigators during the inspection. In addition, SOP 4.030 shall be reviewed and updated where necessary to further define the use of BIs, employees shall be trained, and appropriate documentation shall be generated.

**Time Line:** SOP 4.030 shall be reviewed, updated, with employee training, and appropriate documentation generated by 12/20/13.

#### **Observation 4**

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

Specifically, the Sterility Tests and microbiological testing of sterile parenterals’, finished products and media fill vials, which include for example, the Avastin finished dosage form (100mg & 400mg bottles) that is prepackaged into sterile Bevacizumab 2.5mg/0.1ml Injection 1 cc syringes. That is;

As previously reported, the Avastin finished product vials are repackaged into 1cc T.B., sterile syringes. The repackaged drug is sterility tested by the company’s contract testing laboratory i.e., DynaLabs LLC., St. Louis, Mo. Regarding the sterility tests, the Certificate of Analysis documents that the analysis, “Does not meet all the requirements for sampling and/or method suitability specified in USP<71>”. The aforementioned Sterility Test results are not exclusive to the repackaged syringes of Avastin.

**Observation 4 Response:** This statement from DynaLabs signifies that suitability (Bacteriostasis and Fungistasis) has not been performed for those specific product types. We do wish to state that all inconclusive initial results shall be Gram stained from the apparent turbid broth(s). Any identification of bacterial rods or cocci, fungal structures, or spores from the Gram stain shall constitute a sterility failure. All sterility tests are of the 14-day incubation utilizing TSB (SCD) & FTM broths USP methodology. No rapid sterility analysis is performed on Leiter’s products.

In addition, we are currently in the process of appropriately validating our specific products for private laboratory release testing for USP 14-day sterility and endotoxins for different product types to provide assurance that analytical testing is appropriate for

results obtained. Rapid analysis validation would be performed before any use of rapid methodology for product release testing.

**Time Line:** Further instructions for Gram staining in sterility analyses were provided to DynaLabs no later than 10/02/13. See **attachment 13** for this Gram stain instructional statement requirement provided to DynaLabs by Leiter's Compounding Pharmacy.

Process of validating analytical testing is in progress with documentation maintained. This validation program shall continue as products are identified to be validated. Release of products utilizing validated methods has not begun.

### **Observation 5**

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

a) We observed personnel working in the ISO-5 hoods, which was followed by obtaining equipment/utensils/material from the material transfer cabinet (non-classified/non-sterile environment) and subsequently performing aseptic operations.

**Observation 5.A. Response:** We have taken this opportunity to provide garbed operators working in the cleanroom complete necessary equipment/utensils/materials for each assignment thereby eliminating the need to access non-classified/non-sterile environments.

We have implemented a shift schedule for aseptic garbed operators to remain in the cleanroom for up to three hours maximum (without leaving the cleanroom).

We have increased anteroom assistance for garbed operators in the cleanroom to provide those operators necessary elements through the pass-through into the cleanroom.

**Time Line:** Completed. See **attachment 14** for SOP 1.060 General Aseptic Technique, version 2.0, specifically section 9.2.9 for requirements to not leave the cleanroom while conducting assignments. See **attachment 15** for employee training documentation.

### **Observation 5**

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

b) We observed, on numerous occasions, clean room personnel adjusting the eyewear with their gloved hands. The gloved hands were not subject to 70% isopropyl alcohol prior to or after adjusting the eyewear.

**Observation 5.B. Response:** We were in the process of qualifying appropriate eyewear when the US FDA Investigators began the inspection. The type observed by US FDA Investigators was found to be inappropriate in terms of fitting and we removed on 10/28/13. We are currently in the process of qualifying different eyewear.

**Time Line:** Qualification of different eyewear is in progress, see **attachment 16** for the eyewear type currently being qualified for our intended use.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both dated 3-01-09 established the “gowning requirements for entering the clean room facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

a) The Director of Quality Assurance and the Manager of Quality Control and Clinical Trials confirmed that there is no established procedure regarding the clean room attire for personnel that perform aseptic filling operations. In addition, there is no established procedure to describe the acceptable manner with which personnel are required to don sterile clean room attire e.g., quality controls to preclude cross contamination onto the sterile attire.

**Observation 6.A. Response:** See Observation 3.C. response.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both dated 3-01-09 established the “gowning requirements for entering the clean room facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

b) We observed personnel with head-covers and eyewear that did not cover all of the exposed skin surfaces and as of 10/28/13 no eyewear if work by personnel performing aseptic operations in the ISO-5 room and airflow cabinets.

**Observation 6.B. Response:** See Observation 5.B. response.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both

dated 3-01-09 established the “gowning requirements for entering the clean room facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

c) Eyewear/goggles are not cleaned, sanitized and/or sterilized prior to use; the eyewear is shared by clean room personnel and the eyewear is commonly stored in a drawer in the ISO-7 ante-room.

**Observation 6.C. Response:** See Observation 5.B. response. In addition, eyewear selected for use after qualification shall be provided by the vendor cleaned, sanitized, and/or sterilized. No re-use of eyewear shall be allowed.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both dated 3-01-09 established the “gowning requirements for entering the clean room facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

d) Prior to commencing the aseptic filling operations, the ISO-5 airflow cabinets are initially cleaned with 70% isopropyl alcohol. The clean room operator’s uncovered forehead is exposed to the interior surfaces of the ISO-5 cabinets during the initial cleaning process.

**Observation 6.D. Response:** We are taking this opportunity to increase operator skin coverage to eliminate exposed skin during aseptic operations with the eyewear as described in **attachment 16**.

We are also in the process of discussions with vendors for cleaning extenders to eliminate operators having to enter into the interior of hood cabinets.

**Time Line:** Discussions with vendors are in progress. Eyewear qualification is in progress.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both dated 3-01-09 established the “gowning requirements for entering the clean room

facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

e) Personnel are required to don their clean room attire [i.e., sterile one piece gown (bunny suit) as of April 28, 2013] in the ISO-7 ante-room, which is performed at the entryway that leads into the ISO-5 clean room and it is within the same area that is contaminated with personnel’s street shoes; the sterile shoe covers come in direct contact with the entryway that is contaminated with the street shoes.

**Observation 6.E. Response:** We have taken this opportunity to increase the use of a second set of shoe covers to be applied in the anteroom. This will eliminate any outside shoes to come into contact with the anteroom floor as the first set of shoe covers will not be removed. See Observation 3.C. response and **attachment 17** for SOP 9.100 Required Garb for Cleanroom Facility Access, version 2.0, attachment 2, flow chart defining the use of “don second set of shoe covers”.

**Time Line:** Completed.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both dated 3-01-09 established the “gowning requirements for entering the clean room facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

f) Personnel commonly wear green color scrubs that are worn to and from their residence. During the gowning process there is no assurance that the sterile gowns (bunny suit) does not come in direct contact with the personnel’s green color scrubs.

**Observation 6.F. Response:** We were already in the process of obtaining outside cleanroom laundry service, see **attachment 18** for e-mail communication final date of 11/14/13. The outside service is Uniclean Cleanroom Services, see **attachment 19** for a description of this company. See **attachment 20** for a Customer Service Agreement, dated 10/10/13.

**Time Line:** This service is set to begin 12/06/13 as documented on **attachment 18**.

### **Observation 6**

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, the “Required Garb for Clean Room Facility Access” document #9.100, version 1.0 and the “General Aseptic Technique” document #1.060, version 1.0, both dated 3-01-09 established the “gowning requirements for entering the clean room facility” and the “requirements for using aseptic technique in any area to minimize contamination”, respectively. The following observations pertain to the aseptic operations and personnel activities performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

g) We observed the reusable (disposable) white color lab coats that are worn over the green color scrubs hanging in the men/women restroom with some lab coats observed on the restroom floor (fallen off their hook/hanger). Personnel wear the lab coats in the ISO-8 general compounding area and the ISO-7 anteroom that is used to gown into the sterile gowning attire prior to entry into the ISO-5 clean room. The Manager of Quality Control and Clinical Trials confirmed that they have limited available space for employee lab coats, which has led to the use of the men/women restroom as storage area.

**Observation 6.G. Response:** We have taken this opportunity to discontinue the use of the previously identified storage area. This storage area is now located in the hallway in front of the ISO 8 non-sterile compounding laboratory. See **attachment 21** for photos of the current storage location and removal of items in the previous storage location.

**Time Line:** Completed.

### **Observation 7**

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

a) There are no nonviable particle (NVP) measurements taken for three of the five ISO-5 airflow cabinets. Rather, the Director of Quality Assurance and the Manager of Quality Control and Clinical Trials confirmed that air velocity measurements are taken, which are subsequently used to support that the airflow cabinets are ISO-5 environmental.

**Observation 7.A. Response:** We have performed dynamic particle measurements for all airflow cabinets and controlled rooms and these results support ISO 5 environments for hoods and rooms deemed to be operational at ISO 5 levels. These results support that these rooms and hoods have been operating at the required ISO level since the previous certifications that were performed in May of 2013 as no modifications have been performed on or in these areas at least since 5/13. See **attachment 22** for certifications as performed by Technical Safety Services, Inc. on 10/23/13. See **attachment 23** for a series of photos documenting dynamic activity as performed on 10/23/13 during the cert dynamic readings.

**Time Line:** Completed.

### **Observation 7**

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

b) NVP measurements are taken once every 6-months, that is, during static conditions; there exists no NVP measurements to demonstrate that the ISO-5 environment is maintained under dynamic and/or routine aseptic operations.

**Observation 7.B. Response:** See Observation 7.A. response. In addition, we are in the process of qualifying real time particle monitors for each airflow cabinet to be used during aseptic operations. See **attachment 11** for an instruction manual of these particle counters.

**Time Line:** Qualification is in progress and data shall be evaluated no later than 12/31/13 for our intended use.

### **Observation 7**

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

c) Technicians performing aseptic operations [e.g., Avastin (bevacizumab) Injection] have to access the ISO-5 negative air pressure room via the colorless plastic curtains, which are used to partition the ISO-5 negative air pressure room from the ISO-5 clean room. However, the plastic curtains are not sampled and/or part of the EM sampling program.

**Observation 7.C. Response:** We have taken this opportunity to increase the EM sampling program to include the plastic curtains. Discussions with CCS, outside cleaning company and EM service, are currently in progress, see **attachment 12**.

**Time Line:** Implementation to occur by 12/20/13.

### **Observation 7**

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

d) The “Environmental Monitoring of the Clean Room Facility” document 3.030, version 2.0 dated 7/08/13 establishes “The purpose of this procedure is to establish the requirements for non-viable and viable environmental monitoring (EM) of the clean room facility”, which include personnel monitoring. However, there is no personnel monitoring performed for technicians who work within the ISO-5 clean room, ISO-5 cabinet and personnel who perform the aseptic operations.

**Observation 7.D. Response:** See Observation 3.D. response.

**Time Line:** This increase in personnel monitoring shall commence during the on-site garbing instruction for gown sampling.

This increase in personnel monitoring shall commence during the next scheduled media fill process for glove sampling, currently scheduled to be completed by 12/31/13.

SOP 3.030 Environmental Monitoring of the Clean Room Facility shall be updated and employees trained for these current requirements by 12/20/13.

### **Observation 7**

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

e) The preceding observation regarding personnel monitoring documents that Leiter Compound Pharmacy is not adhering to the requirements established in their standard operating procedure.

**Observation 7.E. Response:** We agree to increase personnel monitoring as stated in observation 3.D. response.

### **Observation 7**

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

f) Currently, the EM program consists of obtaining EM samples (RODAC and air viable samples at the end of the aseptic operations on Friday afternoon. The EM program does not include obtaining EM samples during the preceding four days of aseptic operations.

**Observation 7.F. Response:** We agree to increase EM as stated in observation 3.F. response.

### **Observation 7**

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

g) The "General Aseptic Technique" document #1.060, version 1.0, dated 3-01-09 established the aseptic technique performed in the laminar airflow cabinet, that is, "Work shall always be performed approximately in the center of the work surface. When working in a horizontal LAFW, all work must be performed at a distance of no less than 6 inches from the front edge of the work surface." Despite the establishment of the standard procedure for aseptic technique, the EM sampling consists of obtaining samples from the left and right hand side of the airflow cabinets and not from the work areas that personnel come in direct contact with.

**Observation 7.G. Response:** See observation 3.G. response.

### **Observation 8**

Drug product production and control records, are not reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.

Specifically, the Manager of Quality Control and Clinical Trials confirmed that there is no record to document that the air pressure measurements are periodically reviewed to assure that the appropriate air pressures are maintained during the routine aseptic operations. Note: the air pressure limits for the ISO-5 clean room and ISO-7 ante-room are summarized on the yellow color posted note.

**Observation 8 Response:** We agree to increase documentation of pressure monitoring logs to twice a day and perform weekly oversight reviews of these logs.

**Time Line:** The increase of documentation of the pressure monitoring logs began 11/18/13. Review of these logs will begin 11/22/13.

### **Observation 9**

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

a) There is no HVAC equipment qualification and/or document regarding the validation of the air handling system (HVAC) and ISO-5 airflow cabinets that are used in support of the aseptic operations performed in the ISO-5 airflow cabinets, ISO-5 clean room and the ISO-7 ante-room.

**Observation 9 Response:** See observation 7.A. and 7.B. response.

### **Observation 9**

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

b) Magnehelic gauges are used to monitor the air pressure differentials between the room classifications areas (i.e., ISO-5, ISO-7 and ISO-8). The Manager of Quality Control and Clinical Trials confirmed that the magnehelic gauges are not, and have not been, calibrated to a reference standard.

**Observation 9.A. Response:** Magnehelic gauges have been calibrated by Technical Safety Services, Inc. on 11/14/13. See **attachment 24** for calibration records of the anteroom, buffer room, and negative pressure room.

**Time Line:** Completed.

### **Observation 9**

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

c) The Manager of Quality Control and Clinical Trials confirmed that there is no standard operating procedure that establishes the monitoring of air pressure differentials between the ISO classified areas on a routine base.

**Observation 9.C. Response:** See observation 8 response. In addition, SOP 3.010 Sterile Compounding Area Requirements shall be updated to include this activity to be formally documented.

**Time Line:** SOP 3.010 update, employee training, and appropriate change control/review documentation shall be completed by 12/20/13.

### **Observation 10**

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

a) The “Cleaning and Maintenance of the Clean Room Facility” document #3.020, version 2.0, dated 7-08-13 “establish requirements and documentation for cleaning and maintenance of the clean room facility”, which requires the use of a variety of cleaning solutions e.g., 2% acidified bleach, Sterile 70% IPA, Vesphene and/or LpH. And, a “minimum contact time of 5 minutes is recommended for maximum disinfection efficacy when using bleach.” However, there is no record to document the preparation and/or calculations that are performed when preparing the Vesphene and/or LpH sanitizing solutions and the Compounding Director and Pharmacy Technician confirmed that there is no record to document the “5 minutes recommended for maximum disinfection efficacy.”

**Observation 10.A. Response:** This cleaning activity has been outsourced to Cleanroom Cleaning Services (CCS). Discussions are in progress with obtaining and documenting these formulations and efficacy studies. See **attachment 25** for an e-mail demonstrating these activities to improve are in progress.

**Time Line:** Documentation and proceduralized activities shall be completed by 12/20/13.

### **Observation 10**

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

b) The “Handling of Cytotoxic or Hazardous Drug Compounds” document #7.010, version 1.0, written date 04-12-06 is to “establish guidelines for the handling of cytotoxic or hazardous drug spills in a safe and efficient manner.” However, the standard procedure has not been reviewed and approved by the Quality Unit.

**Observation 10.B. Response:** We recognize this is a system observation. This SOP and all SOPs shall be appropriately reviewed, approved, with necessary formal documentation and employee training performed.

**Time Line:** This process is in progress for upgrading the entire SOP system. Completion of these activities is scheduled for 01/20/14.

### **Observation 10**

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

c) The “Handling of Cytotoxic or Hazardous Drug Compounds” document #7.010, version 1.0, dated 3-01-09 “establish guidelines for safe handling of cytotoxic or hazardous drugs.” The standard operating procedure does not contain any language with respect to the use of decontamination solutions (e.g., sodium hypochlorite 2% and/or sodium thiosulfate 0.9% with benzyl alcohol) for cytotoxic drugs.

**Observation 10.C. Response:** See observation 10.B. response. We recognize this is a system observation. SOP 7.010 along with all SOPs shall be appropriately reviewed, approved, with necessary formal documentation and employee training performed.

**Time Line:** This process is in progress for upgrading the entire SOP system. Completion of these activities is scheduled for 01/20/14.

### **Observation 10**

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

d) The Manager of Quality Control and Clinical Trials confirmed that they do not have any records to document efficacy studies for the Vesphene, LpH, 70% Isopropyl alcohol, sodium hypochlorite 2% and/or for the sodium thiosulfate 0.9% with benzyl alcohol.

**Observation 10.D. Response:** See observation 10.A. response. See **attachment 25** for e-mail communication that this activity is in progress.

**Time Line:** Scheduling of these activities shall be defined by 12/20/13.

### **Observation 10**

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

e) Mitomycin USP Powder is weighed on an analytical balance that is within a small enclosure (something akin to a hood) with air exhaust vented to the outdoor environment.

The mitomycin powder is hand carried (via a small weigh boat) to the ISO-7 ante-room (preparation and personnel gowning area) and subsequently transferred to the ISO-5 hood in the ISO-5 negative room. There is no record to document that the aforementioned areas are decontaminated with an appropriate cytotoxic decontamination solution.

**Observation 10.E. Response:** Containers to enclose these materials during transportation from the weighing hood through to cleanroom use have been purchased, see **attachment 26**.

In addition, documentation of the areas with appropriate decontaminating solution shall be performed after the operation.

We are also in the process of performing swab sampling of the areas for the presence and level of (qualitative and quantitative) these hazardous substances with an outside contract service.

**Time Line:** Purchase of enclosed containers for transporting is completed.

Documentation of decontaminating the areas shall, along with appropriate SOP improvement and employee training, be completed by 01/20/14.

Swab sampling activities and analyses of these swabs by an outside contract service is scheduled for completion by 01/20/14.

### **Observation 10**

Written procedures are lacking for the use of fumigating agents and cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, and drug products.

f) The October 5, 2013 Protocol regarding “Ionized Particle Fogging” provides a plan “to reduce the level of potential bioburden in the cleanroom areas that cannot be effectively addressed through conventional manual cleaning methods after a maintenance shutdown. The fogging will provide Leiters with an opportunity to decontaminate their Sterile room. The project occurred on October 5, 2013.” Hydrogen peroxide (vaporized H<sub>2</sub>O<sub>2</sub>) was used during the 20 minute decontamination process. There is however no record to document that the number of chemical indicators (CI) that were used and/or identification of the CI locations (more difficult areas/locations to decontaminate) and/or a record to document the efficacy [e.g., use of Biological Indicators (BI)] of the VHP.

**Observation 10.F. Response:** Activities for improvement of this operation are in progress with the outside contract service, CCS. See **attachment 27** for an e-mail demonstration of coordinating this activity.

**Time Line:** Scheduling of this activity to be completed is planned for 12/20/13.

### **Observation 11**

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in characteristics of in-process material and the drug product.

a) The “Avastin Processing Procedure” document #12.0, version 3.0, dated 4-26-13 establishes that Avastin vials “are stable at 2 °C-8 °C (36 ° – 46 ° F). Avastin vials shall be protected from light. Do not freeze or shake. Store vial in the original carton until time of use.” Despite the establishment of the aforementioned temperature and controls there is no standard operating procedure that establish quality control conditions for the shipment of the test materials from San Jose, CA, to the contract test laboratory located in St. Louis, MO.

**Observation 11.A. Response:** We agree to ship test materials to private laboratories under the same conditions as we would ship finished product to customers. Training for this requirement was completed on 11/15/13, see **attachment 28** for a copy of this training document. In addition, shipping logs are maintained documenting that the shipment was sent under ice and via priority overnight, see **attachment 29**.

**Time Line:** Completed.

### **Observation 11**

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in characteristics of in-process material and the drug product.

b) There is no record to document that the test materials (i.e., Sterility Tests samples, EM samples, Media fills vials) are shipped under temperature controlled conditions (e.g., 2-8 °C or room temperature)

**Observation 11.B. Response:** See observation 11.A. response.

**Time Line:** Completed.

### **Observation 11**

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in characteristics of in-process material and the drug product.

c) There is a document entitled “Leiter’s Pharmacy Refrigerated shipping validation” dated 4/6/09. There is however, no corresponding protocol or report to describe for example the purpose, scope, shipment procedure, Quality Control conditions and/or the establishment of the acceptance criteria with respect to the shipping conditions. In addition, there has been no evaluation performed to determine that the shipment conditions do not negatively affect the test materials and/or negatively impact the Quality Control tests.

**Observation 11.C. Response:** We commit to observation 11.A. and 11.B. responses above. These shipping conditions as used for finished product shipped to customers shall be maintained for the shipping of test materials to private laboratories for analyses. We also commit to performing a review of these shipping conditions for impact to product quality and formalize this review process.

**Time Line:** This review process and evaluation of shipping conditions shall be completed by 01/20/13.

### **Observation 12**

The building lacks adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, in-process materials, and drug products and to prevent contamination.

a) The ISO-7 personnel ante-room is used as a material transfer and storage area as well as a gowning room for personnel to don the sterile gowning attire. However, the approximate 50 ft.<sup>2</sup> space is insufficient to that there is no manner with which personnel can don their sterile attire without coming into contact with non-sterile attire and/or contaminated areas.

**Observation 12.A. Response:** We have taken this opportunity to improve the direction in SOP 9.100 Required Garb for Cleanroom Facility Access, section 9.0, to define a line of demarcation, see **attachment 17**. We have also taken this opportunity to increase garb instruction as described in above observations relating to the garb process.

**Time Line:** This demarcation and SOP 9.100 update, along with instruction to operators has been completed. Formalized documentation and employee training records shall be completed by 12/20/13.

### **Observation 12**

The building lacks adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, in-process materials, and drug products and to prevent contamination.

b) There are five airflow cabinets (two horizontal and three vertical airflow hoods) that are used to provide and ISO-5 environment for the aseptic operations. The ISO-5 room (approximate 150 – 200 ft.<sup>2</sup>.) also contains a Lyophilizer and dry heat sterilizer. During routine operations there can be up to five technicians performing aseptic operations. The ISO-5 area has insufficient space to perform the aseptic operations.

**Observation 12.B. Response:** We have taken the opportunity to create a second shift of cleanroom operations to limit personnel in the cleanroom areas. We have now limited cleanroom operators to number no more than four operators at one time. We feel this limitation of personnel at one time works in conjunction with the dynamic studies we conducted and demonstrated in above observations that dynamic operations with five personnel met ISO 5 requirements. In addition, we wish to state that lyophilization

activities are not occurring and no plans for this operation are scheduled for anytime in the future based on a lack of lyophilized product orders.

**Time Line:** Limitation of cleanroom operators to four is completed. Dynamic studies with five personnel are completed. Implementation of a second working shift is scheduled for no later than 01/20/14.

### **Observation 13**

Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically, we observed white color paint either peeled and/or rubbed off from the front and sides of the ISO-5 airflow cabinets and on the cabinet's supports.

**Observation 13 Response:** We acknowledge the condition of the hood as needing refinishing. We wish to state that the paint has faded, but no flaking is occurring. We also wish to reference the dynamic study performed and documented above included this equipment and personnel and demonstrated ISO 5 environments. We commit to refinishing and/or replacing these hoods and stands.

**Time Line:** Refinishing and/or replacement of the hood and stand shall occur during the facility move out to Great Oaks, San Jose, CA during the first quarter of 2014.

### **Observation 14**

Written calibration procedures for instruments, apparatus, gauges, and recording devices are deficient in that they do not include specific directions, schedules, limits for accuracy and precision, and provisions for remedial action if limits are not met.

Specifically, the Dapriprazole HCL process specifies subfreezing shelf temperatures ( $^{\circ}\text{C}$ ) with defined vacuums (mBar) for a specified amount of time. However, there is no record to document that the monitoring devices for the aforementioned lyophilization parameters have been calibrated to a reference standard.

**Observation 14 Response:** We commit to performing calibrations of the lyophilizer instrument. We wish to state that no Dapriprazole lyophilization operations are being performed nor are any scheduled in the future due to a lack of product orders.

**Time Line:** Calibration of the lyophilizer instrument is scheduled for 12/13/13, see **attachment 30** for e-mail documentation of this service by Al-Tar Services, Inc.

### **Observation 15**

The master production and control records are deficient in that they do not include a statement concerning any calculated excess of component.

Specifically, Avastin (bevacizumab) is repackaged from Genentech's finished product vial into 1cc T.B., sterile syringes. The Compounding Director and a Pharmacy Technician confirmed that not all of the 1cc sterile syringes of Avastin are identified (e.g., quarantine, approved) and accounted for in the batch records.

**Observation 15 Response:** We commit to improving the documentation to account for all products, not just bevacizumab. Formula Worksheet (lot production) volume shall be tracked through quarantine, private laboratory testing, dispensing, and final destruction.

**Time Line:** Improvement to the destruction of bevacizumab has been completed. Tracking shall include lot number, volume, and reason for destruction to complement accountability of units produced. See **attachment 31** for an example of destruction documentation that shall be maintained to complete product volume accountability.



CHARLES LEITER

Charles Leiter, President, Leiter's Compounding Pharmacy