ICS
Intrathecal Compounding Specialists

December 11, 2017

On behalf of Intrathecal Compounding Specialists (ICS), I authorize the United States Food and Drug Administration (FDA) to publicly disclose the information described 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 0), and 5 U.S.C. § 552(b)(4) that is exempt from public disclosure under those statutory provisions and/or relevant FDA regulations. I agree to hold FDA harmless for any injury caused by FDA's sharing the information with the public.

Information to be disclosed: ICS's letter dated December 08, 2017, excluding attachments/exhibits, which responds to FDA's Form 483 dated November 17, 2017.

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 ICS and my full name, title, address, telephone number, and facsimile number is set out below for verification.

Stuart Burgess
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December 08, 2017

Department of Health and Human Services
Food and Drug Administration
404 BNA Dr., Bldg. 200, Ste. 500
Nashville, TN 37217-2597

Via Fax (615) 366-7802 and Overnight Delivery

Attn: Ms. Ruth P. Dixon, District Director
Ms. Claire M. Minden, Investigator

Re: Response to FDA Form 483

Dear Director Dixon and Investigator Minden:

From November 6-8, 2017 and on November 17, 2017, the FDA field office conducted an inspection of our pharmacy, Intrathecal Compounding Specialists ("ICS"), located at 206-A Jacobs Run, Scott, LA 70583. At the conclusion of the inspection, we received an FDA Form 483. This letter is ICS' response to the FDA Form 483 observations. We respectfully request that this response, excluding the attachments, be posted on the FDA's website with the Form 483, and be included every time the FDA provides a copy of ICS' FDA Form 483 to anyone outside the FDA.

ICS wishes to emphasize that it takes the issues identified in the FDA Form 483 very seriously. For over ten years, ICS has strived to provide safe and efficacious compounded preparations. Within that period, we have dispensed close to 100,000 sterile preparations without any compromise in quality and sterility. We are committed to adhering to the applicable laws and regulations that ensure patient safety and the preparation of high-quality compounded formulations. As a licensed pharmacy, ICS is required to comply with applicable state laws and regulations governing pharmacy compounding, and with the applicable United States Pharmacopoeia chapters <795> and <797> on pharmacy compounding. The FDA's cGMPs for finished pharmaceuticals are not applicable to ICS' pharmacy or compounded medications prepared there. 21 U.S.C. § 353a specifically exempts a compounding pharmacy from the cGMP requirements imposed on a drug manufacturer by 21 U.S.C. § 351 (a)(2)(B). However, since the receipt of the FDA Form 483, ICS has undertaken the process of assessing and updating our standard operating procedures ("SOPs") and aseptic processing operations as part of our continuous quality improvement program.

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Observation 1

You did not make adequate product evaluation and take remedial action where actionable microbial contamination was found to be present in the ISO 5 classified aseptic processing area during aseptic production.

Response to Observation 1:

ICS' SOP 9.07 *Gloved Fingertip Sampling* requires that all sterile compounding personnel perform a gloved fingertip sampling assessment at least every two weeks.

Upon assessment of ICS' gloved fingertip sampling program, it was determined that personnel sampling error may well have contributed to a number of false positive sampling results. Personnel were re-trained on how to properly perform a gloved fingertip sampling test, including proper aseptic handling of the media plates, so as to not touch the non-sterile outside surface of the plates.

ICS has revised its SOP 9.07 *Gloved Fingertip Sampling* to reflect the revised sampling procedures. This SOP also requires that regardless of the number of CFUs recovered, all media plates showing growth will be sent to a credentialed laboratory so that the microorganism(s) recovered can be identified to the genus and species level. Once the microorganism(s) have been identified, further corrective actions will be determined by the identities of the microorganisms recovered, under the guidance of a qualified microbiologist. The recovery of any highly pathogenic and objectionable organisms such as Gram-negative rods, coagulase positive Staphylococcus, molds, and yeasts shall prompt an immediate response to include terminal cleaning (triple-cleaning), re-sampling of the aseptic processing environment, and the end of production until the re-sampling results are available. ICS will also work with a qualified microbiologist to evaluate the potential risk of product contamination or harm to patients to determine if further remedial actions, such as initiating a recall of sterile product, is appropriate.

ICS has also revised its SOP to require an investigation be opened whenever the gloved fingertip sampling test results in the recovery of CFUs, regardless of the number recovered. Recovery of microorganisms will prompt an observational personnel competency audit to evaluate the aseptic technique and cleaning and disinfecting practices of the specific compounder, with re-training or removal from compounding activities as appropriate.

Observations 2, 3, 7

A number of observations stated on the FDA Form 483 were related to proper aseptic processing technique, specifically observations 2, 3, and 7. Upon evaluation of the FDA Form 483, along with review of past personnel records and gloved fingertip sampling results, it was determined that the majority of observed deficiencies and positive results were related to the aseptic techniques of one, specific (b) (6) compounding individual. After re-training and re-qualification, this compounder will only compound under direct supervision.

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In response to the observations stated on the FDA form 483 related to aseptic processing techniques, ICS contracted with a third-party consulting company, Neuro Apothecary LLC, to conduct a dedicated in-service for ICS personnel on November 18-19th 2017. The purpose of the in-service was to perform a third-party assessment of, and re-training on, the compounding techniques and aseptic processing operations of ICS' sterile compounding personnel. (See attached Neuro Apothecary LLC report).

The techniques of ICS' sterile compounding personnel were assessed and validated in the following areas: aseptic techniques in ISO environments; proper personnel gowning procedures and use of PPE; cleaning, sanitization, and decontamination procedures; filter integrity testing; hand washing and personnel hygiene. After instruction, personnel were observed for proper technique. Personnel were also instructed on what constitutes inadequate aseptic processing technique. (See attached competency assessments).

Additionally, the ASHP High Risk Compounding modules were conducted by certified trainers to provide continuing education credits in the following topics as they relate to aseptic processing and high risk compounding: navigating equipment and workflow until the final check; primary engineering controls; secondary engineering controls; compounding basics in laminar airflow systems; sterile product categorization; core competencies and facilities basics; evolution and overview of aseptic processing. All sterile compounding personnel completed all seven continuing education modules. (See attached ASHP training certificates). Upon completion of training, all compounding personnel were given a "High Risk Compounding" test, with a passing result of $\geq$ 80% required.

In order to assess the aseptic technique and cleaning and disinfecting practices of personnel on an ongoing basis, SOP 2.05 *Orientation, Training, Education, and Evaluations* was revised to require that several comprehensive observational competency assessments be added to the semi-annual personnel validation requirements. These competency assessments include: Cleaning & Disinfecting; Contamination Control & Aseptic Processing; Final Release Checks: Filter Integrity Testing; Material Handling; Ongoing Gloved Fingertip Sampling; PEC Laminar Airflow Workbenches; Secondary Engineering Controls; Personnel Hygiene, Hand Washing & Garbing.

While the on-site personnel in-service addressed aseptic processing techniques beyond the scope of the FDA Form 483, it also addressed the specific concerns noted in Observations 2, 3, and 7.

Observation 2

In response to two of the observations of Observation 2, "placing a paper label in the laminar flow hood and multiple products with multiple active ingredients are in the laminar flow hood at the same time with no segregation/separation to prevent mix-ups…"

As a best practice, all sterile compounding personnel are now required to follow specified segregation concepts. In particular, the operational workflow has been revised such that only

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Observation 4
In response to Observation 4, requirements for routine hand sanitization were discussed. Sections 3.4 of SOP 5.04 *Scrubbing, Gloving, and Gowning Procedure* was emphasized, whereby sterile compounding personnel are instructed to disinfect gloved hands whenever they are removed from the ISO 5 environment and whenever non-sterile surfaces are touched.

Observation 5
In response to Observation 5, in addition to re-training and personnel competency assessments, to address the observed concerns and as a best practice, ICS has purchased sterile gowns with a collar that covers the entire neck area.

Observation 6
In response to Observation 6, section 3.5 of SOP 5.04 *Scrubbing, Gowning, and Gloving Procedure* was emphasized, whereby personnel are never permitted to leave the clean-room and re-enter from lower-classed ISO areas without first replacing gowning apparel. In particular, the standard operating procedures prohibit sterile personnel from leaving and returning to higher-classed ISO environments from lower-classed ISO environments without repeating gowning and garbing procedures with new sterile gowning and garbing PPE.

Observation 8

Non-microbial contamination was observed in your production area.

> *HEPA filter in the laminar flow hood was observed to be stained brown in areas directly behind the compounding area.*

In response to Observation 8, which noted that non-microbial contamination was observed in the production area as the HEPA filter in the laminar flow hood was observed to be stained brown in areas directly behind the compounding area, ICS contracted with Allometrics to perform a third party cleanroom certification. Per Allometrics report *"Stains observed on HEPA filter are not effecting the functionality."*. While discoloration was found by Allometrics to have no effect on sterility or compounding processes, to mitigate future appearance concerns, ICS has contracted to with Allometrics to remediate the discoloration.

Observation 9

The ISO 5 classified aseptic processing areas had difficult to clean and particle-generating equipment or surface.

> *Observed thread material in an unused outlet cover in the laminar flow hood which was used throughout this inspection to compound and distribute sterile drugs.*

In response to Observation 9, ICS is having the unused outlet removed and the space replaced and sealed by a qualified, credentialed contractor.

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the equipment, materials, supplies, and components required to prepare any given CSP are permitted to be placed in the ISO 5 LAFW at any given time. Compounders will be evaluated for their adherence to required segregation concepts on a semi-annual basis through use of observational personnel competency assessments.

Additionally, ICS personnel have been trained to place all of the paperwork and paper labels necessary for a given compounded preparation inside of a plastic sleeve that is to be disinfected as it is moved from lower-classed to higher-classed ISO environments. Once the compounder has completed the preparation of a CSP, it will be removed from the ISO 5 environment prior to being labeled in the ISO 7 buffer area.

Observation 3
In response to Observation 3, personnel received re-training on the requirements of hand sanitization during aseptic processing. Staff were directed to SOP 5.04 *Scrubbing, Gloving, and Gowning Procedure* which outlines requirements of hand sanitization during aseptic processing. In particular, as per section 3.4, "gloves shall be disinfected with sterile 70% isopropyl alcohol ("IPA") whenever gloves become or are suspected to have become contaminated, whenever non-sterile surfaces are touched, and whenever gloved hands leave the ISO 5 LAFW".

Observation 7
In response to Observation 7, all personnel were re-trained to sanitize all supplies and materials whenever they are being moved from lower classified to higher classified ISO environments. This will be assessed on an ongoing basis through the personnel Contamination Control and Aseptic Processing competency assessment (see attached).

Observations 4, 5, 6

In response to Observations 4, 5, and 6, ICS contracted with third-party consulting companies to provide on-site education and training on aseptic gowning and garbing practices.

Neuro Apothecary, LLC conducted an onsite in-service on November 18-19th, 2017 to provide education, training, and assessment of the skills and techniques necessary in aseptic processing operations. Hand-hygiene, gowning, and garbing practices was one aspect of aseptic processing that was specifically addressed. After adequate hand-hygiene, gowning, and garbing processes were demonstrated, all personnel were observed performing these processes and their competency in adequately and aseptically following these procedures was assessed. Additionally, ICS will conduct observational personnel audits on a semi-annual basis to address the ongoing competency of personnel in performing gowning and garbing processes as per SOPs.

ICS also reviewed their SOPs on hand-hygiene, gowning, and garbing with the consultants from Eagle and revisions to the SOPs were included as best practices to address specific observations on the FDA Form 483.

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Observation 10

Disinfectant contact time (also known as "dwell time") and coverage of the item being disinfected were insufficient to achieve adequate levels of disinfection.

In response to Observation 10, ICS reviewed their standard operating procedures with consultants from Eagle, led by an aseptic processing expert with a Ph.D in microbiology.

As a best practice, ICS has revised their SOP 1.07 *Cleaning and Disinfecting of the Compounding Areas* to address these observations (See attached). In particular, this SOP was revised to state that contact time shall be followed as per manufacturer's guidelines. The SOP was also updated to include the contact times for each disinfecting agent used. Personnel were re-trained on new cleaning and disinfecting procedures and were instructed to follow contact time guidelines as indicated.

To ensure that personnel follow these cleaning and disinfecting procedures on an ongoing basis, an observational personnel competency assessment will be performed for each sterile compounding employee on at least a semi-annual basis (See attached).

Observation 11

ISO-5 classified areas were not certified under dynamic conditions.

In response to Observation 11, ICS hired a qualified contractor, Allometrics, to perform a semi-annual certification of the cleanroom, which was completed on November 21st, 2017 (See attached report). During the certification, the following tests were performed, and they met the pass/fail criteria. Allometrics tests performed: Viable Air; Viable surface; Calibration of two electronic balances; HEPA filter leak testing of two powder hoods; Air Flow Smoke test of two powder hoods; HEPA filter leak testing of two laminar air flow hoods; Air Flow Smoke test of two laminar air flow hoods; Particle Count of two laminar flow hoods; Air particle count of Buffer Room; Air Volume measurement of Buffer Room; Air particle count of Ante Room; Air Volume measurement of Ante Room; Air particle count of Powder Room; Air Volume measurement of Powder Room (see attached Allometrics results).

ICS also revised its SOP 3.14 *on Cleanroom Requirements & Certification* to outline the specific requirements for each semi-annual cleanroom certification. As per 3.3.1, "ISO areas shall be certified under dynamic conditions by an authorized service provider every 6 months, after facility or equipment maintenance, or if problems arise, and shall include: viable particle sampling; HEPA filter leak tests on all HEPA filters; air exchanges; differential air pressure; smoke studies under dynamic conditions; nonviable particle sampling".

ICS also added section 3.4.1 to the SOP to address the review of the semi-annual cleanroom certification report. As per this SOP, the Director of Pharmacy shall review the report upon

receipt to ensure that all required certifications have been completed and all reports have been received. Missing or incomplete reports shall result in a prompt follow-up with the certification company, and re-testing as needed. The Director of Pharmacy shall also review the report to ensure that all tests fell within acceptable guidelines and have met the passing criteria. Results that fall outside of acceptable guidelines or fail to meet the required criteria will result in the initiation of an investigation and root-cause analysis.

Observation 12

You have no assurance that the endotoxin level of your intrathecal drug products are safe, since you do not have any endotoxin data and your firm doesn't perform endotoxin testing for the finished product. These preparations are made using non-sterile starting material. Furthermore, there is no endotoxin testing data for your bulk solutions (active pharmaceutical ingredients) past the initial compounded date.

As a 503A compounding pharmacy, ICS follows the USP <797> guidelines for bacterial endotoxin testing. Specifically, ICS tests for bacterial endotoxins for all high-risk level CSPs that are prepared in groups of more than 25 identical individual single-dose packages or in multi-dose vials for administration to multiple patients or that are exposed longer than 12 hours at 2 to 8°C and longer than 6 hours at greater than 8°C prior to sterilization.

Since intrathecal drug products are by nature a patient-specific prescription, they are produced in batch sizes of one unit. Due to the batch size of one and the 72-hour shelf life of the product, it is not feasible to test each finished intrathecal drug product for endotoxins. However, ICS has process controls in place to ensure that these products are within bacterial endotoxin limits and are safe for the patients to whom they are being administered.

One such process control is the production and testing of the stock solutions which are ultimately used to produce the individual patient prescriptions. Each batch of stock solution made is tested for sterility, potency, and bacterial endotoxins prior to being dispensed to patients, providing assurance that the stock solutions are sterile and within specifications for potency and bacterial endotoxin limits.

The aseptic processes by which the individual intrathecal drug units are prepared are controlled to reduce the risk that the stock solution that has tested to be within bacterial endotoxin limits is not contaminated with pyrogens during the aseptic manipulation process. All aseptic manipulations are performed using equipment, supplies, and materials that are sterile and pyrogen-free.

ICS is working with a credentialed, FDA-registered laboratory to perform new stability studies for each formulation that is prepared as a stock solution to increase the robustness of the data gathered from previous studies. Each stock solution will be tested for sterility, bacterial endotoxins, and container-closure integrity at both the initial and final time-points of the product's shelf-life, providing additional evidence that the container-closure system can maintain the integrity and sterility of the product throughout the course of its entire BUD.

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Observation 13

Post filtration integrity testing to the sterilizing filter was not performed.

ICS has revised its SOP 5.08 *Filter Integrity Testing* to require that filter integrity testing be performed on every sterilizing filter during the production of sterile product. Personnel were trained on performing this procedure as per the protocols outlined in SOP 5.08. Results of the filter integrity test will be documented on the compounding batch record for every CSP produced, as well as the pass/fail acceptance criteria for the test, as indicated by the manufacturer's guidelines.

Observation 14

Media fills were not performed that closely simulate aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

ICS revised its media fill procedure to develop a media fill that simulates production activities to include stock solution preparation and final product production and dispensing. Non-sterile dry powder TSB media will be dissolved and filtered into sterile water to prepare the stock solutions which will then be used to prepare the final product.

Conclusion

With this response, ICS has sought to address all of the FDA's observations and concerns. We always have, and always will, put our patients' health, welfare, and safety first, and are therefore committed to developing and maintaining a comprehensive set of policies and procedures to ensure that all compounded products are prepared, packed, and held in sanitary conditions. While cGMP requirements are not applicable to the pharmacy's operations, we have accepted the FDA's observations as suggestions for improvement and have committed to implement additional best practices to the extent feasible and compatible with our obligations under state law and the USP guidelines. If the FDA requires additional information or communication from ICS, please contact me at (337) 237-6077 or stuart@icspharmacy.com.

Sincerely,

Stuart Burgess
Pharmacy Director and Pharmacist-in-Charge