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

Re: Posting of FDA Form 483 Response

FEI: 3003434972, Leiter's Compounding Pharmacy
EI: 02/18/2014 – 03/06/2014

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 03/25/2014, 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 03/06/2014, by CSO's Lac (SAN-DO) and Lau (SAN-DO).

Thank you,

Paul K. Yamamoto, R.Ph., Vice President of Operations
Leiter's Compounding Pharmacy
1700 Park Ave., Suite 30
San Jose, CA 95126
Tel: (408) 292-6772

Hard copy to:
US FDA, San Francisco District Office
ATTN: Kay Lewis, SAN-DO District Director
1431 Harbor Bay Parkway
Alameda, CA 94502

CC electronic copy to:
US FDA, San Francisco District Office
ATTN: Anh Lac, SAN-DO Consumer Safety Officer
1431 Harbor Bay Parkway
Alameda, CA 94502

CC electronic copy to:
US FDA, San Francisco District Office
ATTN: Henry Lau, SAN-DO Microbiologist
1431 Harbor Bay Parkway
Alameda, CA 94502

3/26/14,

Responses to Form FDA 483 Inspectional Observations as issued on 3/06/14 by US FDA Investigator Anh Lac and Microbiologist Henry Lau at Leiter's Compounding Pharmacy located at 1700 Park Ave, San Jose, CA 95126:

Observation 1

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

a) The sterility testing performed by the contract laboratory consists of: Aerobic and Anaerobic Bacteria, and Fungi (Mold and Yeasts). Your firm provided no data to demonstrate that the test method is suitable for your sterile drug product, Brilliant Blue G D20 0.025%. In addition, the Certificate of Analysis from your contract laboratory indicates that the sterility testing "does not meet all the requirements for sampling and/or method suitability specified in USP <71>" which ensures that specific product tested for sterility did not give false negative result due to product inhibition.

Observation 1.A. Response:
Leiter's is now in the process of initiating analytical validations from contract laboratory services for demonstration that the release test method is suitable for sterile products in order to assure that false negative results are not reported. This process involves evaluating costs for the analytical tests being validated. We are scoping the products and the required testing for each product type, such as potency, sterility, endotoxins specifications, stability, etc.

Time Line: A teleconference was held with the contract servicing laboratory on 3/20/14 to discuss these services and associated costs. After this teleconference, information obtained will be evaluated by Leiter's management and a determination to apply this information will be decided by 4/30/14.

Observation 1

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

b) Your firm has not established the specification for endotoxin product release testing for Brilliant Blue B D20 0.025%. According to your Laboratory Manager, as long as the associated Certificate of Analysis is provided from the contract laboratory, the finished product lots are approved and released for distribution irrespective of the endotoxin test results. She stated that she assumes the contract laboratory would only send Certificates of Analysis with acceptable results.

Observation 1.B. Response: See Observation 1.A. response. This lack of endotoxin release specifications is only for products that do not have an established USP monograph, such as unapproved new drugs like Brilliant Blue. In addition, Leiter's is currently in the process of evaluating the maximum patient dose in a 24 hour period for these product types to be utilized in the USP <85> calculation for endotoxin limits as determined by Leiter's Pharmacists utilizing standard medical practices. Leiter's contract laboratory has already agreed to utilize this information for all products lacking endotoxin limit USP monographs.

Time Line: See Observation 1.A. time line.

Observation 2

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

a) Your firm's SOP 2.030 Sterile Compounding Personnel Qualification, version 1.0, effective date 3/01/09, requires each employee shall be evaluated on his or her designated aseptic process a minimum of every six months. During the review of your firm's media fill personnel qualification for the Baxa Repeater Pump operation, one operator has not been qualified for the Baxa Repeater Pump operation.

Observation 2.A. Response: We agree to increase media fill qualifications for each operator to include all processes that an operator may be performing. Leiter's performs three different operation types:

1. Syringe repackaging
2. Baxa Repeater Pump vial filling
3. Eye dropper container filling via syringe

An operator may be requested to perform a different process due to availability of operators that particular day. Due to this operator availability, going forward, each

operator shall perform two media fill types to always include the eye dropper container filling via syringe and either the syringe repackaging or the Baxa Repeater Pump vial filling process. All operators may perform the eye dropper container filling. Operators shall perform either the syringe repackaging or Baxa Repeater Pump operation as operators are assigned one process or the other based on needs. Should an operator be deemed to perform an operation that an established media fill is not documented, that media fill process shall be performed prior to the operation being performed for released finished product.

In addition, SOP 2.030 Sterile Compounding Personnel Qualification, version 2.0, effective date 03/05/14, has been reviewed, see **attachment 1**, and training has been completed, see **attachment 2**.

Time Line: Media fill schedules are in place for each operator, see **attachment 3**.

Observation 2

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

b) Your fim's SOP 9.200 Baxa Repeater Pump Media Fills (Aseptic Process Validation), 1 L Filled as 1 ml, version 1.0, effective date 7/17/13; requires media fills to be conducted in the same manner and same quantity as product would be with the Baxa Repeater Pump. The media fill qualification records do not document the identification of the hood used for the non-dedicated Baxa Repeater Pump that can be moved and used in any of the five ISO 5 hoods that are stationed in the cleanroom and none of the records documented the number of operators that worked in the cleanroom at the time of the media fill. According to your management, four operators are allowed in the cleanroom at the same time.

Observation 2.B. Response: In contradiction, Baxa Repeater Pump instruments are dedicated to the cleanroom and operation. Currently, two Baxa Repeater Pump instruments are in use in Leiter's cleanroom:

1. Pump serial number 03181 is located in the negative pressure room for use in only the negative pressure room.
2. Pump serial number 02528 is located in the positive pressure room for use in only the positive pressure room.

In addition, Formula Worksheets for respective media fills are now updated to document the number of operators present in the cleanroom during the process.

Observation 3

Written production and process control procedures are not followed in the execution of production and process control functions.

a) Your firm's SOP 3.030 Environmental Monitoring of the Cleanroom Facility, version 4.0, effective date 01/10/14, section 9.5.2.1, states that the surface sampling of Class 100

(ISO 5) hoods shall be taken with each compounding assignment daily. During review of your environmental monitoring program, surface sampling of the direct sterile compounding area and fingertips were not performed on 01/28-31/14 and 02/6-7/14, due to lack of TSA contact plates in stock. Brilliant Blue G D20 0.025%, lot 01292014@11 was filled on 01/31/14.

Observation 3.A. Response: Procurement of surface sampling media is in the qualification stage to understand quantities used per week to eliminate running out of media as we have increased this monitoring activity. We have established a weekly order with the supplier and will continue to monitor appropriate availability. See **attachment 4** for a copy of the media invoice.

Time Line: This service has begun.

Observation 3

Written production and process control procedures are not followed in the execution of production and process control functions.

b) Your firm's SOP 9.100 Required Garb for Cleanroom Facility Access, version 2.0, dated 11/18/13, section 10.1, outlines personnel must remove all makeup and jewelry prior to entering the laboratory facility. During the inspection on 02/18/14, one operator in the cleanroom was observed to have eye make-up without eye covers while filling sterile injectable drug product, PAP 12mg/Prost 10mcg/ml, lot 02182014@1.

Observation 3.B. Response: An interview was held with the operator at COB 02/18/14 and it was observed and determined that the operator was wearing eye lash extensions, no eye or facial make-up. Discussions with the operator clarified that no accessories are to be worn in the cleanroom. The operator understood. This assessment was documented and provided to CSO Lac on 02/19/14.

1. SOP 9.100 was revised in section 9.1.1 to include "no accessories" are allowed in the cleanroom. Training was provided to all operators for this update on 03/20/14.
2. Particle counter data was reviewed for 02/18/14 and all particle readings were recorded as zero counts.
3. Product lot 02182014@1 was analyzed for sterility and reported passing by our contract laboratory. In addition, eight aseptic lots total were produced on 02/18/14, including one additional lot by the same operator, lot 02182014@2, and all aseptic product lots were reported as passing for sterility by our contract laboratory.
4. This operator in question has never had a product lot fail sterility testing.

Time Line: Completed.

Observation 4

Failure to reject any lot of components that did not meet the appropriate written specifications for identity, strength, quality, and purity.

a) Your firm manufactured and distributed six lots of Brilliant Blue G D20 0.025% using the expired raw ingredient, Sodium Phosphate Monobasic Monohydrate, lot 132517, exp 6/01/13.

Observation 4.A. Response: An assessment of this expired inactive ingredient use was performed and provided to CSO Lac during the inspection. It was determined that the expiration of this inactive ingredient was extended back in 6/2012 for three years using USP guidance. This expiration extension has been eliminated in operations at Leiter's. All ingredients will maintain C of A's with the manufacturer's expiration. Should an ingredient not have a manufacturer's expiration date upon receipt, Leiter's shall assign one year expiration from the date of opening as per SOP 6.010, section 9.3.3.

The assessment provided to CSO Lac determined that the finished product is a diagnostic staining agent, not a therapeutic product. The assessment also determined that the expired inactive ingredient, Sodium Phosphate Monobasic Monohydrate, is utilized as a pH buffering agent at a minimal amount per formulation. All lots utilizing this inactive ingredient are pH checked prior to release and met the pH specification of 7.5 $\pm$0.2. The expiration date of the finished product has been assigned six months. Leiter's maintains one lot of this product, lot 01292014@11, and immediately performed a pH check on finished vials and determined the pH specification is still being met on 02/26/14. A second pH check on 03/20/14 was performed and the pH specification is still being met. See **attachment 5** for this second pH vial check.

Leiter's agreed to cease dispensing of lot 01292014@11 on 02/25/14, see **attachment 6**.

In addition, further review of materials in Leiter's inventory identified one other ingredient that was expiration extended but that material was never opened and the safety seal was intact, therefore never used. This material was destroyed to prevent use.

Time Line: Completed with the pH checks of lot 01292014@11 continuing monthly through the expiration of the product, 7/29/14.

Observation 4

Failure to reject any lot of components that did not meet the appropriate written specifications for identity, strength, quality, and purity.

b) Your assessment, Review of Impact of Utilizing Sodium Phosphate, Monobasic, Monohydrate, in the formula ID 10662 Brilliant Blue, in six lots produced in 2013 after 6/01/13, dated 02/20/14, is deficient for failure to perform comprehensive investigation as well as extend the investigation to other products. You have not assessed the quality impact of the Beyond Use Date for the Brilliant Blue G D20 0.025% product that used

the expired raw ingredient. You disposed the expired Sodium Phosphate Monobasic Monohydrate lot 132517 without further testing.

Observation 4.B. Response: Included with the product assessment impact to CSO Lac during the inspection, a review of all product lots utilizing the expired inactive ingredient was performed and determined to not have been utilized in any other product formulation(s). Therefore, no other product lots have been impacted by the use of this inactive ingredient.

All complaints have been reviewed since 01/2013 and no complaints for this product have been received by Leiter's outside of the one complaint that initiated Leiter's to submit a MedWatch and therefore trigger this inspection.

The expired, inactive, raw material was destroyed to prevent any further use of the material in formulations. Leiter's does not see the value in testing the raw material as pH testing of the actual finished product lot is in progress for the appropriate functionality of the inactive raw material, a pH buffering agent. To date, the finished product lot is still meeting the pH specification.

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, but not limited to the following, your firm has never performed finished product potency testing on Brilliant Blue G D20 0.025%. Between 11/11 and 01/14, 14 lots of Brilliant Blue G D20 0.025% manufactured and distributed by your firm were not tested for potency.

Observation 5 Response: We agree to increase potency release testing of finished products. See Observation 1.A. response in that discussions with our private laboratory are in progress to increase analytical testing and validations.

Time Line: See Observation 1.A. time line response.

Observation 6

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

Specifically, your firm has no scientific data to justify the assigned Beyond Use Date for 180 days at room temperature for your preservative free sterile drug product, Brilliant Blue G D20 0.025%.

Observation 6 Response: We agree to increase stability testing of Leiter's finished drug products.

Time Line: See Observation 1.A. time line for discussions with our private laboratory and Leiter's assessment and implementation of these services.

Observation 7

Reserve samples for drug products are not retained for one year after the expiration date of the drug product.

Specifically, your firm does not maintain retention samples for any finished drug products intended For Office Use and anticipatory dispensing. In addition, your firm has not established a written protocol for retention samples.

Observation 7 Response: We agree to maintain retention samples for finished drug products intended For Office Use and anticipatory dispensing at 5% of the finished batch size. This activity is reflected in SOP 9.060, version 3.0, section 9.5, with the effective date of 3/18/14, see **attachment 7**.

Time Line: SOP 9.060 shall be reviewed, updated, with employee training, and appropriate documentation generated by 4/30/14.

Observation 8

Actual yield and percentages of theoretical yield are not determined at the conclusion of each appropriate phase of manufacturing of the drug product.

Specifically, your firm does not perform calculations for theoretical and actual yields for finished products. Your established batch yield limit of $\pm$ 10% does not require investigation when excursions occur.

Observation 8 Response: As with all Leiter's processes, compounding is a manual process that may have some variability based on operator technique and loss of product in the dispensing instruments. As far as this Observation being specific to Brilliant Blue, Leiter's is taking this Observation as a systems observation and addressing across the board for all Baxa Repeater Pump operations (vial filling). Prior to this Observation, the Baxa Repeater Pump speed setting for dispensing solution into vials was allowed to be set by the operator based on their experience and ability to fill vials at that selected speed. This created yield variability per operator as the speed setting effects yield as per the manufacturer's instruction manual. Leiter's has taken this opportunity to standardize the Baxa Repeater Pump speed setting to the manufacturer's recommendation of "Low 1-3" to minimize variability that is caused by the speed setting for all Baxa filling operations. This speed setting standardizing shall provide Leiter's the ability to further evaluate yields based on this information of variability. See **attachment 8** for SOP 4.110, version 2.0, section 9.1.11.

Time Line: Completed.

Observation 9

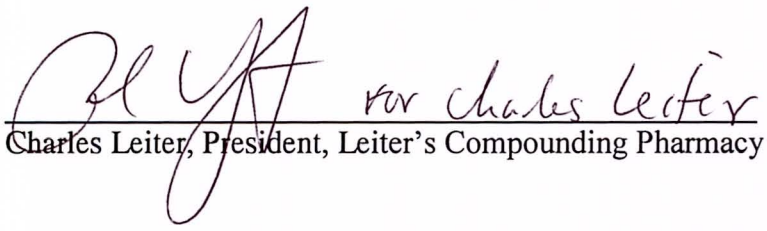
The Master production and control records are deficient in that they do not include complete manufacturing, control, and instructions.

a) Your firm does not consistently document the name/lot number including but not limited to equipment used in the processing of your sterile finished drug product, Brilliant Blue G D20 0.025%.
b) The Formula Worksheet for Brilliant Blue G D20 0.025% does not include the complete step by step instructions for operators to perform the manufacturing process.

Observation 9.A.&B. Response: We have taken this opportunity to improve Formula Worksheet documentation of:

A. Equipment utilized
B. Time performed
C. Identify who performed each step
D. Identify the working hood
E. Improve step by step directions

Time Line: Completed for Brilliant Blue, see **attachment 9**. This Formula Worksheet review and upgrade is in progress for additional products. See **attachment 10** for training record on SOP 9.040 Formula Worksheets.



Charles Leiter, President, Leiter's Compounding Pharmacy