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**VIA OVERNIGHT MAIL**

SHELDON T. BRADSHAW
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FILE NO: 86160.000003

November 20, 2015

Ms. Ruth P. Dixon
District Director, New Orleans District
U.S. Food and Drug Administration
404 BNA Drive, Building 200, Suite 500
Nashville, TN 37217-2597



Re: Posting AIS' 483 Responses to ORA's Electronic Reading Room

Dear Ms. Dixon:

On behalf of Advanced Infusion Solutions ("AIS"), we authorize the United States Food and Drug Administration ("FDA") to publicly disclose the information described below on FDA's website. Specifically, we ask that the information described below be posted in ORA's electronic reading room next to the links to the two Form 483s issued to AIS on October 27, 2015.

Information to be disclosed: Letter from Sheldon Bradshaw, Hunton & Williams LLP to Ruth Dixon, District Director, New Orleans District dated November 16, 2015 and Attachment A (excluding exhibits 1 and 2) and Attachment B (excluding exhibits 1 and 2). Attachments A and B contain AIS' responses to the two FDA Form 483s dated October 27, 2015.

AIS understands 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. § 3310 and 5 U.S.C. § 552(b)(4) that is exempt from public disclosure under these statutory provisions and/or relevant FDA regulations. AIS agrees to hold FDA harmless for any injury caused by FDA's sharing the information with the public.

Sincerely,

Sheldon T. Bradshaw (dac)

Sheldon T. Bradshaw

cc: Charles R. Bell, Jr.
President & Founder
Advanced Infusion Solutions

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FILE NO: 86160.000002

November 16, 2015

**CONFIDENTIAL**

**Via Overnight Mail**



Ms. Ruth P. Dixon
District Director, New Orleans District
U.S. Food and Drug Administration
404 BNA Drive, Building 200, Suite 500
Nashville, TN 37217-2597

**Re: Inspectional Observations at AIS Facilities; FEI Nos. 3011804748 and 3011469631**

Dear Ms. Dixon,

I am writing on behalf of my client, Advanced Infusion Solutions ("AIS"), in regards to the Form FDA 483s issued by Food and Drug Administration ("FDA" or "Agency") investigators to AIS' compounding pharmacies located in Clinton, Mississippi and Ridgeland, Mississippi on October 27, 2015. Attached please find my client's responses to the inspectional observations contained in the FDA 483s.[1] As an organization, AIS is fully committed to complying with all applicable regulatory requirements. While AIS appreciates the opportunity to respond to the inspectional observations contained in the 483s, I write separately to address the questionable legal and regulatory foundation for the observations.

As an initial matter, if FDA releases either of the FDA 483s (either to specific individuals/ entities or more broadly to the general public), basic fairness demands that FDA also release AIS' responses to the FDA 483s, including this letter. Releasing the FDA 483s alone would, at best, leave the reader with an incomplete and misleading picture of AIS' compounding practices. Indeed, in light of the inspectional observations, patients and physicians may be left with the false impression that AIS is compounding drug products under insanitary conditions when, in fact, AIS operates in compliance with Chapter 797 of the U.S. Pharmacopeia ("USP Chapter 797"), which sets forth the standards governing the compounding of sterile injectables. Sterile medications compounded by AIS are safe and appropriate for patients to use, which patients and physicians will not fully appreciate if FDA selectively releases the 483s without AIS' responses to the same.

[1] *See* Attachment A (Ridgeland 483 Response), and Attachment B (Clinton 483 Response).

As you are aware, AIS is regulated under Section 503A of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). AIS is a specialty compounding pharmacy that is engaged exclusively in the practice of traditional pharmacy compounding, i.e., AIS only compounds unique medications for identified individual patients pursuant to a valid prescription issued by a licensed prescriber. Unlike pharmacies operating as outsourcing facilities under Section 503B of the FD&C Act, pharmacies operating under Section 503A are exempt from FDA's current good manufacturing practice ("cGMP") regulations.[2] Instead, 503A pharmacies must comply with state laws and regulations, which, for pharmacies engaged in compounding sterile injectables, typically includes the requirements set forth in USP Chapter 797.

The FDA 483 inspectional observations do not specifically cite FDA's cGMP regulations, nor, curiously, do they cite any rule or regulation actually enforced by FDA. Instead (and, again, without citing the FD&C Act or any regulation promulgated by FDA), the FDA 483s tacitly imply that AIS is compounding drugs "under insanitary conditions" in violation of Section 501(a)(2)(A) of the FD&C Act. Interestingly, however, the inspectional observations primarily identify practices that FDA has previously identified as failing to comply with FDA's cGMP regulations. In practical effect, therefore, the 483 inspectional observations suggest that AIS' compounded drugs are compounded "under insanitary conditions"[3] *because* they are not compounded "in conformity with" FDA's stringent cGMP requirements.[4]

FDA cannot lawfully conclude that a drug compounded under Section 503A was compounded "under insanitary conditions" in violation of Section 501(a)(2)(A) simply *because* it was not compounded "in conformity with" cGMP requirements in violation of Section 501(a)(2)(B).[5] An inspection classification of Official Action Indicated ("OAI")—or any other agency action—based on such a conclusion would be contrary to the FD&C Act and FDA guidance documents. Again, drug products that are compounded under section 503A are not required to be compounded in conformity with cGMP requirements—under the FD&C Act, they are exempt

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[2] *Compare* FD&C Act § 503A(a) (exempting traditional compounding pharmacies from cGMP requirements), *with id.* § 503B(a) (applying cGMP requirements to outsourcing facilities).

[3] *Id.* § 501(a)(2)(A).

[4] *Id.* § 501(a)(2)(B).

[5] *Compare id.* § 501(a)(2)(A) (concerning adulteration caused by "insanitary conditions whereby [a drug] may have been contaminated with filth"), *with id.* § 501(a)(2)(B) (concerning adulteration caused by failing to operate "in conformity with" cGMPs).

from Section 501(a)(2)(B), which states that a drug is adulterated if it is not compounded in conformity with cGMP requirements.[6] By definition, a drug compounded under Section 503A cannot be deemed to be adulterated because it was not compounded in conformity with cGMPs.

To be sure, drugs compounded under section 503A may be deemed to be adulterated if they were, in fact, truly compounded "under insanitary conditions whereby [they] may have been contaminated with filth"—but FDA cannot interpret that adulteration provision so as to create a presumption that a drug not compounded in conformity with FDA's cGMPs is, by definition, compounded under insanitary conditions whereby it may have been contaminated with filth. Section 501(a)(2)(A) (concerning adulteration caused by "insanitary conditions whereby [a drug] may have been contaminated with filth") and section 501(a)(2)(B) (concerning adulteration caused by failing to operate "in conformity with" cGMPs) must be given independent meaning. It is an "elementary canon of construction that a statute should be interpreted so as not to render one part inoperative."[7]

Moreover, federal agencies "cannot interpret federal statutes to negate their own stated purposes."[8] FDA cannot conclude that drugs compounded under section 503A that were not compounded in conformity with cGMPs have, as a result, been compounded under insanitary conditions whereby they may have been contaminated with filth. Such a conclusion would render either section 501(a)(2)(A) or section 501(a)(2)(B) superfluous, as both adulteration sections would regulate the same conduct. There would be no distinction between adulteration due to insanitary conditions whereby a drug may have been contaminated with filth and adulteration due to a failure to operate in conformity with cGMPs—notwithstanding the fact that these two types of adulteration appear in different sections, *one of which the FD&C Act expressly precludes from applying to drugs compounded under section 503A*.

Indeed, FDA cannot circumvent the statutory exemption from cGMP requirements for drugs compounded under Section 503A by conflating the two adulteration provisions found in Section

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[6] *See id.* § 503A(a) (stating that Section 501(a)(2)(B) "shall not apply" to drugs compounded under Section 503A); *see also* FDA, Guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act* § IV(A) (July 2014) [hereinafter "*503A Compounding Guidance*"] (not listing compliance with cGMPs among the requirements that are applicable to compounded drugs that meet the conditions of section 503A).

[7] *Colautti v. Franklin*, 439 U.S. 379, 392 (1979).

[8] *New York State Dept. of Social Servs. v. Dublino*, 413 U.S. 405, 419-20 (1973).

501(a)(2)(A) (concerning adulteration caused by "insanitary conditions whereby [a drug] may have been contaminated with filth") and Section 501(a)(2)(B) (concerning adulteration caused by failing to operate "in conformity with" cGMPs). A stated purpose of the Food and Drug Administration Modernization Act of 1997,[9] which added section 503A to the FD&C Act, was to exempt drugs compounded under section 503A from cGMP requirements.[10] This purpose would be "negated" if FDA could determine that drugs compounded under section 503A that are not produced in conformity with cGMPs are, as a result, compounded under insanitary conditions whereby they may have been contaminated with filth. Such an interpretation of the FD&C Act would effectively nullify the statutory exemption.

Without conceding that FDA has the statutory authority to regulate the practice of pharmacy, FDA should recognize that drug products compounded under Section 503A are not compounded under insanitary conditions whereby they may have been contaminated with filth if they are compounded in compliance with applicable USP requirements. AIS takes great satisfaction in compounding sterile injectables in compliance with state pharmacy law, which in many states incorporates USP Chapter 797 (National Formulary General Chapter <797> Pharmaceutical Compounding—Sterile Preparations). Drug products compounded under Section 503A that have been compounded in compliance with USP Chapter 797 simply are not adulterated under Section 501(a)(2)(A). To the contrary, a drug compounded in compliance with USP Chapter 797 has been compounded using methods that prevent the level of contamination implicated by the "insanitary conditions whereby it may have been contaminated with filth" adulteration section.

Section 501(a)(2)(A) describes a type of adulteration (i.e., adulteration caused by "insanitary conditions whereby [a drug] may have been contaminated with filth") that is characterized by a *significant* level of contamination or potential contamination. Indeed, the statutory term "insanitary conditions" is modified and limited by the statutory phrase "whereby it may have been contaminated *by filth* (emphasis added)." The meaning of a statutory term, like "insanitary," may be determined "by the company it keeps,"[11] i.e., "by reference to the meaning

[9] Pub. L. 105-115.

[10] *See 503A Compounding Guidance* § II (stating that "[s]ection 503A describes the conditions that must be satisfied for drug products compounded by a licensed pharmacist or licensed physician to be exempt from . . . section 501(a)(2)(B) (concerning current good manufacturing practice)").

[11] *Gustafson v. Alloyd Co.*, 513 U.S. 561, 575 (1995); *see also Jarecki v. G.D. Searle & Co.*, 367 U.S. 303, 307 (1961) ("The maxim *noscitur a sociis*, that a word is known by the company it keeps, . . . is often wisely applied

of words associated with it."[12] Insanitary conditions, therefore, can be determined by reference to the term "filth," which in common usage means "offensive or disgusting dirt or refuse; foul matter."[13] Synonyms of "filth" include "dirt, refuse, pollution, muck, shit (taboo slang), crap (taboo slang), garbage, sewage, contamination, dung, sludge, squalor, grime, feces, slime, excrement, nastiness, carrion, excreta, crud (slang), foulness, putrefaction, ordure, defilement, kak (S. African taboo slang), grot (slang), filthiness, uncleanness, putrescence, foul matter."[14] Numerous cases interpreting the term "filth" describe egregious levels of contamination or potential contamination, including, characteristically, the presence of animal droppings.[15]

A drug compounded *in compliance with USP Chapter 797* could not, by definition, ever have the level of contamination or potential contamination sufficient to meet the adulteration standard established in section 501(a)(2)(A). If, in fact, a compounding pharmacy complies with the requirements of USP Chapter 797, then the drugs compounded by that pharmacy will not have been produced under "insanitary conditions whereby [they] may have been contaminated with filth." Accordingly, FDA should determine—as a matter of law and enforcement policy—that a drug compounded under section 503A is not adulterated due to insanitary conditions if the drug was compounded in compliance with USP Chapter 797.

AIS compounds drug products in compliance with USP Chapter 797, as evidenced by its exemplary history of compliance with well-established pharmacy rules and regulations. Since AIS' compounding pharmacy first opened in December of 2008, its compliance with USP Chapter 797 has been annually documented in numerous inspections by multiple states and third-

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where a word is capable of many meanings in order to avoid the giving of unintended breadth to the Acts of Congress.").

[12] *Neal v. Clark*, 95 U.S. 704, 708 (1877) ("It is a familiar rule in the interpretation of . . . statutes that a passage will be best interpreted by reference to that which precedes and follows it" (quotation omitted).).

[13] *See* Dictionary.com (last visited Nov. 4, 2015), *available at* http://dictionary.reference.com/browse/filth.

[14] The Free Dictionary (last visited Nov. 4, 2015), *available at* http://www.thefreedictionary.com/filth.

[15] *See, e.g.*, *United States v. Am. Mercantile Corp.*, 889 F.Supp.2d 1058, 1062-63 (W.D. Tenn. 2012) ("FDA laboratory analysis confirmed the presence of filth, including rodent and insect filth, in the samples collected before and after cleaning."); *United States v. Gel Spice Co.*, 601 F.Supp. 1205, 1211 (E.D.N.Y. 1984) (holding that "laboratory analysis and graphic photographs" proved that food stored with rodent hairs, rodent excreta pellets, mammalian urine, and dead and decaying rodents was "held under conditions whereby it may have become adulterated with filth"); *United States v. H.B. Gregory Co.*, 502 F.2d 700, 703 (7th Cir. 1974) (describing filthy conditions that included "numerous rodent excreta pellets and multiple rodent urine stains, as well as . . . other general insanitary conditions"); *United States v. Cassaro, Inc.*, 443 F.2d 153, 154 (1st Cir. 1971) (holding that "[i]nsects and larvae fragments have been held to constitute 'filth' in numerous cases.").

party consultants. Notably, over the course of the last seven years, AIS has dispensed hundreds of thousands of sterile injectable drug products, yet it has never had sterility-related issues with any of its drug products that has required any remedial action, including recalls, nor has AIS ever had any sterility issues that caused any patient harm.

If compliance with USP Chapter 797 does not ensure that a drug compounded under Section 503A is not compounded under insanitary conditions in violation of Section 501(a)(2)(A), then the standards by which a compounding pharmacy operating under Section 503A must operate are completely opaque. For example, one inspectional observation objects to AIS' practice of conducting *weekly* instead of *daily* environmental monitoring of its cleanroom. AIS' *weekly* environmental monitoring exceeds that required by USP Chapter 797, which only requires that environmental monitoring be conducted semiannually.[16] While FDA's cGMP regulations may require *daily* environmental monitoring of aseptic drug manufacturing,[17] it cannot be (as noted above) that a compounding pharmacy operating under Section 503A must comply with those regulations in order to ensure that its compounded drug products are not compounded "under insanitary conditions whereby [they] may have been contaminated with filth," since such pharmacies are exempt from cGMPs.[18]

Notably, specific standards for ensuring that drugs compounded under Section 503A are not compounded under insanitary conditions (e.g., daily environmental monitoring) cannot be found in any FDA publication. Industry, apparently, must learn to divine the minds of Agency personnel to ascertain the applicable standards. However, as the U.S. Court of Appeals for the Seventh Circuit specifically reminded FDA, standards are not binding on industry if they can be found "just in the oral testimony of an agency employee."[19] As the Court made clear, the

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[16] *See* USP Chapter 797 ("Air sampling shall be performed at least semiannually (i.e., every 6 months) as part of the re-certification of facilities and equipment.").

[17] *See* FDA, Guidance for Industry, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* § X.A.1 (Sep. 2004) (stating that, per cGMPs, the "timing, frequency, and location" of environmental monitoring "should be carefully selected based upon their relationship to the operation performed"); *see also id.* (providing that "[a]ll environmental monitoring locations should be described in SOPs," which also "should also address . . . frequency of sampling"); *see also id.* App. 1, § F (stating that an "environmental monitoring program should be established that routinely ensures acceptable microbiological quality of air, surfaces, and gloves," and that "[a]ir quality should be monitored periodically during each shift").

[18] *See* FD&C Act § 503A(a).

[19] *United States v. Farinella*, 558 F.3d 695, 699 (7th Cir. 2009).

standard cannot be "some bureaucrat's secret understanding of the law. 'The idea of secret laws is repugnant. People cannot comply with laws the existence of which is concealed.'"[20]

The Supreme Court has made it clear that regulated parties are not expected to "divine the agency's interpretations" of its rules in advance of the agency announcing such interpretations.[21] An attempt to impose cGMP requirements, or to enforce standards relating to a never-before-announced interpretation of the "insanitary conditions" adulteration provision, on a 503A compounding pharmacy through observations in an FDA 483 would violate principles of the well-established Fair Notice Doctrine. Additionally, the imposition of new and previously unannounced standards would constitute rulemaking under the Administrative Procedure Act ("APA") while skirting the notice-and-comment requirement that the APA requires agencies to follow.[22] Critically, FDA has never announced that compliance with USP Chapter 797 standards by a 503A compounding pharmacy is insufficient to meet the FD&C Act's requirement that drugs not be compounded under insanitary conditions. Accordingly, absent specific written standards for pharmacies to follow, it must be that sterile drug products compounded under Section 503A are not compounded under insanitary conditions whereby they may have been contaminated with filth if they are compounded in compliance with USP Chapter 797.

We would further note that FDA's inspection of AIS' pharmacies greatly exceeded the Agency's inspectional authority. Although FDA may have the authority to inspect a 503A compounding pharmacy to confirm that it is operating within the parameters set forth in Section 503A of the FD&C Act, its authority to inspect pharmacies that operate in conformance with applicable local (state) laws is limited.[23] Indeed, although the overwhelming majority of the practices identified by the FDA investigators were, in fact, fully compliant with state law, including USP Chapter 797, we would further emphasize that even if the identified practices were inconsistent with state law (and left uncorrected), it would be inappropriate to include them as observations in an FDA 483. Specifically, while Section 503A requires that compounding pharmacies use ingredients that "comply with the standards of an applicable United States Pharmacopoeia . . . monograph,"

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[20] *Id.* (quoting *Torres v. INS*, 144 F.3d 472, 474 (7th Cir. 1998)).

[21] *Christopher v. Smithkline Beecham Corp.*, 132 S.Ct. 2156, 2168 (2012) ("It is one thing to expect regulated parties to conform their conduct to an agency's interpretations once the agency announces them; it is quite another to require regulated parties to divine the agency's interpretations in advance or else be held liable when the agency announces its interpretations for the first time in an enforcement proceeding and demands deference.")

[22] *See* 5 U.S.C. § 553.

[23] *See* 21 U.S.C. § 374 (2)(a).

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there is no general requirement under Section 503A that a pharmacy's compounding practices comply with USP Chapter 797. Instead, that requirement is imposed by state law. As a result, the practices in question are a matter of state (rather than federal) law.

Finally, AIS is confident that its processes result in the production of compounded products that are safe and appropriate for use by its patients. Accordingly, AIS allowed FDA's investigators to review its systems and processes, unaware that those investigators would attempt to hold AIS to undefined and inapplicable standards and make unfounded allegations of "insanitary conditions." AIS denies that its products are adulterated by any standard, and the company specifically rejects the notion that compliance with USP Chapter 797 could support observations that its products were compounded "under insanitary conditions whereby [they] may have been contaminated with filth."

AIS welcomes the opportunity to answer any questions you may have. To that end, we request a meeting with you to discuss this letter and AIS' responses to the FDA 483 inspectional observations as soon as possible. In light of the significant legal issues raised by the FDA 483, we respectfully request that officials from FDA's Office of the Chief Counsel be invited to attend the meeting. Because it is our understanding that the inspection was part of an initiative overseen by the Compounding and Pharmacy Practices Branch ("CPPB") in the Office of Compliance at the Center for Drug Evaluation and Research, we request that the appropriate representatives from CPPB be invited to participate as well.

Sincerely,

Sheldon Bradshaw by KS

Sheldon T. Bradshaw

Attachments

cc: Amanda Edmonds (via e-mail)
Deputy Chief Counsel
Office of the Chief Counsel
U.S. Food and Drug Administration

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B. Todd Vinson (via e-mail)
Branch Chief
Compounding and Pharmacy Practices Branch
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

# ATTACHMENT A

**CONFIDENTIAL**

*Via Overnight Mail*

November 16, 2015

Ms. Ruth P. Dixon
District Director, New Orleans District
404 BNA Dr., Bldg. 200, Suite 500
Nashville, TN 37217-2597

**Re: Response to Inspectional Observations – FEI Number 3011804748**

Dear Ms. Dixon,

Please accept this correspondence in response to the FDA Form 483 provided to Advanced Infusion Solutions' ("AIS") facility in Ridgeland, Mississippi on October 27, 2015. As an organization, AIS is committed to complying with all applicable regulatory requirements. We appreciate the opportunity to respond to the inspectional observations contained in the 483. For ease of reference, the inspectional observations are repeated in bold text and our responses are set forth below each observation.

While AIS believes its practices are in compliance with applicable regulatory requirements, including USP <797>, AIS views the FDA's 483 process as an opportunity for improvement. AIS has used this process to inquire, evaluate, bolster, and re-approach its entire quality assurance program, including but not limited to the ongoing engagement of a third-party consultant (CV attached as Exhibit 1) and the retention of a Director of Quality.

Since its inception, AIS has been committed to improving performance by implementing pharmacy best practices and the USP <797> standards in sterile compounding. AIS recognizes the value of the USP <797> observations that FDA has brought to AIS's attention. Based on the FDA inspector's observations and USP <797> standards, corrective and preventive action (CAPA) plans and Key Performance Indicators (KPIs) were developed immediately to correct any observations, as well as to prevent recurrence of any future deviations from USP <797> standards. For AIS, quality improvement will continue with management monitoring the effectiveness of the KPIs using established audit tools.

The AIS leadership team has assigned managers as observers to conduct unannounced random audits in established frequencies to make sure that the compounding staff are strictly following the USP <797> standards. All observations (sufficient or insufficient) are documented and reviewed by the Pharmacist-in-Charge or a member of the senior leadership team. Any insufficient observations are addressed immediately and handled through remedial retraining/re-

education. Any insufficient observations are reevaluated and documented within 48 hours. All KPI-related findings are presented to AIS senior leadership to evaluate the effectiveness of the program.

For the AIS pharmacy location referenced above, based on the FDA inspectors' observations and the USP <797> standards, the leadership team has identified 11 KPI metrics in the areas of aseptic garbing, aseptic technique, cleanroom state of control, and the sterile product integrity. The KPI metrics began on 09/28/15. AIS will continue to audit and report these observations to the leadership team based on the established audit tool frequencies for each specific KPI (weekly, biweekly and monthly). The KPI dashboard from Ridgeland is attached as Exhibit 2.

**OBSERVATION 1**

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

**Specifically,**

- **On or about 7/10/2015, air and surface samples were collected and analyzed by Hayes Microbial Consulting. Results of these samples identified multiple organisms of bacteria and fungus in your firm's ISO 7 and ISO 8 areas. Your firm failed to conduct appropriate follow-up investigations. Your firm failed to provide documentation identifying the organisms or species for each colony growth.**

- **On 7/17/2015, Hayes Microbial Consulting reported 6 air samples and 2 contact sample exceed, or found to be equal to, the limit of detection (1 CFU/M3):**

    - **An air sample was taken at location #37: Bacteria: Bacillus, Corynebacterium, Micrococcus, and Staphylococcus sp. were detected, exceeding the prescribed action level set forth in your firm's SOP, AIS-PHA-210: "Pharmacy Cleanroom Viable Air Sampling". The ISO 7 action level is> 10, the Hayes microbial consulting report documents 12 CFU's was recorded.**

        - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #37 is in the middle of your firm's gown room (ISO 7 area).**

        - **On 7/17/2015, your firm conducted in-house environmental air sampling, which was entered into your firm's in-house report, Simplify 797.**

            - **Your firm's in-house report indicates sampling occurred on the far W and E side of the gown room (ISO 7 area). This sampling location is not equivalent to sampling location #37 conducted by Hayes Microbial Consulting.**

    - **A contact sample was taken at location #46: Bacteria: Staphylococcus sp. was detected.**

- **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #46 is your firm's staging area (ISO 8 area).**

    - **Your firm's documentation supporting in-house environmental contact plate sampling indicates sampling was not conducted in your firm's staging area.**

- **A contact sample was taken at location #40: Bacteria: Staphylococcus sp. was detected.**

    - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #40 is in the firm's anteroom- on the NE side of the door entrance from the unclassified area (ISO 8 area).**

        - **Your firm's documentation supporting in-house environmental contact plate sampling indicates 3 sampling locations occurred on the SW side of the anteroom while 0 (zero) samples were taken on the NE side of the anteroom. These sampling location are not equivalent to sampling location #40 conducted by Hayes Microbial Consulting.**

- **An air sample was taken at location #35: Bacteria: Staphylococcus sp. was detected.**

    - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #35 is your firm's stock solution room (ISO 7 area).**

    - **On 7/17/2015, your firm conducted in-house environmental air sampling, which was entered into your firm's in-house report, Simplify 797.**

        - **Your firm's in-house report documents zero colonies were detected at location (5A) LAFW 40647-Stock Solutions Room (ISO 5 area) and zero colonies were detected at location (4A) Stock Solutions Room. Your firm's in-house environmental monitoring locations was compared to your firm's 3rd party contractor's environmental monitoring locations. Upon comparison, it appears your firm's sampling location are not equivalent to the sampling location #35 conducted by Hayes Microbial Consulting.**

- **An air sample was taken at location #39: Bacteria: Bacillus, Micrococcus, and Staphylococcus sp. Were detected.**

    - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #39 is in the middle the firm's anteroom (ISO 8 area).**

- **On 7/17/2015, your firm conducted in-house environmental air sampling, which was entered into your firm's in-house report, Simplify 797.**
    - **Your firm's in-house report documents colony growth, 32 CFU's, in the ISO 8 anteroom- gown room door (ISO 8 area). This sampling location is not equivalent to sampling location #39 conducted by Hayes Microbial Consulting.**

- **An air sample was taken at location #41: Bacteria: Staphylococcus sp. was detected.**
    - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #41 is your firm's cart pass thru area (ISO 8 area).**
    - **On 7/17/2015, your firm conducted in-house environmental air sampling, which was entered into your firm's in-house report, Simplify 797.**
        - **Your firm's 7/17/2015 in-house report does not document sampling was conducted at this location.**

- **An air sample was taken at location #43: Bacteria: Staphylococcus sp. was detected.**
    - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #43 is your firm's materials handling area (ISO 8 area).**
    - **On 7/17/2015, your firm conducted in-house environmental air sampling, which was entered into your firm's in-house report, Simplify 797.**
        - **Your firm's 7/17/2015 in-house report does not document sampling was conducted at this location.**

- **An air sample was taken at location #45: Fungi: Cladosporium, unspecified mold. Bacteria: Bacillus, Micrococcus, and Staphylococcus sp. were detected.**
    - **According to the pharmacy cleanroom room layout located in the Controlled Environment Performance Test and Certification Report, location #45 is your firm's staging area (ISO 8 area).**
    - **On 7/17/2015, your firm conducted in-house environmental air sampling, which was entered into your firm's in-house report, Simplify 797.**
        - **Your firm's 7/17/2015 in-house report does not document sampling was conducted at this location.**

- **Your firm's environmental monitoring data from July- October 2015, documents several instances indicating colony growth in your firm's ISO 5, ISO 7, and ISO 8**

**areas. However, your firm did not conduct adequate investigations assuring these areas are free from microbial contamination.**

Based on USP <797> standards, AIS does not agree that its system for monitoring environmental conditions is deficient or poses any risk of harm to the public. Moreover, this observation fails to identify any applicable standard that AIS is alleged to have violated. AIS operates in strict compliance with USP <797>, and tests its systems, processes, and equipment regularly in accordance with USP <797> standards. Although our objective is no microbial growth in aseptic processing environments, AIS disagrees with the premise that an aseptic environment must at all times be free of microbial growth in order to safely produce CSPs.

USP <797> states, "Air sampling shall be performed at least semiannually (i.e., every 6 months) as part of the re-certification of facilities and equipment," and "Surface sampling shall be performed in all ISO classified areas on a periodic basis." As a pharmacy that dispenses high risk CSPs, AIS exceeds this USP <797> standard by performing weekly surface sampling and weekly viable air sampling. If any microbial growth is recovered during sampling activities, AIS uses Hayes Microbial Consulting, an appropriately-credentialed laboratory, to comply with the USP <797> requirement of identifying recovered microorganisms to at least the genus level.

USP <797> lists action levels for microbial growth recovered in classified environments. Please note the tables below for recommended action levels for viable air and surface sampling.

**Table 2. Recommended Action Levels for Microbial Contamination***

†(cfu per cubic meter [1000 liters] of air per plate)

| Classification | Air Sample† |
|---|---|
| ISO Class 5 | > 1 |
| ISO Class 7 | > 10 |
| ISO Class 8 or worse | > 100 |

* Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice–US HHS, FDA September 2004.

**Table 4. Recommended Action Levels for Microbial Contamination***

| Classification | Fingertip Sample | Surface Sample (Contact Plate) (cfu per plate) |
|---|---|---|
| ISO Class 5 | > 3 | > 3 |
| ISO Class 7 | N/A | > 5 |
| ISO Class 8 or worse | N/A | > 100 |

* Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-6, 5 April 2007.

AIS reviews and trends all environmental sampling results in compliance with USP <797>. If *action levels* are exceeded, AIS cleans and disinfects the area within the cleanroom where actionable microbial growth is recovered. It is important to note that AIS not only cleans and disinfects the area of actionable microbial growth, but also the complete environment – and, many times, the complete room by the time sampling results are reviewed and documented (due to the required two- to seven-day incubation interval for the respective media type). This was the case in the above-referenced AirSafe (Hayes) report. AIS did not immediately receive the AirSafe (Hayes) report because it takes time for the vendor to analyze and document the testing results. During that time period, AIS cleaned and disinfected the entire cleanroom suite for several weeks upon receipt of the report.

If *actionable trends* are observed, AIS reevaluates "the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency with the aseptic compounding location," in compliance with USP <797>. As a continuous-quality organization,

AIS monitors and evaluates our aseptic processing environments and processes for actionable trends and corresponding improvement opportunities.

AirSafe, our vendor for controlled environment testing and certification, tests and certifies our cleanroom on a quarterly basis, exceeding the USP <797> semi-annual requirement. AIS has requested that AirSafe conduct surface sampling and viable air sampling semi-annually in conjunction with cleanroom recertification activities. This is done so that AIS can review the results obtained by a third-party vendor relative to our internal weekly results. Since no microbiological sampling plan can prove the absence of microbial contamination, and USP <797> states that sampling locations should be chosen "based on a risk assessment of compounding activities performed," AIS has not historically dictated the locations where AirSafe performs its environmental sampling. AIS will now ensure, however, that AirSafe synchronizes its surface and viable air sampling locations with AIS's environmental sampling plan, as you have recommended.

USP <1116>, an informational chapter of the U.S. Pharmacopeia, discusses the microbiological control and monitoring of aseptic processing environments. The chapter acknowledges the microbiological realities of aseptic processing in manned cleanrooms by stating: "In any environment where human operators are present, microbial contamination at some level is inevitable. Even the most cautious clean-room environment design and operation will not eliminate the shedding of microorganisms if human operators are present. Thus, an expectation of zero contamination at all locations during every aseptic processing operation is technically not possible and thus is unrealistic." AIS always gives suitable attention to its environmental monitoring results. USP <1116> provides appropriate perspective by stating: "Environmental monitoring is one of several key elements required in order to ensure that an aseptic processing area is maintained in an adequate level of control. Monitoring is a qualitative exercise, and even in the most critical applications such as aseptic processing, conclusions regarding lot acceptability should not be made on the basis of environmental sampling results alone."

AIS acknowledges the microbiological realities of aseptic processing in manned cleanrooms. In order to maintain a state of control within our aseptic processing pharmacy, AIS will continue to follow its current policy for weekly surface sampling and viable air sampling in compliance with USP <797>.

- **Surface and air monitoring of the ISO 5 environment are not performed each day sterile drug products are produced, Your firm's current practice is to perform weekly surface and air monitoring. This is inadequate as environmental conditions are not monitored every day production occurs.**

Daily environmental monitoring, including surface sampling and viable air sampling, is a cGMP requirement. As stated above, AIS conducts weekly surface sampling and viable air sampling. Of note, USP <1116> states: "Environmental monitoring is usually performed by personnel and thus requires operator intervention. As a result, environmental monitoring can both increase the risk of contamination and also give false-positive results. Thus, intensive monitoring is unwarranted, particularly in the ISO 5 environments that are used in the most critical zones of aseptic processing."

- **Personnel monitoring is not performed each day sterile drug products are produced.**

- **Your firm's management stated in-house personnel monitoring is performed weekly. However, management did not provide documentation assuring your firm conducted personnel monitoring prior to the beginning the production of sterile drug products on 2/10/2014 through 6/4/2015.**

- **According to your firm's SOP, AIS-PHA-408: "Gloved Fingertip Sampling", all new compounding personnel (compounding technicians, as well as, all pharmacist, regardless, of whether they physically perform the duties of compounding or they supervise compounding) must successfully complete 3 Gloved Fingertip sampling occurrences prior to compounding CSPs for human use. For high risk level compounding, subsequent gloved fingertip sampling will occur semi-annually.**

    - **On 9/15/2015, I observed 2 stock solution pharmacists actively compounding stock solutions of 6 - 600mL bags of Morphine 62.5 mg/mL and 5 - 200mL bags of Fentanyl 10 mg/mL. Your firm did not provide personnel monitoring data for the stock solution pharmacist for 2015.**

    - **In addition, your firm did not provide documentation supporting fingertip monitoring was conducted for all pharmacists I observed actively compounding in your facility on 9/15/2015.**

Daily environmental monitoring, including personnel monitoring, is a cGMP requirement. In the observation, FDA correctly states a section from our SOP governing Gloved Fingertip Sampling: "[A]ll new compounding personnel (compounding technicians, as well as, all pharmacists, regardless, of whether they physically perform the duties of compounding or they supervise compounding) must successfully complete 3 Gloved Fingertip sampling occurrences prior to compounding CSPs for human use. For high risk level compounding, subsequent gloved fingertip sampling will occur semi-annually." Please note that this policy is consistent with USP <797> requirements: "All compounding personnel shall successfully complete an initial competency evaluation and gloved fingertip/thumb sampling procedure (zero CFU) no less than three times before initially being allowed to compound CSPs for human use." USP <797> also states: "After completing the initial gowning and gloving competency evaluation, re-evaluation of all compounding personnel for this competency shall occur at least annually for personnel who compound low- and medium-risk level CSPs and semi-annually for personnel who compound high-risk level CSPs . . . ."

**OBSERVATION 2**

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

**Specifically,**

- **On 9/15/2015, a HEPA filter (ISO 5 area) appeared dirty; a thermaplate (ISO 7 area) used for compounding appeared dirty; several storage bins containing sterile**

**components, located directly under the ISO 5 hood, appeared to have residue from splatter or spills; a trash receptacle (ISO 7 area) appeared dirty.**

As discussed with FDA inspectors, the residue described as "dirty" in the observation was simply adventitious drug residue. The drug residue from the shift's compounding activity observed on the hot plate (thermaplate), the LAFW protective grill (HEPA filter), and the trash receptacles were immediately cleaned per SOP PHA-304. Of note, AIS's cleaning protocols, which include morning, mid-day, end of day, weekly, and monthly cleaning regimens, are robust in maintaining an aseptic processing environment that is compliant with USP <797>. Please see Ridgeland KPI #9, which states that AIS will inspect primary engineering controls (PECs) after compounding activities are completed and ensure each PEC is cleaned and disinfected appropriately. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPI #9) to ensure our aseptic processes are in strict compliance with USP <797>. Also, AIS immediately removed the storage bins containing compounding supplies that were located directly under the ISO Class 5 LAFW. While there is no USP <797> prohibition on storing compounding supplies in ISO Class 7 environments, AIS relocated these bins when pharmacy leadership noted an opportunity to optimize compounding workflow.

- **On 9/15/2015, a stock solution compounding pharmacist was observed improperly cleaning the LAFW prior to performing aseptic bulk compounding of fentanyl. The pharmacist sprayed 70% Sterile IPA directly on a sterile disposable cloth and wiped the workbench in a circular fashion, moving from front to back.**

AIS reviewed the organization's policy for cleaning and disinfecting of aseptic processing areas (PHA 304) and determined that it is in compliance with USP <797>. AIS re-educated all pharmacy staff on 09/17/15 regarding USP <797> compliant cleaning and disinfection processes for ISO Class 5 environments. Please see Ridgeland KPI #2. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPI #2) to ensure our aseptic processes are in strict compliance with USP <797>.

**OBSERVATION 3**

**Separate or defined areas to prevent contamination or mix ups are deficient regarding operations related to aseptic processing of drug products.**

AIS disagrees with this observation, including the premise that its practices are deficient to prevent contamination or mix-ups. The compounding workflow used by pharmacy personnel is necessitated by the reality that in pharmacy practice, patient-specific prescriptions issued by physicians often require aseptic combination of several medications. This observation, and the specific examples listed, address pharmacy practice issues that fall outside the scope of FDA's jurisdiction. AIS operates in compliance with pharmacy laws and regulations, as well as USP <797>. AIS has nevertheless reviewed each observation and has implemented improvements, as noted below, to further optimize compounding workflow.

**Specifically,**

- **Your firm's SOP, AIS-PHA-412: Conduct of Personnel in Controlled Areas and Aseptic Technique Overview, section 7.12 states Area Clearance: is an activity that ensures that only one "batch" is present at a compounding workstation to avoid error and mix-ups of the components and labels from which the CSP is being prepared.**

AIS has revised SOP PHA-412 in order to provide clarity regarding processes for our compounding personnel. Please note that AIS *does not batch produce end product*. The patient-specific prescriptions that AIS dispenses often require the aseptic combination of multiple medications.

- **On 9/15/2015, a pharmacist was observed pulling from 7 different stock medications in one ISO 5 hood.**

The patient-specific prescriptions that AIS dispenses often call for the aseptic combination of multiple medications. It is necessary for compounding personnel to have immediate access to multiple medications while fulfilling orders for patient-specific prescriptions.

- **On 9/15/2015, multiple unlabeled syringes from different stock solutions, for multiple patients, were observed lying on a cart waiting to be compounded.**

- **On 9/15/2015, multiple pharmacists were observed holding two separate prescriptions for two different patients, all syringes are unlabeled.**

Please note that AIS protocol dictates that patient-specific prescription labels travel with all patient-specific medication syringes as they rotate to different compounding stations in the cleanroom.

- **On 9/15/2015, powdered APIs were observed being weighed and staged, uncovered, in the ISO 7 area. The unlabeled, uncovered powder APIs were placed on a staging cart with multiple unlabeled syringes before being brought to the ISO 5 area.**

Please note that AIS protocol dictates that patient-specific prescription labels travel with all patient-specific medication syringes or powder APIs as they rotate to different compounding stations in the cleanroom.

- **On 9/15/2015, we observed multiple unlabeled compounded patient specific medications were placed in a hot water bath.**

Please note that AIS protocol dictates that patient-specific prescription labels travel with all patient-specific medication syringes or powder APIs as they rotate to different compounding stations in the cleanroom. AIS has augmented the labeling requirements for all patient-specific medications in a hot water bath.

AIS noted an opportunity to optimize compounding workflow by revising the protocol for transportation of patient-specific medications within the cleanroom. As noted above, AIS has

revised SOP PHA-412 in order to provide clarity regarding processes for our compounding personnel. Please see Ridgeland KPI #7. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPI #7) to ensure that compounding processes are unlikely to lead to the mix up of patient-specific CSPs.

**OBSERVATION 4**

**Each batch of drug product purporting to be sterile and pyrogen-free is not laboratory tested to determine conformance to such requirements.**

**Specifically,**

- **Your firm's stock solutions undergo endotoxin testing one time prior to processing. However, your stock solutions are punctured multiple times during processing over several days. Your firm's stock solutions, at time of use, is not representative of the endotoxin testing conducted prior to processing.**

USP <797> mandates criteria for bacterial endotoxin (pyrogen) testing. Please note the *circumstances* that trigger the requirement for testing (numbered) as well as AIS's practice (*bulleted*):

All high risk levels CSPs, except for inhalation and ophthalmic administration, which are prepared in . . . .

1) groups of more than 25 identical single-dose packages (e.g., ampules, bags, syringes, vials)

    - Does not apply to AIS. As a pharmacy that only compounds unique medications for identified individual patients pursuant to a valid prescription issued by a licensed prescriber, AIS does not batch prepare end product.

2) in MDVs (multi-dose vials) for administration to multiple patients

    - Does not apply to AIS. AIS does not compound multi-dose vials, as this practice is incompatible with the patient population we serve.

3) that are exposed longer than 12 hours at 2 degrees C to 8 degrees C and longer than 6 hours at warmer than 8 degrees C before they are sterilized

    - Does not apply to AIS. AIS follows protocols to efficiently prepare each CSP. Even for the most complex CSPs, AIS completes all aseptic processing for each patient-specific CSP within 6 hours.

shall be tested to ensure that they do not contain excessive bacterial endotoxins . . . .

As mentioned above, AIS's compounding procedures do not trigger the USP <797> requirements for endotoxin testing. AIS nonetheless follows procedures and protocols that

minimize the introduction and generation of endotoxins during aseptic processing. AIS acquires its APIs from Medisca, a reputable, FDA-registered repackager. A Certificate of Analysis (COA) is provided and retained on file for each lot of API received by AIS, and one of the acceptance criteria listed on each COA is endotoxin levels. Also, AIS uses DynaLabs, an FDA-registered analytical lab, to test the endotoxin levels of each compounded stock solution, and the company ensures that endotoxin quantities are within acceptable limits before releasing the stock solution for use.

**OBSERVATION 5**

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

**Specifically,**

- **On 9/15/2015, a pharmacist was observed crossing into the clean side of the anteroom with no shoe cover over their street shoes.**

AIS reviewed the organization's policy for garbing (PHA-404) and has determined that it is in compliance with USP <797>. AIS re-educated all pharmacy staff on 09/17/15 regarding the USP <797> compliant garbing procedures specified in PHA-404. Please see Ridgeland KPI #10. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPI #10) to ensure the garbing procedures of cleanroom personnel are in strict compliance with USP <797>.

- **On 9/15/2015, a pharmacist was observed reaching under the ISO 5 workbench to gather supplies to continue aseptic processing 24 times without sterilizing their gloves or the components entering ISO 5 area form a dirtier area.**

- **On 9/15/2015, a pharmacist compounding a stock solution of fentanyl was observed leaving the ISO 5 area, entering the ISO 7 area, and returning to the ISO 5 area 13 times before sanitizing their gloves.**

AIS reviewed the organization's policy that addresses the conduct of personnel in controlled environments (PHA-412) and had determined that it is in compliance with USP <797>. AIS re-educated all pharmacy staff on 09/17/15 regarding USP <797> compliant behavior for working in controlled environments specified in PHA-412. The training for pharmacy staff included instruction regarding how operators must interface with ISO Class 5 environments while engaged in aseptic processing. Please see Ridgeland KPIs #3 and #4. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPIs #3 and #4) to ensure that the conduct of all cleanroom personnel is in strict compliance with USP <797>.

- **On 9/15/2015, multiple pharmacists were observed with their heads under the ISO 5 hood.**

AIS reviewed the organization's policy that addresses the conduct of personnel in controlled environments (PHA-412) and has determined that it is in compliance with USP <797>. AIS re-educated all pharmacy staff on 09/17/15 regarding USP <797> compliant behavior for working in controlled environments specified in PHA-412. The training for pharmacy staff included instruction regarding how operators must interface with ISO Class 5 environments while engaged in aseptic processing. Please see Ridgeland KPI #1. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPI #1) to ensure that the conduct of all cleanroom personnel is in strict compliance with USP <797>.

* * *

In conclusion, AIS appreciates the opportunity to formally respond to each 483 observation. Evaluating and responding to each observation has reaffirmed for AIS that all of the pharmacy's processes, whether aseptic or procedural, are in place for the sole purpose of creating a sterile end product for our patients. AIS is proud that its pharmacy has never encountered a sterility failure with any of its CSPs.

# ATTACHMENT B

**CONFIDENTIAL**

*Via Overnight Mail*

November 16, 2015

Ms. Ruth P. Dixon
District Director, New Orleans District
404 BNA Dr., Bldg. 200, Suite 500
Nashville, TN 37217-2597

**Re: Response to Inspectional Observations – FEI Number 3011469631**

Dear Ms. Dixon,

Please accept this correspondence in response to the FDA Form 483 provided to Advanced Infusion Solutions' ("AIS") facility in Clinton, Mississippi on October 27, 2015. As an organization, AIS is committed to complying with all applicable regulatory requirements. We appreciate the opportunity to respond to the inspectional observations contained in the 483. For ease of reference, the inspectional observations are repeated in bold text and our responses are set forth below each observation. Please note that the "Clinton" facility is a very small, local Jackson, Mississippi-area pharmacy that dispenses only patient-specific medications in a *low to medium risk* facility with an average daily census of approximately thirty (30) local patients.

While AIS believes its practices are in compliance with applicable regulatory requirements, including USP <797>, AIS views the FDA's 483 process as an opportunity for improvement. AIS has used this process to inquire, evaluate, bolster, and re-approach its entire quality assurance program, including but not limited to the ongoing engagement of a third-party consultant (CV attached as Exhibit 1) and the retention of a Director of Quality.

Since its inception, AIS leadership has been committed to improving performance by implementing pharmacy best practices and the USP <797> standards in sterile compounding. AIS recognizes the value of the USP <797> observations that FDA has brought to AIS's attention. Based on the FDA inspector's observations and USP <797> standards, corrective and preventive action (CAPA) plans and Key Performance Indicators (KPIs) were developed immediately to correct any observations, as well as to prevent recurrence of any future deviations from USP <797> standards. For AIS, quality improvement will continue with management monitoring the effectiveness of the KPIs using established audit tools.

The AIS leadership team has assigned managers as observers to conduct unannounced random audits in established frequencies to make sure that the compounding staff are strictly following USP <797> standards. All observations (sufficient or insufficient) are documented and

reviewed by the Pharmacist-in-Charge or a member of the senior leadership team. Any insufficient observations are addressed immediately and handled through remedial retraining/re-education. Any insufficient observations are re-evaluated and documented within 48 hours. All KPI-related findings are presented to AIS senior leadership to evaluate the effectiveness of the program.

For the AIS pharmacy location referenced above, based on the FDA inspectors' observations and the USP <797> standards, the leadership team has identified 16 KPI metrics in the areas of aseptic garbing, aseptic technique, cleanroom state of control, and the sterile product integrity. The KPI metrics began on 09/25/15. AIS will continue to audit and report these observations to the leadership team based on the established audit tool frequencies for each specific KPI (weekly, monthly, quarterly, and yearly). Please see the attached KPI dashboard from Clinton (attached as Exhibit 2).

**OBSERVATION 1**

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

**Specifically,**

- **On 1/15/2015, air and surface samples collected and analyzed by Hayes Microbial Consulting found multiple organisms of bacteria and fungus in your ISO 5 and ISO 8 areas. Your firm did not provide sufficient evidence indicating these areas are free of microbial contamination prior to your firm beginning operations at this facility on 2/9/2015.**

Based on USP <797> standards, AIS does not agree that its system for monitoring environmental conditions is deficient or poses any risk of harm to the public. Moreover, this observation fails to identify any applicable standard that AIS is alleged to have violated. AIS operates in strict compliance with USP <797>, and tests its systems, processes, and equipment regularly in accordance with USP <797> standards. Although our objective is no microbial growth in aseptic processing environments, AIS disagrees with the premise that an aseptic environment must at all times be free of microbial growth in order to safely produce CSPs.

The above observation does not reflect the full context and chronology of the facility's startup activities, as AIS did not begin dispensing low and medium risk CSPs until 02/09/15. After a period of inactivity, AIS relocated its home infusion operations to this facility. In anticipation of the relocation and for purposes of risk assessment, AIS requested that AirSafe, our vendor for controlled environment testing and certification, test and certify the cleanroom as a part of our validation efforts to recommission the facility for sterile compounding. Please note that this certification was performed in order to verify performance concerning the requirements set forth in USP <797>.

AIS requested that AirSafe ensure that the cleanroom complied with predetermined engineering specifications and operated in a sufficient a manner to provide and maintain a USP <797> compliant environment. Relevant measurements included air change rates, HEPA filter integrity,

room pressurization measurements, and non-viable particle counts. Regarding these measurements, AirSafe certified the cleanroom to be USP <797> compliant. AirSafe did recover microbial growth during its environmental sampling activities. In response to their findings, AIS performed a complete startup cleaning and disinfection of the cleanroom prior to commencing operations on 02/09/15. All startup cleaning was performed on 02/07/15 in accordance with our cleaning and disinfection policies and included the use of Peridox, a sporicidal disinfectant. Documentation of the startup cleaning, as well as subsequent cleaning activities, was provided to FDA inspectors. Of note, AIS's cleaning protocols at this facility, which include morning, end of day, and weekly cleaning regimens, are robust in maintaining an aseptic processing environment that is compliant with USP <797>.

Although the above observation does not reflect the full context and chronology of this facility's startup activities, AIS will nevertheless engage a third-party consultant to assist in developing a policy that defines AIS's procedures for startup and commissioning of cleanrooms. The policy will rely on industry best practices from relevant documents such as:

1. USP <797>; Pharmaceutical Compounding – Sterile Preparations
2. CETA CAG-003-2006-11; REV 31JAN12 – Certification Guide for Sterile Compounding Facilities
3. CETA CAG008-2010 REV 31JAN12 – Certification Matrix for Sterile Compounding Facilities
4. IEST-RP-CC006.3; Testing Cleanrooms (Institute of Environmental Sciences and Technology)
5. IEST-RPCC002.3; Unidirectional Flow Clean-Air Devices (Institute of Environmental Sciences and Technology)
6. IEST-RP-CC0034.3; HEPA and ULPA Filter Leak Tests (Institute of Environmental Sciences and Technology)
7. ISO 14644-1; Cleanrooms and Associated Controlled Environments – Part 1 – Classifications of Air Cleanliness
8. USP <1116>; Microbiological Evaluation of Cleanrooms and Other Controlled Environments

The policy will be completed in 90 days, and AIS will approve and add a policy to our library of SOPs. Please note, however, that AIS has no immediate future plans to recommission a facility.

- **Your firm's management states it performs surface and air monitoring in the ISO 5, ISO 7, and ISO 8 areas weekly. This is inadequate as environmental conditions are not performed each day sterile drug products are produced. In addition, the documentation provided by your firm indicates Bond Pharmacy did not start in-house environmental monitoring until on or about 7/30/2015, more than 5 months after your firm started production.**

Daily environmental monitoring is a cGMP requirement. USP <797> states: "Air sampling shall be performed at least semiannually (i.e., every 6 months) as part of the re-certification of facilities and equipment," and "Surface sampling shall be performed in all ISO classified areas on a periodic basis." In an effort to follow pharmacy best practices for *low and medium* risk

sterile compounding, AIS is currently performing both viable air and surface sampling on a monthly interval.

- **On 9/14/2015, gaps were observed around the perimeter of the pass through door from an unclassified area leading into the ISO 7 area.**

The FDA inspector made this observation on 09/14/15, and AIS provided evidence to FDA shortly thereafter that AIS remediated this finding by sealing these gaps around the perimeter of the pass through with cleanroom-appropriate caulk. AIS believes that the frequent cleaning of the pass through surfaces may have eroded the original caulking agent. Please see Clinton KPI #13. As previously noted, AIS has translated the inspectors' observation into an institutionalized audit program (KPI #13) to ensure that the cleanroom and compounding facilities are maintained in strict compliance with USP <797>.

- **According to your firm's SOP, AIS-PHA-408: "Gloved Fingertip Sampling", all new compounding personnel (compounding technicians, as well as, all pharmacist, regardless, of whether they physically perform the duties of compounding or they supervise compounding) must successfully complete 3 Gloved Fingertip sampling occurrences prior to compounding CSPs for human use. For low/medium risk level compounding, subsequent gloved fingertip sampling will occur annually.**

    - **Documentation provided by your firm indicates one pharmacy technician completed gloved fingertip sampling on 10/20/2015, 8 1/2 months after your firm became operational on 2/9/2015. Furthermore, on 9/14/2015, I observed 2 pharmacy technicians in your facility, only one pharmacy technician completed gloved fingertip sampling on 10/20/2015.**

All pharmacy compounding personnel are required to complete the sterile compounding training using Critical Point Sterile Compounding training program and 3 Gloved Fingertip sampling initially prior to actively compounding any patient specific sterile products, then annually for low to medium risk compounding per USP <797> standards. The observation (e.g., deviation from standard operating procedures) noted here resulted in immediate removal of the pharmacy technician from compounding any drugs until the technician completed gloved fingertip sampling on 10/20/2015. The Clinton pharmacy became operational on 02/09/15, but the new pharmacy technician did not start employment with AIS until 07/07/15. Please see Clinton KPIs #6 and #15. As previously noted, AIS has translated the inspectors' observation into an institutionalized audit program (KPIs #6 and #15) to ensure that the cleanroom and compounding facilities are maintained in strict compliance with USP <797>.

**OBSERVATION 2**

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

**Specifically,**

- **Per your firm's SOP~ AIS-PHA-404: "Hand Hygiene and Garbing", section 4.3.5 describes hand washing will be performed for at least 30 seconds.**

    - **On 9/14/2015, a pharmacy technician was observed washing their hands in anteroom for approximately 10 seconds and drying their hands with a non-sterile disposable cloth.**

Sterile towels for hand hygiene is a cGMP requirement. In describing hand hygiene procedures, USP <797> states: "Hands and forearms to the elbows will be completely dried using either lint-free disposable towels or an electronic hand dryer." AIS reviewed the organization's policy for hand hygiene (PHA-404) and has determined that it is in compliance with USP <797>. AIS re-educated and trained all pharmacy staff on 09/17/15 regarding USP <797> compliant hand hygiene procedures specified in PHA-404. Please see Clinton KPI #16. As previously noted, AIS has translated the inspectors' observation into an institutionalized audit program (KPI #16) to ensure the hand hygiene procedures of cleanroom personnel are in strict compliance with USP <797>. To aid personnel with effective hand hygiene, AIS will add a clock to its anteroom to facilitate compliance with PHA-404.

- **According to your firm's SOP, AIS-PHA-404: "Hand Hygiene and Garbing", section 4.4.9, gloved hands will be sprayed with sterile 70% IPA prior to entering the ISO 5 area and anytime the employee's hand re-enters the ISO 5 area.**

    - **On 9/14/2015, a pharmacy technician was observed placing the outer covering of a 0.9% NaC11000-mL bag into the trash receptacle in the ISO 7 area and returning to the ISO 5 area without sanitizing their gloves.**

AIS reviewed the organization's policy for hand hygiene (PHA-404) and has determined that it is in compliance with USP <797>. AIS has re-educated and trained all pharmacy staff on 09/17/15 regarding USP <797> compliant hand hygiene procedures specified in PHA-404. Please see Clinton KPI #4. As previously noted, AIS has immediately translated the inspectors' observation to an institutionalized audit program (KPI #4) to ensure the hand hygiene procedures of cleanroom personnel are in strict compliance with USP <797>.

**OBSERVATION 3**

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

**Specifically,**

- **Per your firm's SOP, AIS-PHA-404: "Hand Hygiene and Garbing", section 4.3.8 states to don a clean, lint free cover garment (Tyvek or equivalent) with sleeves that fit snugly around the wrists and which securely encloses the neck. In addition, section 4.3.10 of the aforementioned SOP, states to fasten the closures of the gown completely.**

    - **On 9/14/2015, a pharmacy technician was observed wearing a non-sterile gown that was open, exposing their street clothes to the sterile environment.**

AIS reviewed the organization's policy for garbing (PHA-404) and has determined that it is in compliance with USP <797>. AIS immediately re-educated and trained all pharmacy staff on 09/17/15 regarding USP <797> compliant garbing procedures specified in PHA-404. Please see Clinton KPI #14. As previously noted, AIS has translated the inspectors' observation into an institutionalized audit program (KPI #14) to ensure the garbing procedures of cleanroom personnel are in strict compliance with USP <797>.

- **Per your firm's SOP, AIS-PHA-404: "Hand Hygiene and Garbing", section 4.5.1.3, gowns may be saved for subsequent use during the same shift/day and must be hung on a hook on the clean side of the anteroom.**

    - **On 9/14/2015, a pharmacy technician was observed dragging their gown on the floor of the anteroom from the clean side to the dirty side and then hung up the gown on the dirty side of the anteroom to be reused.**

    - **On 9/14/2015, another pharmacy technician was observed entering the anteroom from the buffer room, and then hung their gown on the dirty side of the anteroom for subsequent use.**

AIS reviewed the organization's policy for garbing (PHA-404) and has determined that it is in compliance with USP <797>. AIS immediately re-educated and trained all pharmacy staff on 09/17/15 regarding USP <797> compliant garbing procedures specified in PHA-404. Please see Clinton KPI #14. As previously noted, AIS has translated the inspectors' observation into an institutionalized audit program (KPI #14) to ensure the garbing procedures of cleanroom personnel are in strict compliance with USP <797>.

- **The gowning components your firm uses during aseptic processing are not sterile. The gowns, hair covers, face masks, and shoe covers are stored in an unclassified area. Furthermore, the gowns are stored in an open bag.**

    - **On 9/14/2015, a pharmacy technician was observed without a beard net and no eye protection while processing in the ISO 7 and ISO 5 areas.**

Sterile garb is a cGMP requirement. AIS reviewed the organization's policy for garbing (PHA-404) and has determined that it is in compliance with USP <797>, which requires cleanroom personnel to don non-sterile shoe covers, a non-sterile hair net, a non-sterile facemask, and a non-sterile gown. Eye protection is not required by USP <797>, nor is it mandated by AIS policy as the pharmacy does not dispense hazardous drugs.

**OBSERVATION 4**

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

- **In the ISO 7 area (Buffer Room), rust spots were observed on floor, and what appears to be residue streaks were observed on the walls. Your ISO 7 area is adjacent to your**

**firm's ISO 5 area, where production occurs. Furthermore, no physical barrier distinguishes your firm's ISO 7 area from the ISO 5 area.**

As discussed with FDA inspectors, the residue described as "rust spots" on the floor in the observation was adventitious residue from a stainless steel cart wheel. AIS cleaned the areas noted by the inspectors, per protocol, on the same day that the observation was made. A new cleanroom floor that is smooth, seamless, impervious, and easily cleanable was installed in this cleanroom in January 2015, prior to commencing operations. Also the finding described as "residue streaks" is a cosmetic imperfection in the plastic wall of the ISO Class 7 buffer room. AIS confirmed with FDA inspectors while onsite that the area on the wall is smooth, impervious, and easily cleanable.

A physical barrier between the ISO Class 5 and ISO Class 7 areas is not a USP <797> requirement. AIS has conducted smoke studies, a USP <797> requirement, of the cleanroom's primary and secondary engineering controls. These studies demonstrate that the vertical laminar flow bench is providing unidirectional air flow throughout the direct compounding area.

- **According to the SOP, AIS-PHA-304: "Cleaning and Disinfecting of the Compounding Facility", cleaning will be performed in the ISO 5 area (VLAFW) prior to the beginning of each shift, immediately prior to each batch, every 30 minutes throughout the shift when ongoing drug production activities are occurring, after spills, and when microbial contaminations known to have been or is suspected of having been introduced.**

  - **Your firm provided a sample of the cleaning log for 9/14/2015 and a sample log from 7/10-16/2015 which shows daily cleaning only occurs at the beginning and end of the day.**

AIS has revised and clarified PHA-304 to require only documentation of beginning and end-of-the-day cleaning activities. USP <797> does not require the documentation of cleaning activities that are performed throughout a prolonged period of aseptic processing. AIS is concerned that requiring strict documentation of all in-process cleaning and disinfecting activity would force compounding personnel to exit ISO Class 5 environments during aseptic processing. Pharmacy leadership believes this is an unnecessary intervention.

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In conclusion, AIS appreciates the opportunity to formally respond to each 483 observation. Evaluating and responding to each observation has reaffirmed for AIS that all of the pharmacy's processes, whether aseptic or procedural, are in place for the sole purpose of creating a sterile end product for our patients. AIS is proud that its pharmacy has never encountered a sterility failure with any of its CSPs.