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February 24, 2015

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Natasha C. Johnson, J.D.
Food and Drug Administration
US Customhouse, Room 900
200 Chestnut Street
Philadelphia, PA 19106

Re: Infusion Partners' WAIVER for Publication of Response to Amended FDA Form 483 Issued December 12, 2014; FEI No. 3011127887

Dear Ms. Johnson

On behalf of Infusion Partners', I hereby authorize the United States Food and Drug Administration ("FDA") to publicly disclose the information described below on FDA's website. 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: Infusion Partners' Response to Amended FDA Form 483 Issued December 10, 2014; FEI No. 3011127887 dated January 9, 2015, excluding attachments/exhibits, which responds to FDA's Form 483 dated December 12. 2014.

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 Infusion Partners, and my full name, title, address, telephone number, and facsimile number is set out above for verification. Thank you.

Sincerely,

K. L

Kathryn M. Stalmack

KMS:rl

January 9, 2015

Via Electronic Mail and Federal Express
Anne Johnson, Deputy District Director
Food and Drug Administration
US Customhouse, Room 900
200 Chestnut Street
Philadelphia, PA 19106

Re: Infusion Partners' Response to Amended FDA Form 483 Issued December 10, 2014; FEI No. 3011127887/ Thomas E. Friel, Investigator/ Dorcas Ann Taylor, Investigator

Dear Ms. Johnson:

By way of introduction, I am the Senior Vice President, General Counsel of BioScrip, Inc., the parent company of Infusion Partners. Please allow this letter to serve as our response to the Federal Food and Drug Administration's ("FDA") Philadelphia District Office inspection of Infusion Partners, LLC (a subsidiary of BioScrip, Inc.) located in Sharpsburg, Pennsylvania, which occurred on December 1-5, 2014. At the conclusion of the inspection, FDA Investigators Thomas E. Friel and Dorcas Ann Taylor conducted a close-out meeting at the facility, in the presence of counsel and company management, at which time they presented an FDA Form 483 ("Form 483"), listing five observations.

Following the December 5, 2014 close-out meeting, FDA Investigators Friel and Taylor amended the FDA's December 5, 2014 Form 483, and presented a summary of the amendments made to the Form 483 via a telephone conference with Infusion Partners.[1] Infusion Partners received the final amended Form 483 on Friday, December 12, 2014 which contained the FDA's final observations ("Observations"). The FDA's Observations and Infusion Partners' responses to all Observations are due today, January 9, 2015, and are outlined in detail below.

Introduction

Infusion Partners, located in Sharpsburg, Pennsylvania, is an infusion therapy pharmacy duly licensed by the state of Pennsylvania.[2] For the past eleven (11) years, it has been providing

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1 Any reference hereinafter to "FDA Form 483" includes the original FDA Form 483 List of Inspectional Observations dated December 5, 2014 and the subsequent Amendment 1 dated December 10, 2014.

2 While most of its patients for whom it provides sterile preparations reside in Pennsylvania, Infusion Partners also holds non-resident pharmacy licensure for the states of Ohio and West Virginia.

quality sterile preparations to its patients, for a multitude of conditions to fulfill their otherwise unmet medical needs. Infusion Partners has and maintains an impeccable safety record concerning patient care, and complies with the guidelines set forth in United States Pharmacopeia Chapter on Pharmaceutical Compounding - Sterile Preparations, also known as USP<797> ("USP<797>"), although Pennsylvania has not yet formally adopted USP<797>. Most importantly, Infusion Partners is a compounding pharmacy that not only adheres to rigorous safety and quality standards for its compounded sterile preparations, but also *only* fills prescriptions for individually identified patients pursuant to a valid prescription from a prescriber, as required by Section 503A of the Federal Food, Drug, and Cosmetic Act ("FDCA"). Infusion Partners does not engage in *any* compounding for office stock, or compounding in anticipation of receiving prescriptions from prescribers - it only compounds preparations for specific patients. Lastly, Infusion Partners does not compound so-called "high-risk" sterile preparations; in fact, approximately eighty percent (80%) of its preparations are low-risk sterile preparations.

FDA's Observations Are Inconsistent with Section 503A's Explicit Exemption from cGMP

Infusion Partners' review of FDA's Form 483 Observations at the initial close-out meeting and subsequent conference call immediately revealed that the Investigators based the five (5) Observations on the application of FDA's current good manufacturing practices ("cGMP"). When directly asked during the close-out meeting and subsequent conference call regarding the legal basis for the Observations, Investigators Friel and Taylor stated that they could not confirm the legal or regulatory basis for the Observations; the discussion of the Observations that ensued was not based on any standards FDA applied either during the inspection or in the Observations. During the course of the discussions, counsel for Infusion Partners asked again for Investigators Friel and Taylor to confirm the applicable standard, which again they were unwilling to do. In fact, at no time during the FDA inspection, the exit conference or subsequent conference call could the FDA investigators cite the standard that they were applying to Infusion Partners despite being asked several times to do so. Even without this confirmation, it is clear that the Observations are based on cGMP, specifically, 21 C.F.R. Part 211.

FDA's Observations ignore the fact that Infusion Partners - which complies with the requirements set forth in Section 503A - is statutorily exempt from cGMP. Pharmacies operating under Section 503A of the FDCA are exempt from cGMP in accordance with the newly enacted Drug Quality and Security Act. Specifically, on November 27, 2013, President Obama signed into law the Drug Quality and Security Act ("DQSA"), Pub. L. No. 113-54. Title I of the DQSA, the Compounding Quality Act ("CQA"), eliminated certain unconstitutional advertising provisions from Section 503A, thus effectively re-enacting those provisions and allowing Section 503A unequivocally to go into effect. The statutory provisions, however, do not expand FDA's inspection authority or alter in any way applicable standards for compounding pharmacies, like Infusion Partners, that comply with FDCA Section 503A.

A critical aspect of Section 503A is the explicit recognition by Congress that pharmacies acting in compliance with Section 503A are exempt from certain provisions of the FDCA. In light of this Congressional mandate, FDA must adhere to Section 503A and cannot impose more stringent standards on Infusion Partners, such as the cGMP.

Section 503A provides:

> Sections 501(a)(2)(B), 502(f)(1) and 505 shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner . . . .[3]

FDA's non-binding guidance, published July 2, 2014,[4] is utterly consistent with the statute. It reiterates that drugs compounded in compliance with Section 503A will be exempt from certain sections of the FDCA including cGMP requirements (Section 501(a)(2)(B)); labeling with adequate directions for use (Section 502(f)(1)); and new drug requirements (Section 505). Guidance at 2.

FDA's website also acknowledges Section 503A's exemption from cGMP in its description of the law:

> Section 503A describes the conditions under which certain compounded human drug products *are entitled to exemptions* from three sections of the FDCA requiring:
>
> - Compliance with current good manufacturing practices (cGMP) (section 501(a)(2)(B));
> - Labeling with adequate directions for use (section 502(f)(1)); and
> - FDA approval prior to marketing (section 505).[5]

Infusion Partners is fully entitled to the statutory exemption from cGMP set forth in Section 503A. Infusion Partners compounds prescriptions only for individually identified patients, and it complies with local laws concerning compounding of sterile and non-sterile preparations. Although Pennsylvania has not yet adopted USP<797>, Infusion Partners complies

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3 Section 503A(b) further provides that a drug may be compounded if the pharmacist uses bulk substances that (1) comply with the standards of an applicable United States Pharmacopeia ("USP") or National Formulary ("NF") Monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are substances that are components of approved drug products; or (3) if neither of the above, then the drug appears on a shortage list developed by the FDA through regulations. Infusion Partners does not compound from bulk substances, so the bulk substances provisions are inapplicable here. It also does not compound medications on FDA's drug shortage list.

4 Final Guidance; Pharmacy Compounding of Human Drug Products under Section 503A of the Federal Food, Drug, and Cosmetic Act; Availability; 79 Fed. Reg. 37742 (Jul. 2, 2014).

5 FDA, Compounding: *available at* http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/.

with the stringent USP<797> guidelines that pertain to sterile compounding. FDA's Observations - and its application of the incorrect cGMP standard - make no different or otherwise inconsistent findings. FDA cannot inexplicably apply inapplicable cGMP requirements to make an end-run around other less rigorous, reasonable standards that are applicable to pharmacies that compound preparations for individually identifiable patients thereby entitling the pharmacies to an exemption under Section 503A. FDA also cannot leave compounding pharmacies, like Infusion Partners, guessing concerning what compliance standards they should be held to during FDA inspections.

The category of establishment FDA lists on the Form 483 - "Producer of Sterile Drugs" - is not a category recognized in any statute, rule or guidance. Similarly, FDA also has not published any regulations or even non-binding agency guidance that would provide inspection standards. Congress passed Section 503A, which, along with its statutory exemption from cGMP, applies to Infusion Partners. For all of these reasons, the cited Observations are not only incorrect, but also reflect FDA's wrongful application of inapplicable cGMP standards that adversely affect Infusion Partners' strong reputation and long history of patient safety in the provision of high-quality compounded preparations.

Preparation of this Response to FDA's Observations does not constitute an admission or agreement by Infusion Partners to the deficiencies or conclusions set forth in the Observations contained within the Form 483. None of the actions that may be taken by Infusion Partners pursuant to its response should be considered an admission that an Observation existed or that additional measures should have been in place at the time of the inspection. Without conceding that any of the Observations are applicable, set forth below are FDA's Observations, followed by Infusion Partners' Responses thereto. Infusion Partners respectfully requests that FDA rescind all Observations relative to Infusion Partners. Should FDA publish the Form 483 on its website, Infusion Partners respectfully requests that it publish this Response along with it. Infusion Partners also requests that FDA furnish a copy of this Response along with the Form 483 Observations if the Form 483 is disseminated to any third parties.

OBSERVATION 1

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

Investigator Allegations:

1. *On 12/01/14, the production of Rx# 140651666 (Total Parenteral Nutrition (TPN) 3-in-1 1270m1) was observed taking place in the ISO 6 Compounding Room and not under ISO 5 conditions. Three (3) ampoules of Addamel (lot 12G1B20) were opened and exposed in the ISO 6 environment at the beginning and the continued staging of materials and components in preparation for compounding. Additionally, components were staged in a manner*

requiring the technician to extend arms and upper torso over the opened and exposed ampoules.

2. *On 12/2/14, during the production of Rx# 014651945 (Vancomycin 1.5g/250m1NS bag) and Rx# 0140651917 (Cefepime 1g/10 ml syringe), technicians were observed vigorously shaking product after addition of a diluent to aid in dissolution of lyophilized powder.*

3. *Technicians were observed making frequent contact using gloved hands with nonsterile components and surfaces, such as door handle, trash bag, scissors and packaging material, prior to initiating aseptic processing without the application of sterile 70% isopropyl alcohol to sanitize hands.*

4. *On 12/2/2014, during the setup of the B. Braun Pinnacle TPN Management System (Part Number 60084, Serial number 1233), the technician was observed reusing the same sanitizing sterile pad over 15 times on tops of stoppered vials and the connections to the "6-Lead Transfer Set (Vented) for the use with Pinnacle TPN Management System" tubing which was labeled as sterile. During the reuse of the sanitizing sterile pad, the technician was observed rewetting the pad with sterile 70% isopropyl alcohol.*

5. *There is no evidence that media fills are performed under the most stressful or challenging conditions. The firm uses an aseptic technique validation kit which doesn't utilize equipment and containers used in normal processing.*

6. *Technicians were observed not practicing good aseptic technique while performing aseptic manipulations in the ISO 5 critical area. For example:*

    a. *On 12/3/14, a technician was observed applying non-sterile Alcare Foamed Antiseptic Handrub to sterile gloves prior to initiating aseptic processing in the ISO 5 area.*
    b. *On 12/2/14, a technician was repeatedly observed immediately wiping gloved hands with non-sterile wipes after sanitizing with sterile 70% isopropyl alcohol prior to initiating aseptic processing in the ISO 5 area, thereby not allowing for sufficient contact time of the isopropyl alcohol.*
    c. *During the production of the Rx 0140649338 (TPN), the technician was observed picking up paper trash from the floor. The technician immediately resumed aseptic processing of the TPN drug product without sanitizing his hands.*

Infusion Partners Response: Infusion Partners objects to Observation 1 and the allegations therein because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 1 copies verbatim 21 C.F.R. § 211.113(b). Specifically, it requires: "Appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile shall be established, written, and

followed." FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP, Infusion Partners submits the following as its response to Observation 1:

1. It is Infusion Partners' practice not to open the vials on the ISO 6 side of the curtain then place them onto the ISO 5 bench top. All Infusion Partners actions will occur in the ISO 5 space going forward. Once the compound batch is staged as described (opened vials), all technicians will not put their arms and torso over top of the vials, as the gown and garb is not sterile. All staff engaged in this practice will be retrained on proper procedure. [Attachment A, Documentation of Staff Training.]

2. cGMP guidance requires slow and deliberate motions in the cleanroom. However, the USP Chapter 797 only states that "operators may also create disruptions in airflow by their own movements". And while cGMP does not apply to Infusion Partners, it does not engage in the practice of vigorous shaking of vials to speed product dissolution. The impact of the action as described is offset by the high number of air changes per hour in the ISO 5 and ISO 6 spaces. Nevertheless, staff will be retrained on proper procedure for handling vials.

3. Infusion Partners' practice and procedure requires the application of sterile 70% isopropyl alcohol to sanitize hands as its basic aseptic technique. All staff will be retrained on proper procedure for hand sanitation and aseptic technique.

4. It is not Infusion Partners' practice to swab the TPN tubing connection because it is sterile, and therefore, it contests the validity this Observation. With respect to Infusion Partners use of wipes in general, aseptic technique training materials do permit the use of sanitizing sterile wipes on more than one vial as long as the wipe is still moist with alcohol. Rewetting the wipe with sterile alcohol is not part of Infusion Partners' training. Specifically, Infusion Partners' policy states "the vial tops will be swabbed (not sprayed) with sterile alcohol pad prior to breaking the products seal with the introduction of a needle or transfer device. The IPA must remain wet for at least ten seconds." [Attachment B, Policy CLIN-PH214, General Compounding Procedures] While it is not Infusion Partners' common practice to use the same alcohol swab over 15 times to swab a vial top as noted in the Observation, the vial tops in this situation did remain "wet" for 10 seconds after being swabbed with sterile alcohol in compliance with policy. Nevertheless, staff will be retrained to use more alcohol wipes on fewer vials.

5. The aseptic validation kit was changed from the Valiteq media kit to a duplication of parenteral nutrition compounding in Q2 2014. This is an annual test, and therefore, the staff had not completed the new aseptic technique validation test. Accordingly, Infusion

Partners request that this observation be deleted. Notwithstanding the inapplicability of FDA's cGMP, Infusion Partners has implemented and follows appropriate written procedures to prevent microbial contamination of drug preparations purporting to be sterile; its procedures are not deficient in any applicable respect. In particular, Infusion Partners' policies and procedures for preventing microbial contamination are adopted from USP<797>. USP<797> requires a media fill test that represents the most challenging or stressful conditions actually encountered by the personnel being evaluated when they prepare low- and medium-risk level CSPs. The Valiteq RL-2 media validation kits used by Infusion Partners reflect both low- and medium-risk compounding processes (85% of the compounding activity at this pharmacy is low-risk). A new process simulation test representing low- and medium-risk aseptic compounding was implemented by Infusion Partners on July 1, 2014, which the compounding staff at the pharmacy will complete during their annual competency requirement. This newer procedure is a better representation of the most challenging medium-risk sterile compounding processes they employ. In addition, process simulation media fill evaluations are an annual event for low- and medium- risk compounding and are part of the Competency Manual; specifically the Orientation and Annual Competency. [Attachment C, Competency Policies - COMP-PH04, COMP-PH07, COMP-PH01 and COMP-PH05]. Documentation of completion is contained in each employee file. Infusion Partners does not perform high-risk sterile compounding.

6. Infusion Partners' technicians practice good aseptic technique while performing aseptic manipulations in the ISO 5 critical area.

   (a) Staff has been retrained that nonsterile antiseptic handrub is not intended for use on sterile gloves.

   (b) Infusion Partners' policy requires that sterile alcohol sanitizer be allowed to air dry on the gloves before initiating compounding. Staff has been retrained on this policy. [Attachment B, Policy CLIN-PH214]

   (c) Infusion Partners' policy requires sanitization of sterile gloves that have touched nonsterile surfaces prior to commencing compounding activity. Staff has been retrained regarding this process.

OBSERVATION 2

Aseptic processing areas are deficient regarding systems for maintaining any equipment used to control the aseptic conditions.

Investigator Allegations:

1. *The (TPN) workbench and Chemo Biological Safety Cabinet where sterile injectable products are produced are deficient in their ISO 5 classification in that these areas have not been properly qualified through the performance of airflow studies (smoke studies) to assure unidirectional airflow under static and dynamic conditions.*

2. *Technicians were observed throughout the time moving in a manner that did not appear measured, slow, or deliberate. The technicians freely move in the entire ISO 6 area without restriction. There was no clear line of demarcation between the ISO 5 and ISO 6 environments except for a clear plastic liner which hangs down approximately 3 feet from the 9 foot ceiling.*

Infusion Partners Response: Infusion Partners objects generally to Observation 2 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy operating under FDCA Section 503A. Observation 2 repeats verbatim 21 C.F.R. § 211.42 (c)(10)(vi). Specifically, it requires: "A system for maintaining any equipment used to control the aseptic conditions." FDA's cGMP regulations (and non-binding guidance related thereto)[6] are inapplicable because Section 503A pharmacies are statutorily exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP to Infusion Partners, Infusion Partners' aseptic processing areas are *not* deficient regarding systems that Infusion Partners uses for maintaining equipment used to control aseptic conditions.

1. USP<797> does not require a particular frequency to perform smoke testing; it states that, "In situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions." Infusion Partners policy requires that clean room certification testing, including smoke studies, be conducted under dynamic conditions. Controlled Environment Certification Guidelines (CETA) similarly states, as does USP<797>, that there is no explicit requirement for smoke testing the clean room. Infusion Partners complied with the applicable guidelines and its internal policies and procedures.

2. USP Chapter<797> neither uses the terms "measured, slow or deliberate" in terms of staff movement in the cleanroom nor provides any indication of limitations of movement within the ISO 6 environment. There is also no requirement for clear lines of demarcation of the difference between ISO 6 and ISO 5 areas. With that being said, the curtain affixed to the ceiling is in place to clearly mark the line of demarcation as is the fixed placement of the ISO 5 compounding bench. The ceiling height is 8'6" and the

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[6] *See, e.g.*, FDA, Center for Drug Evaluation and Research, Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, Pharmaceutical cGMPs (September 2004).

curtain hangs down to 5'6" which is adequate to indicate appropriate position of the operators' head and arms in the ISO 5 space. Infusion Partners Policy CLIN0-PH211 regarding Clean Room Access and Transport supports this practice. [Attachment D, Policy CLIN0-PH211.]

OBSERVATION 3

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

Investigator Allegations:

1. *Your firm has not conducted cleaning efficacy studies to assure the suitability and effectiveness of non-sterile Accel TB (0.5% hydrogen peroxide), bleach solution mixed 1:10 dilution with potable water, and sterile 70% isopropyl alcohol used to clean and disinfect ISO 5 areas, Compounding Room, Chemo Room and ante room.*

2. *The firm does not use a sporicidal agent to disinfect the clean room including the ISO 5 area. Daily cleaning of the ISO 5 critical areas consists of Sterile 70% isopropyl alcohol.*

3. *On 12/1/14, a spray bottle labeled "water" was observed on a tray in the ISO 6 Compounding Room. The firm reported that the spray bottle contains Sterile Water For Irrigation used to clean up crystallized drug residue resulting from spills in the ISO 5 area that cannot be removed using sterile 70% isopropyl alcohol. The spray bottle is non-sterile but sanitized externally using sterile 70% isopropyl alcohol prior to entry into the ISO 6 Compounding Room.*

Infusion Partners Response: Infusion Partners objects to Observation 3 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 3 copies verbatim 21 C.F.R. § 211.42(c)(10)(v). Specifically, it requires: "a system for cleaning and disinfecting the room and equipment to produce aseptic conditions." FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of cGMP, Infusion Partners has processes and procedures in place that assure aseptic conditions when cleaning and disinfecting the clean room and equipment. The USP<797> guideline that most appropriately applies to the activities cited in a) through c) is as follows: "Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material and residue from spills; for example, water-soluble solid residues are removed with sterile water (for injection or irrigation) and low-shedding wipes. This shall be followed by wiping with a residue-free disinfecting agent such as sterile 70% IPA, which is

allowed to dry before compounding begins." Infusion Partners policy Nos. CLIN-PH212, Preparing to Compound Sterile Preparations [Attachment E]; CLIN-PH304, ISO Class 5 (Class 100) Clean Rooms: Cleaning [Attachment F] and CLIN-PH306, ISO Class 7 (Class 10,000) Clean Rooms: Cleaning [Attachment G] contain the requirements for cleaning and disinfecting the compounding rooms and equipment as well as the compounding surfaces. The policies comply with USP<797>, including the use of disinfectants like accelerated hydrogen peroxide (Accel TB™), sterile isopropyl alcohol, and a sporicidal concentration (10:1) of bleach once a month.

1. Since cleaning efficacy studies are neither required nor mentioned anywhere in USP<797>, Infusion Partners does not perform these studies. Relative to the use of Accel TB, sterile 70% isopropyl alcohol is the preferred final disinfecting agent described in USP<797>, as noted above. One-step disinfectants like Accel TB™ (accelerated hydrogen peroxide), which is non-sterile, are addressed in USP<797> as being "effective in the presence of light to moderate soiling without a pre-cleaning step" with sterile water. USP <797> routinely refers to the "approved" or "suitable" disinfectant with isopropyl alcohol, which is listed not as a definitive requirement, but an "example" of a suitable disinfecting agent.

2. USP<797> does not require the use of sporicidal agents to disinfect the ISO 5 surfaces, and in fact recommends the use of sterile isopropyl alcohol. Infusion Partners has implemented the USP position on disinfectants as stated in USP<1072> and referenced in USP<797> as the source for USP<797> statements: "Because it is theoretically possible that the selective pressure of the continuous use of a single disinfectant could result in the presence of disinfectant-resistant microorganisms in a manufacturing area, in some quarters the rotation of disinfectants has been advocated. However, the literature supports the belief that the exposure of low numbers of microorganisms on facility and equipment surfaces within a clean room where they are not actively proliferating will not result in the selective pressure that may be seen with the antibiotics. It is prudent to augment the daily use of a bactericidal disinfectant with ***weekly (or monthly) use of a sporicidal agent.*** The daily application of sporicidal agents is not generally favored because of their tendency to corrode equipment and because of the potential safety issues with chronic operator exposure." The sporicidal agent is bleach in a 10:1 concentration.

3. USP<797> states, "when the surface to be disinfected has heavy soiling, a cleaning step is recommended prior to the application of the disinfectant. Trained compounding personnel are responsible for developing, implementing and practicing the procedures for cleaning and disinfecting the DCAs written in the SOPs. Cleaning and disinfecting shall occur before compounding is performed. Items shall be removed from all areas to be cleaned, and surfaces shall be cleaned by removing loose material and residue form spills….." It is not Infusion Partners' policy to transfer sterile water into a nonsterile bottle for subsequent use in cleaning drug residue. Any such practice has ceased and

staff retrained to use sterile water from a sterile container to clean drug residue. [Attachment F Policy CLIN-PH304]

OBSERVATION 4

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

Investigator Allegations:

1. *Environmental monitoring of surfaces for microbial contamination is not performed during routine processing of sterile injectable drug products in the ISO 5 area. Your firm only performs such monitoring on a monthly basis. Additionally, the product information sheet for the Hycon YM contact plates used for yeast and mold growth promotion requires incubation parameters of 3-7 days at 20-25° C. Review of documentation relevant to plates for surface contamination identifies incubation parameters of 35° C for 3 days.*

2. *Technician's gloves are not monitored for microbial contamination during routine processing of sterile drug products. Glove tips are monitored on an annual basis for current employees and 3 times during a two week period for new hires as part of qualification.*

3. *Environmental monitoring for non-viable particulates and viable air counts is not performed during routine production of sterile injectable drug products. Such monitoring is performed on a semi-annual basis during cleanroom certification by an outside vendor.*

4. *Pressure gauges in the ISO 6 Compounding Room and ISO 7 Ante Room are not continuously monitored for air pressure differential. Instead personnel perform a daily visual inspection of the pressure gauges to verify they are reading within the specification of 0.02-0.05" H_20.*

Infusion Partners Response: Infusion Partners objects to Observation 4 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 4 copies verbatim 21 C.F.R. § 211.42(c)(10)(iv). Specifically, it requires: "A system for monitoring environmental conditions." FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of cGMP, Infusion Partners' environmental monitoring is not deficient. The environmental monitoring performed by Infusion Partners is in compliance with USP<797> and our accreditation standards[7].

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[7] Infusion Partners is accredited for Infusion Pharmacy Services (including Sterile Compounding, see USP<797>) by the Accreditation Commission for Health Care, Inc. ("ACHC"). [Attachment H - ACHC Certificate of Accreditation, 12/19/2013 – 12/18/2016]. ACHC requires its accredited Infusion Pharmacy providers to adhere to USP <797> in

1. USP<797> guidelines state that surface sampling shall be performed in all ISO classified areas on a periodic basis. Sampling can be accomplished using contact plates or swabs, and it shall be done at the conclusion of compounding. Infusion Partners policy CLIN-PH307, Environmental Monitoring of the Clean Room requires surface sampling every month according to the prescribed facility plan. Infusion Partners is in compliance with this policy and in fact performs surface sampling on a monthly basis. Additionally, Infusion Partners' policy for contact plate testing requires samples be incubated at temperatures outlined on contact plate package inserts. The documentation referenced showed that the Hycon YM contact plates had been incubated at the incorrect temperature. As soon as this was noted to Infusion Partners by the investigator, the correct incubation parameters for these plates were immediately implemented as shown on the attached bacterial and fungal surface sampling logs and package inserts for the bacterial and fungal. [Attachment J - Infusion Partners Surface Sampling Logs – CLIN-PH005-3A, PH005-3B] and [Attachment K – Package Inserts for Contact Plates]

2. USP<797> requires 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. It also requires using one or more sample collections during any media fill test procedure before they are allowed to continue compounding CSPs for human use. The policy is found under COMP-PH04 and COMP-PH07 (annual competencies) and COMP-PH01 and COMP-PH05 (the initial 90-day competency policies); which requirement meets verbatim guidelines set forth in USP<797>. [Attachment C.] Infusion Partners complies with these policies concerning gowning and gloving evaluations and re-evaluations, and media fills. Documentation of personnel testing is available upon request.

3. The USP<797> guidelines state as follows: "Environmental sampling shall occur as part of a comprehensive quality management program and shall occur minimally under any of the following conditions:

   - as part of the commissioning and certification of new facilities and equipment;
   - following any servicing of facilities and equipment;
   - as part of the re-certification of facilities and equipment (i.e., every 6 months);
   - in response to identified problems with end preparations or staff technique; or
   - in response to issues with CSPs, observed compounding personnel work practices, or patient-related infections (where the CSP is being considered as a potential source of the infection)."

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order to meet its accreditation standards. [Attachment I - ACHC Letter dated September 19, 2013 – "Accreditation Commission for Health Infusion Pharmacy Accreditation Includes USP 797".] ACHC's Accreditation Standards for Infusion Pharmacy Services are available upon request.

Infusion Partners addresses these USP<797> requirements in several policies. Certification of new facilities and equipment is required prior to start-up in policy No. CLIN-PH007, Infusion Pharmacy Gap Analysis. [Attachment L]. The requirement for recertification every six months and after any servicing of facilities and equipment is found in policy Nos. CLIN-PH 303, ISO Class 5 (Class 100) Clean Bench Rooms: Routine and Preventive Maintenance, [Attachment M] CLIN-PH305, ISO Class 7 Clean Rooms: Routine and Preventive Maintenance [Attachment N] and CLIN-PH307, Environmental Monitoring of the Clean Room [Attachment O]. Environmental sampling in response to identified problems with end preparations or staff technique falls under policy Nos. CLIN-PH300, Validation Testing of Aseptic Technique [Attachment P], CLIN-PH301, Testing of Products Dispensed to the Patient Environment [Attachment Q] and CLIN-PH307, [Attachment O].

4. USP <797> requires as follows: "A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the buffer area and the ante-area and between the ante-area and the general environment outside the compounding area. The results shall be reviewed and documented on a log at least every work shift (minimum frequency shall be at least daily) or by a continuous recording device." Applicable Pennsylvania State pharmacy regulations and Infusion Partners' accreditation standards do not require continuous monitoring; therefore, the investigator's allegations do not reflect the requirements applicable to this pharmacy location. Per Infusion Partners' policy, the pressure gradient is monitored and documented daily and per shift. Documentation of Infusion Partners' monitoring of the pressure gradient is available upon request.

OBSERVATION 5

Clothing of personnel engaged in the processing of drug products is not appropriate for the duties they perform.

Investigator Allegations:

1. *Gowns/coveralls, facemasks, bouffant hair nets and goggles worn by operators working inside ISO 5 zones are not sterile. Additionally, the technician's face and neck are not fully covered allowing exposed facial skin and hair over the ISO 5 critical area.*

Infusion Partners Response: Infusion Partners objects generally to Observation 5 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 1 applies 21 C.F.R. § 211.28 (a). Specifically, "Personnel engaged in the . . . processing . . . of a drug product shall wear clean clothing appropriate for the duties they perform." FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

1. Notwithstanding the inapplicability of cGMP, Infusion Partners' clean room operators were in fact wearing appropriate garb for the duties they perform, based on applicable standards and guidance. USP<797>, applicable state pharmacy regulations, and ACHC's accreditation standards require "shoe covers, head and facial hair covers, face mask, fingernail cleansing, hand and forearm washing and drying; non-shedding gown" as well as "donning sterile gloves." There is no requirement for sterile garb other than gloves, or for preventing exposure of all facial skin. Infusion Partners requires its operators to use coveralls with integral booties and hood, used in combination with a hair cover.

Further, USP<797> states, "Eye shields are optional unless working with irritants such as germicidal disinfecting agents or when preparing hazardous drugs." As a result, Infusion Partners clean room operators' use of goggles complies with USP<797>.

Conclusion

Based on the foregoing, Infusion Partners respectfully asserts that FDA's Observations are based on an inspection where FDA applied inapplicable and incorrect standards to the pharmacy, compounding operations, personnel and procedures - namely, the cGMP. Infusion Partners is a compounding pharmacy acting in accordance with FDCA Section 503A and the Section 503A statutory exemptions. Thus, FDA's Form 483 Observations concerning alleged cGMP violations were inappropriately issued and should be rescinded, or in the alternative, amended to reflect the correct standard to which Infusion Partners should be held. Likewise, any public dissemination of FDA's Form 483 that pertains to the inspection at issue should be accompanied by Infusion Partners' Response contained herein. Thank you for your cooperation.

Respectfully Submitted,

Kimberlee C. Seah
Senior Vice President, General Counsel and
Secretary

KMS:hln

cc: Kathryn M. Stalmack
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