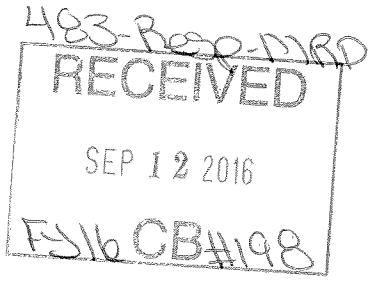

RE: FDA Disclosure of 483 Response on FDA's Website
LaTonya Mitchell
Denver District Director
Matthew Dionne
HFR-SW200
Denver District, (DEN-DO)
6th Ave & Kipling St. (P.O. Box 25087)
Building 20,
Denver Federal Center,
Denver, CO 80225-0087

Dear Mr. Matthew Dionne
Dear Mrs. LaTonya Mitchell

I understand that it is the policy of the United States Food and Drug Administration (FDA) to publish Form 483 Reports issued to compounding pharmacies to its webpage entitled, "Compounding: Inspections, Recalls, and other Actions." I request that the FDA ***not*** publish our 483 on this webpage at any point in the future.

In case you elect not to honor my request, then on behalf of Maple Rose Enterprises, Inc., doing business as Pencol Compounding Pharmacy, I request the FDA to publicly disclose my responses to each observation listed on the Form 483 that appears on our Response Letter below. I understand that the information 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 U), and 5 U.S.C. § 552(b)(4) and, as such, would be exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I hereby agree to hold FDA harmless for any injury caused by FDA's publishing the information to the public.

Information to be disclosed: Maple Rose Enterprises' letter dated September 12, 2016, which responds to FDA's Form 483 issued on August 22, 2016.

Authorization is given to the FDA to disclose the above-described information, which may include said commercial, financial, or trade secret information. As indicated by my signature, I am authorized to provide this consent on behalf of Maple Rose Enterprises and my full name, title, address, telephone number, and facsimile number is set out below for verification.

Respectfully,

Tony E. Jones, R.Ph.
Pharmacy Manager
Maple Rose Enterprises, Inc. (DBA Pencol Pharmacy)
Telephone Number: 303.388.3613
Facsimile Number: 303.388.6182

September 12, 2016

Matthew Dionne
FDA Denver District, (DEN-DO)
6th Ave & Kipling St. (P.O. Box 25087)
Building 20,
Denver Federal Center,
Denver, CO 80225-0087

Attn: LaTonya M. Mitchell (District Director)
Zachary L. Miller (Investigator)
Zachary A. Bogorad (Investigator)
Michael E. Maselli (Microbiologist)

Between August 8 and August 22 of 2016, the Denver District of the United States Food and Drug Administration (FDA) undertook an inspection of the pharmacy (Maple Rose Enterprises, Inc., doing business as Pencol Compounding Pharmacy at 1325 South Colorado Boulevard, Denver, CO 80222. We were not told whether this inspection was undertaken "For Cause" or as a routine matter. At the end of the inspection we were issued an FDA Form 483, which included ten (10) Observations.

Pencol is a pharmacy, not a drug manufacturer. Pencol is duly licensed by the state of Colorado as a "Prescription Drug Outlet- In-State," (License Number: PDO.1680000087). Pencol is governed by the laws of Colorado and is subject to the rules and regulations of the Colorado Board of Pharmacy. Pencol's license is in Good Standing with the Colorado Board of Pharmacy and has never been subjected to discipline or to Board Actions. Pencol was most recently inspected by the Colorado Board of Pharmacy on April 26th 2016 and received no violations.

Pencol does not ship compounded preparations across state borders and we believe that we do not participate in interstate commerce. Nothing said by the FDA inspection team implied that the Agency believes we participate in interstate commerce.

Pencol is aware of General Chapters <795> and <797> of the United States Pharmacopeia and attempts to practice in conformance with most of their provisions, however the Colorado Board of Pharmacy requires conformance only with certain very specific provisions of those chapters.

Pencol believes that the FDA Inspection team made its observations based on the standards of Current Good Manufacturing Practices (cGMP) rather than the standards of the USP or the standards of the Colorado Board of Pharmacy. There are a great number of material differences between cGMP and current professional compounding standards.

Pencol recognizes that:

- FDA has an important role in protecting the health and welfare of the American public and that it received a great deal of undeserved blame for the Fungal Meningitis Outbreak of 2012;
- FDA inspectors are trained to enforce 21CFR 210 and 211 and are not trained in the less rigorous state regulations and professional standards that govern the traditional practices of pharmacists, physicians, veterinarians, dentists and optometrists;
- FDA feels a responsibility to compel health care professionals and hospital organizations to meet more rigorous standards than they currently do

Although Pencol does not believe that cGMP is the current standard to which health care practitioners are held, nor that it should be, this does not imply that the Observations recorded by the FDA investigators

should be discounted or ignored. Pencol intends to address the issues detailed in the Observations as follows:

Facilities and Equipment System

Observation 1:
Buildings used in the processing of a drug product are not maintained in a good state of repair. The firm's ante room as well as clean room where the ISO 5 laminar air flow workbench and biosafety cabinet are located have not been maintained in a good state of repair.

i. A ceiling tile in the positive pressure room was observed to be pushed into the ceiling space creating a ¾ inch gap on one side. The tile is located directly above and one tile to the right of the LAF.
ii. Just above the ante-room pass through, the west wall of the ante-room had the outer paint/paper layer of missing drywall exposing a 2"x 3/4" oblong shape.

Response to Observation 1.i
While doing our monthly terminal clean the technician accidently pushed up a tile approximately ¾ of an inch. The correction was made within 24 to 48 hours of the inspector bringing the issue to our attention.

Response to Observation 1.ii
A hook that holds our smocks and is used while changing in the Ante Room, was unintentionally pulled off the wall, leaving an exposed oblong shape of approximately 2''x 3/4 inches. This correction was made within 24 to 48 hours of the inspector bringing it to our attention.

Observation 2:
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Environmental monitoring is never conducted during aseptic filling operations in order to give information on the quality of the aseptic processing environment.

i. Dynamic particulate monitoring is never performed.
ii. Dynamic viable air sampling has not been performed prior to August 2016.
iii. Passive air sampling is never performed.
iv. Pressure, temperature, and humidity monitoring devices installed in each clean room of the suites are not monitored or recorded during sterile operations. Pressure devices are not monitored during sterile operations. Although the data is recorded electronically, the data files have never been utilized due to software malfunctions.

Response to Observation 2:
Appropriate action has been taken with a medical equipment management service as of 9/08/2016. There are recorded videos demonstrating aseptic filling operations alongside a particulate counting instrument. In addition to our regular practices of daily fingertip glove testing, daily surface sampling of areas inside the laminar flow hood and biological safety cabinet, and daily viable air sampling, we have now added daily passive air sampling as part of our routine.

We took appropriate steps to have our pressure, temperature, and humidity monitoring devices software replaced during the week of the FDA visit. The malfunctioning electronic devices were installed this year as a redundant system to support the analogue pressure, temperature, and humidity monitoring devices.

Observation 3.
Routine calibration, inspection and checking of mechanical and electronic equipment is not performed according to a written program designed to assure proper performance. Equipment used to ensure the

quality, strength, and purity of drug substances are not calibrated. All drugs manufactured on site are manufactured using a scale and are stored in a space monitored for temperature and humidity.

i. Ongoing calibrations of 14 analytical scales used to measure ingredients and finished drugs in the non-sterile pharmacy were not maintained between 2/5/16 and 8/8/16.
ii. Calibration has never been performed for the analytical scale located in the sterile clean room. This scale is used to weight raw materials.
iii. Temperature, humidity, and pressure monitoring equipment including the Holland Safety Equipment door monitoring pressure system and magnahelic analog pressure gauge calibrations have never been performed.
iv. The Millipore pressure gauge used to perform sterile filter integrity testing after manufacturing has never been calibrated. More than 75% of sterile drugs manufactured on site require sterile filtration. Approximately 30% of drugs manufactured on site are sterile.
v. Temperature monitoring devices built into the sterility testing media incubator and environmental sample incubators have never been calibrated.
    a) Binder Incubator HSS#0032681-surface and personnel sample storage
    b) Boekel Scientific Incubator HS#0012813-anaerobic sample storage
    c) Boekel Scientific Incubator Model 133000-aerobic sample storage
    d) Quincy Lab Model 10-140- active air sample storage

Response to Observation 3.
The analytical scales were purchased and installed in August 2015. These scales were new and calibrated upon receipt. Our firm's SOPs require that we calibrate our scales yearly. The aforementioned scales were calibrated this year, August 2016, and during the investigator's visit, this documentation was provided.

Response to Observation 3.ii
The scale mentioned in this observation was purchased in August of 2015 and certified when installed. Our SOPs requires calibration yearly. We had this scale calibrated again in August 2016, while the inspectors were present, and provided a copy of the certificate.

Response to Observation 3.iii

We have taken the necessary steps to have the equipment calibrated the month of September 2016 and our SOPs' will indicate the monitors be calibrated yearly moving forward.

Response to Observation 3.iv

We had the equipment calibrated 9/8/2016 and have taken the necessary steps moving forward to have the equipment calibrated on a yearly basis.

Response to Observation 3.v

We had the equipment calibrated 9/8/2016 and have taken the necessary steps moving forward to have the equipment calibrated on a yearly basis.

Observation 4.
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting room and equipment to produce aseptic conditions.

i. The autoclave sterilization cycle has not been shown to be effective. The glassware sterilization cycle and load patterns have not been performed in at-use conditions. Equipment qualifications and load patterns have not been performed.
ii. Hand washing of multi-use equipment (beakers, stirrers, stirring rods) has not been shown to be effective.
iii. The firm failed to perform room disinfection with Spore-Klenz. Spore-Klenz sanitizer labeling requires an undiluted chemical contact time of 30 minutes. The sterile technicians stated that a 10-minute contact time is used for sporicidal treatment of the aseptic processing room and equipment surfaces.

Response to Observation 4

When disinfecting the room equipment, we first hand-wash our beakers, stirrers, metal spatulas with a surfactant to remove residue. We next autoclave the above equipment on an appropriate cycle to disinfect the equipment and include an autoclave indicator vial that includes *Geobacillus stearothermophilus* with each cycle to validate sterilization. Since your visit in August 2016, the autoclave was calibrated on 09/08/2016 by an independent contractor to ensure compliance. The autoclave was shown to pass temperature, time, and pressure standards. The recorded calibration values were run at 273 degrees Celsius and measured at 273 degrees Celsius, the cycle ran for 30 minutes and was measured at a 30-minute interval, and pressure was set at 31 PSI and was measured at 30.7 PSI.
Additionally, the directions for use for Spor-Klenz include sterilization, broad spectrum disinfection, fogging, germicidal disinfectant spray, cleaner/sanitizer, and use as a sporicide. Spor-Klenz is rotated through the monthly cleaning process at Pencol Compounding Pharmacy along with a bleach solution, and Virex solution. On the bottles of Spor-Klenz, a 10-minute contact time is written in black permanent marker for the purposes of broad spectrum disinfection. The directions for use of Spor-Klenz states that 10 minutes is the required contact time for broad spectrum disinfection. Our technician explained to the FDA examiner how it is used at Pencol, and indicated the marker written 10-minute contact time on the bottle. Further training will follow of aseptic processing of room and equipment surfaces.

Production System

Observation 5.

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

i. The firm does not perform a bubble point post-filtration integrity testing of the sterilizing filter.
ii. The firm has not conducted dynamic smoke studies in either cleanroom or the laminar-flow hood in service in cleanroom 1 or the biosafety cabinet in service in cleanroom 2.
iii. From 8/8/16-8/12/16 equipment used in the production of sterile injectables including glassware, utensils, and stir equipment was not processed in a way that eliminates pyrogens. The following sterile drugs were manufactured during the course of the inspection using non-depyrogenated glassware and utensils.
a) Methylcobalamin, Folic Acid Injection 1mg/ 0.4 mg/ 0.12 mL solution, lot MTFA2206, compounded 8/8/16
b) Methionine Inosital Choline with Hydroxocobalamin 25 mg/ 50 mg/ 175 mcg/ 1 mL solution, Lot MICH2236, compounded 8/11/16
iv. Validated sterility and bacterial endotoxin testing is performed only on products whose batch size is greater than 24 units. Approximately 5% of products have a batch size greater than or equal to 24 units. In conjunction with this, media used for sterility testing for products whose batch size is less than 24 units is not tested for growth promotion prior to use.

Response to Observation 5
Pencol has implemented the performances of bubble-point post-filtration integrity testing in place of testing the pressure capacity of the sterilizing filter.

Pencol Compounding Pharmacy has conducted dynamic smoke studies on 9/08/2016 that were recorded via video by an independent medical equipment management contractor for all ISO 5 level laminar flow hoods and biological safety cabinet.

Pencol has changed the procedure for depyrogenation of the equipment used in the production of sterile products. Compliance of depyrogenation will be in accordance to USP <797> guidelines. Additionally, Pencol has never exceeded bacterial endotoxins when compounded sterile products were submitted to an independent laboratory for microbial analysis. Lastly Pencol Compounding Pharmacy does not consider itself a manufacturer of compounded medication.

Observation 6.
Protective apparel was not worn as necessary to protect drug products from contamination. Specifically, on 8/8/16 sterile processing gowning material (hoods, suits, masks, and booties) were donned using non-gloved hands. Gowning was stored rolled up in an ante-room drawer, inside-out, for re-use. In conjunction with this, gowning materials do not completely cover skin. Exposed skin was noted around the face of the operator. At this time LOT MICH2206 of Methionine-Inositol-Choline-Hydroxocobalamin was being sterile filled and compounded.

Response to Observation 6
Pencol Compounding Pharmacy exceeds USP <797> standards for compounding pharmacies in regards to protective apparel. The apparel that is used daily includes sterile coverall suits, sterile shoe covers, sterile masks, and sterile hair bouffant caps, and protective eye wear. One set of sterile garb is worn daily by each technician and discarded at the end of each work shift. When the sterile garb is removed for later shift use during a single shift, it is stored inside out to reduce contamination. As observed by the FDA examiner, before donning the sterile garb, technicians scrub their hands and nails with a betadine scrub sponge and nail cleaner, and subsequently wash their hands with the broad-spectrum, extended bacteriostatic action, chlorhexidine gluconate. The sterile garb is donned with scrubbed and washed hands in accordance with USP <797> guidelines. Prior to compounding in an ISO 5 environment, sterile gloves are applied and sprayed with sterile alcohol to reduce possible bioburden. Additional training to avoid exposing skin around the temples will be employed.

Quality System

Observation 7.
The responsibilities and procedures applicable to the quality control unit are not in writing.

i. Procedures outlining the responsibilities of the quality control unit to approve or reject all components, drug containers, closures, in process materials, packaging material, labeling, and drug products have not been established.
ii. Procedures to approve and reject all procedures or specifications impacting the identity, strength, quality, and purity of drug products have not been established. There are no procedures for:
    a) The assessment of personnel qualifications or responsibilities
    b) Adequate buildings and facilities
    c) Equipment qualification, cleaning and maintenance
    d) Control of components, drug product containers, and closures
    e) Production and Process controls
    f) Packaging and Labeling controls

g) Holding and Distribution controls
h) Laboratory controls
i) Records and Reports
j) Complaint Handling
k) Returned and Salvaged Drug Products
l) Change Controls
m) Specifications for components, drug product containers, closures, packaging materials, and in-process materials

iii. There are no written procedures which describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, approval, and rejection of components, drug product containers, and closures.

Response to Observation 7.

Regarding the quality systems and procedures, our firm has Standard Operation Procedures in place, and we are currently in the process of enhancing them. Our ongoing plans should make our firm more compliant, as we convert from a manual to electronic system. We will have the new SOPSs fully implemented by the first quarter of 2017. The SOPSs and template will allow Pencol Compounding Pharmacy to be more compliant than what is currently required by <795> and <797>, while implementing the responsibilities and qualifications discussed in Observation 7. Onward plans and implications were mentioned to the investigators throughout the course of their assessment.

Observation 8.

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

i. The firm's beyond use date (BUD) is not based upon completed stability studies. There is no sterility program than 1) Establishes the number and size of batches to be tested, 2) addresses accelerated studies and test intervals, 3) speaks to storage conditions (e.g. store ambient in an upright position) and the integrity of the container closure system; and 4) specifies the testing attributes of the drug products that are susceptible to change during storage.

ii. There is no justification for only one batch being used to determine the BUD of all of the firm's sterile drug products. There is no BUD sterility data for any of the firm's sterile drug products-sterility is only performed on day 0. Additionally, there is no antimicrobial effectiveness testing data for any sterile drug products containing preservatives.
   a) Pumice 2.35mg/mL Lidocaine HCL 5 mg/mL injection has a BUD of 206 days. This BUD is based solely on an un-validated potency analysis of the active ingredient Lidocaine.
   b) Cardioplega Concentrate Injectable solution has a BUD of 96 days. This BUD is based solely on an un-validated potency analysis of the active ingredients: lidocaine, magnesium sulfate heptahydrate, mannitol, and potassium chloride.
   c) Methylcobalamin PF 25 mg/mL solution (dispensed in a syringe) has a BUD of 200 days. This BUD is based solely on a non-validated potency analysis of the active ingredient: methylcobalamin

Response to Observation 8

Pencol Compounding Pharmacy determines beyond use dates based on predefined time point studies using an independent laboratory. Compounding pharmacy sterility testing guidelines are based upon USP <797> guidelines, not cGMP commercial manufacturing standards. Independent sterility and endotoxin testing is done with batch sizes of at least 25 articles in accordance with USP <797> guidelines and Colorado State Board of Pharmacy guidelines. An additional testing program will be implemented to comply with this FDA 483.

Laboratory System

Observation 9
Each lot of a component, drug product containers, and closures liable to objectionable microbiological contamination is deficiently subjected to microbiological tests before use.
No procedures exist and your Lead Sterile Pharmacist confirmed that none of your components or drug product containers and closures are subjected to any microbiological testing or bioburden assessment, after receipt from supplier. No certificate of analysis is received or reviewed for any lot of incoming components.

Response to Observation 9
Pencol Compounding Pharmacy is a registered 503A compounding pharmacy and verifies all drug certificate analysis. This process was explained to the FDA examiner to show the calculation of activity weight that needs to be added to certain drugs. Pencol is a 503A pharmacy and is unaware of any Federal or state law that states a requirement for microbiological tests of drug product containers and closures. Pencol will look to have outside consultation to comply with this noted observation.

Observation 10.
Testing and release of drug product for all distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.
Not all of the firm's sterile products are released with testing for active ingredient identification and potency. Furthermore, it is undeterminable how many formulations have been shipped without identity and potency determinations as approximately 95% of manufactured drugs are patient specific.

i. The Tri-mix 30 mg/ 1 mg/ 10 mcg/mL (Papaverine, Phentolamine, Prostaglandin) finished drug product is dispensed without determining identification and potency of each active ingredient of the final product.

Response to Observation 10
As stated in Observation 10 from the FDA form 483, 95% of the medications compounded, not manufactured, at Pencol Compounding Pharmacy are patient specific. Colorado State Board of Pharmacy permits casual sales from a compounding pharmacy in the state of Colorado to, specifically, compound and distribute no more than 10 percent of the total number of drug dosage units the prescription drug outlet dispenses and distributes on an annual basis. An in-state compounding prescription drug outlet registered pursuant to CRS 12-42.5-118(15) (a), (b)(I) and (II). Drugs that are compounded as patient specific are not required to independently tested for determination of conformance to final specification of identity and strength of active ingredient by Colorado State Board of Pharmacy. As mentioned in the FDA form 483, the drug Tri-Mix had three drug components. Each of the three drug components were individually sent out for independent laboratory testing. These components are then combined to make a patient specified dose to be dispensed to the patient. In addition, every drug compounded at Pencol Compounding Pharmacy, is tested in-house for gram positive and gram negative bacterial growth for a 14-day time span.