September 6, 2016

RE: FDA Disclosure of 483 Response on FDA's Web Site

Arthur O. Czabaniuk
FDA Detroit District, (DET-DO),
300 River Place, Suite 5900,
Detroit, MI 48207

Dear Mr. Czabaniuk,

It is my understanding that it is the policy of the United States Food and Drug Administration (FDA) to publish Form 483s issued to compounding pharmacies on its webpage called, "Compounding: Inspections, Recalls, and other Actions." I would like to request that the Agency **not** publish our 483 on this website, as any such publicity could be unfavorable to our business.

If you are unable to refrain from publishing our 483 on the webpage, then on behalf of Rx Compounding, Inc, doing business as Nora Apothecary, I authorize FDA to publicly disclose the information in our Response Letter below on FDA's web site. I understand that the information that is disclosed may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C. § 1905, 21 U.S.C. § 331 U), and 5 U.S.C. § 552(b)(4) and that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I agree to hold FDA harmless for any injury caused by FDA's sharing the information with the public.

Information to be disclosed: Rx Compounding's letter dated September 6, 2016 which responds to FDA's Form 483 issued August 19, 2016.

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

Respectfully yours,

Antonios S. Kantzavelos, Pharm.D.
President and Owner
Rx Compounding, Inc. (DBA Nora Apothecary)
1101 E. 86th Street,Indianapolis, In 46240
Telephone Number: 317-251-9547
Facsimile Number: 317-251-9556

FDA CC System
Entry No: 5584

September 6, 2016

Arthur O. Czabaniuk
FDA Field Office, Detroit District
300 River Place, Suite 5900
Detroit, MI 48207

Attn: Arthur O. Czabaniuk (District Director)
Robert M. Barbosa (Investigator)

On 8/8/2016 through 8/12/2016, as well as on 8/16/2016 and 8/19/2016, the Detroit Field Office of FDA undertook an inspection of Rx Compounding, doing business as Nora Apothecary, at 1101 East 86th Street, Indianapolis, IN 46240. Under its previous ownership, Nora Apothecary and Alternative Therapies had some interactions with the FDA, but this is the first encounter my company has had since we purchased the pharmacy on 5/14/2015. We believe this inspection was undertaken for reasons of routine follow-up based on the Agency's history with the previous ownership, rather than "For Cause". At the end of this inspection, we were informed by Inspector Robert Barbosa that we were being issued a Form 483 with eight (8) Observations.

Before we address the individual Observations listed on the 483 Form, we want to establish three key facts:

1. Rx Compounding is a pharmacy, duly licensed by the State of Indiana (60002143A) and regulated by the Indiana Board of Pharmacy under all applicable Indiana Rules. Our most recent inspection by the Indiana Board of Pharmacy was undertaken on May 7, 2015 and we passed that inspection.
2. Rx Compounding does not perform any "Office Use" compounding, and we have a prescription on file from a valid prescriber for every compounded preparation we have dispensed. We believe this was verified by Investigator Barbosa in his review of our records.
3. Rx Compounding does not transport prescriptions or compounds across state borders and does not intend to start doing so. Therefore we do not participate in interstate commerce.

We believe that the observations recorded by Investigator Barbosa were based on the standards of Current Good Manufacturing Practices (cGMP). We assert that cGMP standards are much more stringent than state rules, professional best practices, and USP standards, which are the standards to which all pharmacies, medical practices, and veterinary practices currently aspire. We believe that any attempt to apply the stringent standards of cGMP to the sterile compounding techniques of pharmacies, medical practices, or veterinary practices would likely result in Observations analogous to those made in our inspection by Investigator Barbosa.

Rx Compounding has reviewed FDA's webpage entitled "Compounding: Inspections, Recalls, and other Actions," and we see that more than 200 pharmacies like ours have already had 483

Forms posted to that page. We hope that you **will not** post our 483 to that webpage, but if you elect to do so, we hope you will also post this Response Letter as FDA has done in the cases of more than 30 other pharmacies in various jurisdictions.

In review of that webpage, we note that twenty-five organizations have received Referral Letters to the pharmacy board of their primary jurisdiction, and we ask the FDA for such a Referral Letter to the Indiana Board of Pharmacy for Rx Compounding, Inc.. We are a pharmacy, not a drug manufacturer, and we believe we fit the criteria FDA has apparently used in the past for the issuance of such State Board Referral Letters (i.e.: individual prescriptions in hand from valid prescribers, no interstate commerce).

We will now address each of the Observations recorded on the 438 Form we were issued. Even though we fervently believe that cGMP is not the appropriate standard to which we should be held, we recognize that some of the Observations by the investigator are in line with USP General Chapter <797> standards to which Rx Compounding does aspire.

- Observation # 1 - "Equipment, materials, and/or supplies are not adequately disinfected prior to entering the aseptic processing areas."
    - At Rx Compounding, a Compounding Aseptic Isolator (abbreviated in USP <797> as "CAI" and sometimes called a "glovebox" in the common pharmacy vernacular) is used in the compounding of sterile preparations. All compounded sterile preparations produced by Rx Compounding are prepared in the CAI. Only registered pharmacists, licensed to practice in the state of Indiana, perform compounding of sterile preparations at Rx Compounding. By policy, pharmacy technicians do not take part in compounding sterile preparations. The following is a revision to standard operating procedures at Rx Compounding that was put into place during the FDA inspection to ensure that materials and supplies are adequately disinfected prior to entering the CAI:
        - 1) Remove any jewelry from hands or wrists.
        - 2) Thoroughly wash hands with antibacterial soap and water for at least 30 seconds.
        - 3) Thoroughly dry hands using a lint-free disposable towel.
        - 4) Gather all the supplies and materials (Drug products/packages, syringes, needles, alcohol swabs, sterile vials/bottles, sterile gloves, etc.) that are needed in order to compound the sterile product.
        - 5) Place products *into a sterile bag (Whirl Pak Sterile Sampling Bags from Cole-Parmer).* Remove any product packaging to minimize contamination.
        - 6) Open the exterior pass through door of the Aseptic Isolator and place the *sterile bag* containing the products into the pass through chamber, then re-close the exterior door.

- 7) Open the interior pass through door of the Aseptic Isolator. Transfer the *sterile bag* from the pass through chamber to the work chamber. Close the interior pass through door.
- 8) Clean and wipe down the entire inside surface of the work chamber including back and side walls with Sterile TechniSat pre-wetted wipes. Allow time for the alcohol to completely dry.
- 9) Remove all materials from the sterile bag and arrange them in the work area to minimize movement within the Aseptic Isolator. Always keep the air grilles clear and unobstructed.
- 10) Thoroughly wipe all materials with Sterile TechniSat pre-wetted wipes including the disposable nitrile gloves that are attached to the sleeves of the compounding Aseptic Isolator. Each sterile wipe contains 70% USP Isopropyl Alcohol and 30% USP Purified Water. Every wipe is gamma irradiated to the sterility assurance level of 10^{-6}.
- 11) Carefully remove the sterile glove package and properly place the sterile compounding gloves over the disposable nitrile gloves being careful not to contaminate the sterile gloves. The sterile gloves should be tightly fitted without any finger bumps or creases.

- Observation # 2 - "Personnel were observed performing aseptic manipulations that blocked the movement of first pass air around an open unit, whether before or after it is filled with sterile product."
    - Rx Compounding recognizes that mechanically blocking "First Air," is incompatible not only with cGMP, but with USP <797> as well. Investigator Barbosa's interpretation of blocking "First Air" was markedly different than ours, but we acknowledge that his interpretation has merit and we are undertaking a review of our practices related to hand movements by our operators and placement of materials and equipment within the CAI. We intend to revise our SOPs as appropriate. We have already determined to edit SOP language to include, but not necessarily to be limited to:
        - 1) Aseptic manipulations are performed at least 6 inches inside the Aseptic Isolator to prevent any reflected contamination.
        - 2) Aseptic manipulations are completed in front of the pharmacist's hands to prevent any obstruction of airflow. This is the principle of "First Air" keeping the airflow between the HEPA filter and the sterile products unobstructed.
        - 3) All materials are strategically placed to minimize movement within the Aseptic Isolator. Products are lined up side-by-side and not in a front-to-back fashion. The purpose of this is to prevent hands being placed over open sterile bottles at any point in the compounding process.

        - 4) Perform all manipulations directly on the solid work surface of the work chamber.
        - 5) Keep air grilles clear and unobstructed. Poorly placed objects can affect the sterile compounding environment.
- Observation # 3 - "Personnel engaged in aseptic processing were observed wearing non-sterile gloves."
    - Rx Compounding recognizes that sterile gloves are required not just by cGMP, but by USP <797> as well. Once this was brought to our attention during the inspection, we immediately ordered sterile white nitrile gloves. When they arrived the following day, we began using them for every sterile preparation, and continue to do so. Rx Compounding is currently undertaking a review of its garbing and gloving processes and intends to revise its SOPs as appropriate. We have already determined to amend SOP language to include, but not necessarily to be limited to:
        - 1. Open the sterile glove package by peeling apart the outer packaging from its corners. Be careful not to touch the sterile inner pack.
        - 2. Use your right thumb and index finger to grab the bottom of the cuff of the left sterile glove.
        - 3. Make a fist with your left hand and using your right hand, guide the cuff of the glove over your left fist. Then gently straighten the fingers of your left hand and continue to pull the glove up the hand with your right hand until all left fingers are snugly in the glove. Then completely pull up the cuff until it is completely straightened out. Make sure the glove is on snug without any visible creases or folds.
        - 4. Repeat the above procedure for the other sterile glove. Using your gloved left hand, slide a left finger inside the top of the cuff, make a fist with your right hand, and stretch the cuff over your right fist. Then gently straighten the fingers of your right hand and continue to pull the glove up the hand with your left hand until all right fingers are snugly in the glove. Then completely pull up the cuff until it is completely straightened out. Make sure the glove is on snug without any visible creases or folds.

- Observation # 4 - "The ISO 5 classified area is located within a non-classified room."
    - Rx Compounding retains an outside vendor to certify its CAI. The outside vendor also conducts non-viable particle counts and viable particle testing within the Secondary Engineering Control (i.e. the environment surrounding that CAI) using the methodologies published in USP <797>. These activities occur on a regularly scheduled basis, as per USP <797>. Rx Compounding scheduled an extra certification which took place on August 24, 2016, to ensure that the secondary engineering control maintains an acceptable air qualification. This certification did confirm this condition (see Appendix #1).

- Observation # 5 - "Chemical sanitizing agents are not used in your facilities cleanrooms."
    - Rx Compounding acknowledges that this Observation is a requirement of USP <797> as well as cGMP and that the Investigator's Observation has merit. We have undertaken a review of the cleaning and disinfecting processes of our Secondary Engineering Control. While the cleanroom was being cleaned daily, although not with chemical sanitizers, we are committed to implementing improvements that include, but are not necessarily limited to the following:
        - Only specifically trained personnel will undertake cleaning and disinfection of the Secondary Engineering Control. Cleaning and disinfection will be comprehensive and performed thoroughly and regularly in the secondary engineering control. Cleaning starts with the cleanest area first and moves outward to the dirtiest. All cleaning materials such as mops and wipes are disposable and are discarded after one use.
        - Materials and equipment that are used:
            - 1. Low particulate shedding cellulose mops
            - 2. Sterile TechniSat pre-wetted wipes as cleaning and sanitizing agents
            - 3. 2% sodium hypochlorite solution (Clorox) as a sanitizing solution
            - 4. Decon Spor 200+ used as a sporicide and sanitizing agent
            - 5. Pre-moistened swiffer cloths
        - Daily cleaning requirements in the secondary engineering control include cleaning the exterior of the aseptic isolator, trash removal, floors mopped using a sporicide solution (Decon Spor 200+) which contains 27.5% hydrogen peroxide and 5.8% of peroxyacetic acid. Daily cleanings are performed at the end of each compounding day.
        - Weekly cleaning requirements in the cleanroom include: Cleaning walls, shelves, emptying, cleaning and sanitizing storage shelving bins, non-compounding furniture such as the cart, stool bench, trash can, and anteroom curtain.
        - Monthly cleaning requirements in the cleanroom include: Cleaning the ceiling of the room, and cleaning the interior and exterior of the refrigerator and incubator.
        - For all cleanings, the pharmacist is required to wear a protective gown, protective nitrile gloves, mask, and safety goggles.
        - It important to make certain that all surfaces are thoroughly coated and wetted with the cleaning agent and left to dry. The mop goes over every surface of the cleanroom, walls, molding, and ceiling. Areas that are not

entirely flat are cleaned by gloved hands with lint-free cloths dampened with the cleaning agent to clean the surfaces.

- Observation # 6 - "The environmental monitoring performed is not representative of aseptic conditions."
    - Rx Compounding acknowledges that this Observation is representative of USP <797> as well as cGMP. We have already improved our environmental controls by updating our previous plates to TSA contact plates with added lecithin and polysorbate 80, and we have changed our incubation period to 3-5 days at 33-35 ℃ as recommended by the inspector. Rx Compounding is undertaking an examination of our processes and tightening our controls for microbiological test media and environmental surveillance using consultation with an expert microbiologist, we intend to revise our SOPs as appropriate.

- Observation # 7 - "The certification of ISO 5 classified area is not representative of its condition of use."
    - Reports supplied by Champion Air Testing showing that tests performed and passed on 1/26/16 and 7/26/16 included both static and dynamic particle testing (see Appendix #2). If further dynamic testing is needed, Rx Compounding will work with its certifier to ensure that future testing meets FDA requirements.

- Observation # 8 - "Beta-lactam drugs were produced without providing adequate containment, segregation, and/or cleaning of work surfaces, utensils, and/or personnel to prevent cross-contamination."
    - In an effort to remove traces of beta lactam drugs, we undertook a thorough attempt of deactivation and decontamination of our engineering controls.
    - While we have never had any patient complaints or adverse reactions reported, as of Monday, August 15, 2016, Rx Compounding suspended compounding of all beta-lactam antibiotic preparations. We commit to inform the FDA if, and when, we resume such compounding.
    - Because we do so few of such preparations (32 prescriptions between August 1, 2015 and August 1, 2016), ceasing such compounding will not impact the viability of our business. We note, however, that this standard is purely a standard of cGMP, and not a rule of the Indiana Board of Pharmacy or a published standard within USP <797>, and that we were within USP <797> guidelines while compounding these preparations.