POLSINELLI

161 N. Clark Street, Suite 4200, Chicago, IL 60601-3316 • 312.819.1900

March 24, 2015

Kathryn M. Stalmack
(312) 873-3608
(312) 873-4006 Direct Fax
kstalmack@polsinelli.com

Mr. Ronald Pace, Acting District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433-1034

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

Dear Mr. Pace,

On behalf of BioScrip, Inc., the parent company of Lake Success ("Lake Success") located in Jamaica, New York, 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: Lake Success' October 10, 2014 Response to FDA Form 483 Issued September 19, 2014; FEI No. 3011022663 dated, excluding attachments/exhibits, which responds to FDA's Form 483 dated September 19, 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 Lake Success, and my full name, title, address, telephone number, and facsimile number is set out above for verification. Thank you.

Sincerely,

Kathryn M. Stalmack

172 Facility 7725814880 2/12/15

POLSINELLI

161 N. Clark Street, Suite 4200, Chicago, IL 60601-3316 • 312.819.1900

February 10, 2015

Kathryn M. Stalmack
(312) 873-3608
(312) 873-4006 Direct Fax
kstalmack@polsinelli.com

Mr. Ronald Pace, Acting District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433-1034

**Re: Lake Success' REQUEST TO PUBLISH Response to FDA Form 483 Issued September 19, 2014; FEI No. 3011022663**

Dear Mr. Pace:

By way of introduction, I am one of the attorneys for BioScrip, Inc., the parent company of Lake Success ("Lake Success") located in Jamaica, New York. After an inspection of Lake Success on September 9, 11, 12 and 19, 2014, the Food and Drug Administration ("FDA") issued a Form 483 dated September 19, 2014. Lake Success submitted a Response to FDA's amended Form 483 on October 10, 2014. On January 22, 2015, Lake Success learned that FDA published the FDA Form 483 on its website.

To that end, please allow this correspondence to serve as Lake Success' request for FDA immediately to publish Lake Success' Response to FDA's 483. We appreciate your immediate attention to this matter. If you have any questions, please do not hesitate to contact me directly at 312-873-3608.

Sincerely,

K. L

Kathryn M. Stalmack

KMS:rl

Enc.

**SENT VIA EMAIL (ronald.pace@fda.hhs.gov)**
**& OVERNIGHT DELIVERY**

October 10, 2014

Mr. Ronald M. Pace, District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433-1034

**Re: BioScrip Pharmacy (NY), Inc. Response to FDA Form 483 Issued September 19, 2014; FEI No. 3011022663/ James A. Liubicich, Investigator**

Dear Mr. Pace:

By way of introduction, I am the Senior Vice President, General Counsel of BioScrip, Inc., the parent company of BioScrip Pharmacy (NY), Inc. ("BioScrip NY"). Please allow this letter to serve as our response to the Federal Food and Drug Administration's ("FDA") New York District Office, Inspection of BioScrip NY which occurred on September 10, 11, 12 and 19, 2014. At the conclusion of the inspection, FDA Investigator, James A. Liubicich, conducted a close-out meeting at the facility, in the presence of counsel and company management at which time he presented an FDA Form 483, listing nine Observations. BioScrip NY's response to those Observations is outlined in detail below.

**Introduction**

BioScrip NY is an infusion therapy pharmacy duly licensed by the State of New York. For the past twelve years, it has been providing the highest quality sterile preparations to its patients throughout greater New York for a multitude of conditions to fulfill their otherwise unmet medical needs. BioScrip NY has and maintains an impeccable safety record with no issues concerning assurance of sterility. Most importantly, BioScrip NY is a compounding pharmacy that not only adheres to rigorous safety and quality standards for its compounded 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"). BioScrip NY does not engage in *any* office use compounding, or compounding in anticipation of receiving prescriptions from prescribers – it only compounds preparations for specific patients. Lastly, BioScrip NY does not compound so-called "high-risk" sterile preparations; eighty-five percent (85%) of its preparations are low-risk sterile preparations.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

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

BioScrip NY's review of FDA's Form 483 Observations at the close-out meeting immediately revealed that the Investigator based the nine Observations on the application of FDA's current good manufacturing practices ("cGMP"). When directly asked during the close-out meeting the legal basis for the Observations, Investigator Liubicich confirmed that *"each and every"* Observation was based on cGMP, specifically, 21 C.F.R. "part 211."

FDA's Observations ignore the fact that BioScrip NY – which complies with the requirements set forth in Section 503A – is 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, 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 that comply with FDCA Section 503A.

A critical aspect of Section 503A is the explicit recognition that pharmacies acting in compliance with Section 503A are exempt from certain provisions of the FDCA. 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 . . . .[1]

FDA's non-binding guidance, published July 2, 2014,[2] is utterly consistent with the statute. It reiterates that drugs compounded in compliance with Section 503A will be

---

[1] 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.

[2] 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).

exempt from certain sections of the FDCA including cGMP requirements (Section 503(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).[3]

BioScrip NY is fully entitled to the exemption from cGMP set forth in Section 503A. It compounds prescriptions only for individually identified patients, and it complies with local laws concerning compounding of sterile and non-sterile preparations. FDA's Observations – and its application of the incorrect cGMP standard – make no different or otherwise inconsistent findings. FDA admitted repeatedly during the close-out meeting that all of the nine Observations were based on cGMP; it cited to no other legal or regulatory basis for the Observations. FDA cannot inexplicably apply inapplicable cGMP requirements to make an end-run around other reasonable standards that are applicable to pharmacies that compound preparations for specific patients pursuant to state law and USP guidelines consistent with Section 503A. FDA also cannot leave compounding pharmacies like BioScrip NY 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 exemption from cGMP, applies to BioScrip NY.

For all of these reasons, the cited Observations are not only incorrect, but also reflect FDA's wrongful application of an inapplicable standard that adversely affects BioScrip NY's strong reputation and long history of patient safety in the provision of high-quality compounded preparations to those patients.

---

[3] FDA, Compounding; *available at* http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

Preparation of this Response to FDA's Observations does not constitute an admission or agreement by BioScrip NY to the alleged deficiencies or conclusions set forth in FDA's Observations.. None of the actions that may be taken by BioScrip NY 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 BioScrip NY's Responses thereto. BioScrip NY respectfully requests that if FDA publishes on its Website the Form 483 issued to BioScrip NY, then it publish this Response along with it, and also provide this Response when FDA provides the Observations to third parties.

## OBSERVATION 1

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

***Investigator Allegations:*** *Smoke studies were not performed under dynamic conditions to verify that operators processing equipment or activities of the ISO 7 clean rooms do not alter or impede the unidirectionality of air from the HEPA filters in the two ISO 5 laminar flow hoods, nor the one operational ISO 5 biological safety cabinet where drug products are aseptically processed.*

**BioScrip NY Response**: BioScrip NY objects generally to Observation 1 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy operating under FDCA Section 503A. Observation 1 repeats verbatim 21 C.F.R. § 211.42 (c)(10)(vi). (Specifically, that section of 21 C.F.R. part 211 states, "A system for maintaining any equipment used to control the aseptic conditions.") FDA's cGMP regulations (and non-binding guidance related thereto)[4] are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP to BioScrip NY, BioScrip NY's aseptic processing areas are *not* deficient regarding systems that BioScrip NY uses for maintaining equipment used to control aseptic conditions. Smoke studies (both under static and dynamic conditions) were conducted by our third party testing company, ENV Services ("ENV"), on July 3, 2014, and are conducted by ENV every six (6) months as part of BioScrip NY's policies and procedures. [See Attachment A - CLIN-PH305, ISO

---

[4] *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).

Class 7 Clean Rooms: Routine and Preventive Maintenance, and Attachment B - BioScrip and ENV Services Service Agreement 110113.] The studies reflect passing results. The smoke studies performed inside the two ISO 5 laminar flow hoods in the clean room and the ISO 5 biological safety cabinet were completed under dynamic aseptic conditions, but not while employees were compounding preparations to be dispensed to patients because the presence of the testing equipment and the smoke itself in the ISO 5 zones were deemed a threat to aseptic compounding by the pharmacist-in-charge. The United States Pharmacopeia ("USP") Chapter on sterile compounding (USP<797> - Compounding Sterile Preparations) 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." BioScrip NY policy requires that cleanroom certification testing, including smoke studies, be conducted under dynamic conditions, but under simulated compounding conditions since USP<797> neither specifies nor requires "actual" patient compounding to conduct smoke studies under dynamic conditions. Controlled Environment Certification Guidelines (CETA) similarly state, as does USP<797>, that there is no explicit requirement for smoke testing the clean room. [See Attachment C - CETA Certification Guide for Sterile Compounding Facilities, CAG-003-2006-11, Revised January 31, 2012, and Attachment D - CETA Certification Matrix for Sterile Compounding Facilities (Secondary Engineering Controls) CAG-008-2010, January 31, 2012.] This pharmacy complied with the applicable guidelines and its internal policies and procedures.

***Investigator Allegations:*** *The two ISO 7 clean rooms, the ISO 7 anteroom, and the unclassified surrounding areas are not continuously monitored for air pressure differentials during production.*

**BioScrip NY Response:** 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 New York State pharmacy regulations and BioScrip NY's accreditation standards[5] do not require continuous monitoring; therefore, the investigator's

[5] BioScrip NY is accredited for Infusion Pharmacy Services (including Sterile Compounding, Ref. USP<797>) by the Accreditation Commission for Health Care, Inc. (ACHC). [See Attachment E – ACHC Certificate of Accreditation, December 19, 2013-December 18, 2016]. ACHC requires its accredited Infusion Pharmacy providers to adhere to USP <797> in order to comply with its accreditation standards. [See Attachment F ACHC Letter dated September 19, 2013 – "Accreditation Commission for Health Infusion Pharmacy Accreditation Includes USP 797".] ACHC Accreditation Standards for Infusion Pharmacy Services are available upon request.

allegations do not reflect the requirements applicable to this pharmacy location. Per BioScrip NY policy, the pressure gradient is monitored and documented daily and per shift. [See Attachment G, CLIN-PH005 – Pharmacy Checklist Documentation of BioScrip NY's monitoring of the pressure gradient is available upon request.

***Investigator Allegations:*** *During the semi-annual clean room certification performed by an outside vendor on 1/06/14, the differential pressure in the non-hazardous (IV mix room) was found not to meet the required firm's limit. The measurement was at negative 0.007 below the limits of 0.02-0.05, yet no investigation was performed to determine the cause of the recorded value.*

**BioScrip NY Response**: The certification report issued by the third party testing company reads "DIFFERENTIAL PRESSURE IN IV MIX ROOM (-0.007) NEGATIVE WHILE POSITIVE PRESSURE 0.02-05 REQUIRED". There is no record of immediate actions taken to resolve the discrepancy because none was required. The cleanroom manometer that measures the differential was reading "0.05" when the written report was received from ENV, the certifying agency, on or about January 20, 2014, and no action was deemed necessary at that time. Specifically, BioScrip NY policy requires maintenance of the air pressure gradient of 0.02 – 0.05, verified daily by visual check of the manometer reading (per USP<797>). [See Attachment A - CLIN-PH305, ISO Class 7 Clean Rooms: Routine and Preventive Maintenance.]

***Investigator Allegations:*** *An operator was observed opening a package of sterile gloves by placing the outer non-sterile wrapping onto an ISO 5 working surface where sterile drugs were being processed. Additionally, during sterile drug processing the operator was observed placing a non-sterile cloth wipe onto the same ISO 5 working surface.*

**BioScrip NY Response:** BioScrip NY's aseptic compounding policy does not permit placing non-sterile items in the sterile field. [See Attachment H - CLIN-PH214, General Compounding Procedures.] During subsequent counseling, the operator attributed the error to nervousness (specifically, being observed by the inspector during compounding operations). The operator has been re-trained on the aseptic policy and proper procedure. Such retraining has been documented, and documentation is available upon request.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

**OBSERVATION 2**

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

***Investigator Allegations:***
a) *Sterile drug products are aseptically manipulated by clean room operators who were observed wearing non-sterile gowns, non-sterile glasses/goggles, non-sterile footwear, non-sterile facial masks, and non-sterile bonnets.*

b) *The operator's face and neck are not fully covered allowing exposed facial skin and hair over that critical ISO 5 laminar flow areas where sterile injectable drug products are processed.*

**BioScrip NY Response:** BioScrip NY objects generally to Observation 2 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 2 repeats 21 C.F.R. § 211.28 (a). (Specifically, that section of 21 C.F.R. part 211 states, "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.

Notwithstanding the inapplicability of cGMP, BioScrip NY's clean room operators were in fact wearing appropriate garb for the duties they perform, based on applicable standards and guidance. USP<797>, applicable pharmacy regulations, and our 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. Notwithstanding BioScrip NY's compliance with applicable guidance, and although not a requirement of USP<797>, BioScrip NY has converted to requiring its operators to use coveralls with integral booties and hood, used in combination with a hair cover. [See Attachment I.] BioScrip NY will retrain all operators working in the sterile field to ensure that there is no exposed hair or skin, and documentation of this training will be made available upon request.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

## OBSERVATION 3

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

***Investigator Allegations:***
a*) Environmental monitoring for viable air counts in the ISO 5 zones is not performed at least daily during periods of production. The firm only monitors viable air counts during the semi-annual cleanroom certification by an outside vendor, lastly on 07/01/2014.*

*b) Environmental monitoring for non-viable particulates in the ISO 5 zones is not performed under dynamic conditions. This was last performed on 07/01/2014.*

*c) The work surfaces, inside the ISO 5 hoods, are not tested for microbial contamination at least daily during periods of production and at the end of operations. This monitoring is only performed monthly.*

*d) Operators' gloves are not tested for microbial contamination at least daily during periods of production. Glove fingertips are only monitored annually.*

**BioScrip NY Response**: BioScrip NY 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)(iv). (Specifically, that section of 21 C.F.R. part 211 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, BioScrip NY's environmental monitoring is not deficient. The environmental monitoring performed by BioScrip NY, and as described above, is in compliance with USP<797> and our accreditation standards. The USP<797> guidelines state as follows:

"a.) 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)."

BioScrip NY addresses these USP<797> requirements in several policies. Certification of new facilities and equipment is required prior to start-up in policy CLIN-PH007, Infusion Pharmacy Gap Analysis. [See Attachment J.] 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, [See Attachment K] CLIN-PH305, ISO Class 7 Clean Rooms: Routine and Preventive Maintenance [See Attachment A] and CLIN-PH307, Environmental Monitoring of the Clean Room [See Attachment L]. Environmental sampling in response to identified problems with end preparations or staff technique falls under policy Nos. CLIN-PH300, Validation Testing of Aseptic Technique [See Attachment M], CLIN-PH301, Testing of Products Dispensed to the Patient Environment [See Attachment N] and CLIN-PH307, Environmental Monitoring of the Clean Room [See Attachment L].

b) The ENV Certification Report from July 1, 2014 reports that testing was performed at rest, notwithstanding BioScrip NY's policy CLIN-PH305, ISO Class 7 Clean Rooms: Routine and Preventive Maintenance [See Attachment A] requires that testing must be performed under dynamic conditions. The staff has been retrained on the policy and documentation of retraining can be provided upon request.

c) 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. BioScrip NY policy CLIN-PH307, Environmental Monitoring of the Clean Room [See Attachment L] requires surface sampling every month according to the prescribed facility plan. BioScrip NY is in compliance with this policy and in fact performs surface sampling on a monthly basis.

d) 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 policy Nos. COMP-COMP01, Competency Program, COMP-PH01, 90 Day Competency Assessment-Pharmacist; COMP-PH04, Annual Competency Assessment Pharmacist; COMP-PH05, 90 Day Competency Assessment-Pharmacy Technician and COMP-PH07, Annual Competency Assessment-Pharmacy Technician [See Attachment O] which requirement meets verbatim guidelines set forth in USP<797>. BioScrip NY complies with these

policies concerning gowning and gloving evaluations and re-evaluations, and media fills. Documentation of personnel testing is available upon request.

## OBSERVATION 4

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

***Investigator Allegations:***
*a) Non-sterile wipes are used to disinfect the ISO 5 hoods' sterile processing surfaces and they are composed of particle shedding material.*

*b) The firm does not use sporicidal agents to disinfect the ISO 5 surfaces.*

*c) A non-sterile liquid, Accel TB, is used in disinfecting ISO 5 surfaces.*

*d) No disinfectant effectiveness study has been performed to determine if disinfection procedures and disinfectants that are used can maintain the ISO 5 environment in the hoods.*

**BioScrip NY Response:** BioScrip NY 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)(v). (Specifically, that section of 21 C.F.R. part 211 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, BioScrip NY 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 d) 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." BioScrip NY policies CLIN-PH 212, Preparing to Compound Sterile Preparations [See Attachment P]; CLIN-PH304, ISO Class 5 (Class 100) Clean Rooms: Cleaning [See Attachment Q] and CLIN-PH306, ISO Class 7 (Class 10,000) Clean Rooms: Cleaning [See Attachment R] 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.

a) Wipes - USP<797> does not require the use of sterile wipes, and appears to have conflicting requirements for low-shedding and non-shedding wipes. However, the commonly used IEST Recommended Practice RP-CC003.3: Garment System Considerations for Cleanrooms and Other Controlled Environments, defines a cleanliness classification system in which the optimal Category I garments have the lowest particle shed requirements and are the "cleanest." In accordance with these standards, the wipes used by BioScrip NY and for which documentation was provided to the inspector are classed as low shedding. The Connecticut Clean Room CR-9300 wipes in use at the time of the inspection are reported to be low-shedding and suitable for ISO 5 and ISO 7 environments. [See Attachment S.] BioScrip NY is testing wipes in Category I.

b) Sporicidal agent - 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. BioScrip NY 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.

c) 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 General Chapter <797> routinely refers to the "approved" or "suitable" disinfectant with isopropyl alcohol listed not as a definitive requirement, but an "example" of a suitable disinfecting agent.

d) Disinfectant effectiveness studies - Since such studies are neither required nor mentioned anywhere in USP<797>, BioScrip NY does not perform these studies.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

**OBSERVATION 5**

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

***Investigator Allegations:*** *No media fills/process simulations have been performed under the most stressful or challenging conditions. Instead, the firm uses an aseptic technique validation kit that doesn't utilize equipment and containers used in normal processing.*

**BioScrip NY Response:** BioScrip NY objects to Observation 5 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 5 copies verbatim 21 C.F.R. § 211.113(b). (Specifically, that section of 21 C.F.R. part 211 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, BioScrip NY 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, BioScrip NY's procedures and policies 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® media validation kits used by BioScrip NY do reflect the aseptic manipulations characteristic of low-risk compounding, which constitutes 85% of the compounding activity at this pharmacy. [See Attachment T - CLIN-PH300, Validation Testing of Aseptic Technique. See also, Attachment O.] A process simulation test representing low- and medium-risk aseptic compounding was implemented by BioScrip NY in July 2014, which the compounding staff at the pharmacy will complete during their annual competency requirement. This test represents the most challenging 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. Documentation of completion is contained in each employee file. BioScrip NY does not perform high-risk sterile compounding.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

**OBSERVATION 6**

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

***Investigator Allegations:*** *Your firm has not conducted any sterility testing for any products.*

**BioScrip NY Response:** BioScrip NY objects to Observation 6 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 6 copies verbatim 21 C.F.R. § 211.167. (Specifically, that section of 21 C.F.R. part 211 requires: "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements.") FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP, BioScrip NY has implemented, and follows, appropriate procedures to assure that the preparations it compounds are sterile and pyrogen free. BioScrip NY follows USP<797>, which requires that pre-administration storage duration and temperature limits as specified in the microbial contamination risk level subsections (low-risk, medium-risk and high-risk) shall apply. USP<797> does not require sterility testing for individually compounded sterile preparations; direct sterility testing is only required by USP<797> if the storage/beyond use dating of compounded sterile preparation exceeds those limits. BioScrip NY complies with the required USP<797> storage/beyond use dating for all preparations it compounds. Accordingly, because it adheres to the dating set forth in USP<797> for its low-, and medium-risk compounded preparations, it is not required to perform sterility testing under USP<797>.

**OBSERVATION 7**

**The separate or defined areas necessary to prevent contamination or mix-ups are deficient.**

***Investigator Allegations:***
*a) Your firm is processing Penicillin-type injectable drugs, such as Penicillin, Nafcillin, and Oxacillin, in the same ISO 5 hood with your non-penicillin products. The absence of structurally isolated areas creates the potential that accidental breakage of vials of penicillin powders could contaminate your other sterile products.*

*b) There is no separate air handling system for penicillin drugs.*

*c) There are no separate facilities, for processing operations, to prevent contamination from beta-Lactam non-penicillin injectable drugs, such as Cefazolin, Ceftazidime, Aztreonam, and others. These beta-Lactam powders, which are contained in glass vials, are processed in the same ISO 5 hood as are other sterile injectable non beta-Lactam drugs. There is no assurance that a potential breakage of the glass vial and consequent powder spill would not contaminate other sterile drug products.*

**BioScrip NY Response:** BioScrip NY objects to Observation 7 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 7 copies verbatim 21 C.F.R. § 211.42(c). (Specifically, that section of 21 C.F.R. part 211 requires: "There shall be separate or defined areas . . . necessary to prevent contamination or mixups.") FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP, BioScrip NY has in place appropriate procedures and policies to prevent contamination or mix-ups. USP<797> contains several references to cleaning of the ISO 5 compounding area, but it does not reference any requirement of structurally isolated areas, separate air handling systems, or separate facilities to segregate beta-lactam antibiotics. There are no state pharmacy regulations or accreditation standards requiring such segregation and BioScrip NY's practice is consistent with the prevailing standard of pharmacy care.

USP General Chapter <797> states that "cleaning and disinfecting surfaces in the ISO 5 compounding area are the most critical practices before the preparation of compounded sterile products. Consequently, such surfaces shall be cleaned and disinfected frequently, including at the beginning of each work shift, before each batch preparation is started, every 30 minutes during continuous compounding periods of individual compounded sterile products, when there are spills, and when surface contamination is known or suspected from procedural breaches." BioScrip NY policy and process complies with these guidelines. BioScrip NY policy CLIN-PH 212, Preparing to Compound Sterile Preparations [See Attachment P] describes the cleaning of the ISO 5 compounding area to remove any residual drugs, then disinfection with sterile isopropyl alcohol. The cleaning is documented on the CLIN-PH005-1 Pharmacy Checklist. [See Attachment G.] Training on the cleaning process is part of the initial and ongoing competency [See Attachment O, Policies COMP-COMP01, Competency Program, COMP-PH01, 90 Day Competency Assessment-Pharmacist; COMP-PH 04, Annual Competency Assessment Pharmacist; COMP-PH 05, 90 Day Competency Assessment-Pharmacy Technician and COMP-PH 07, Annual Competency Assessment-Pharmacy Technician] required of all relevant employees. The removal of all drug residue during the cleaning process is emphasized in the training. Documentation of training is available upon request.

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

**OBSERVATION 8**

**For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug products.**

***Investigator Allegations:*** *Specifically, visual checks of sterile injectable drugs for clarity/discoloration or particulate/contaminants are not performed against contrasting backgrounds.*

**BioScrip NY Response:** BioScrip NY objects to Observation 8 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 8 copies verbatim 21 C.F.R. § 211.165(a). Specifically, that section of 21 C.F.R. part 211 requires: "there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient...".) FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP, BioScrip NY has in place appropriate procedures and policies to determine the satisfactory conformance of final specifications of its compounded preparations. As per USP<797>, all finished CSPs are individually inspected in accordance with BioScrip NY's written procedures after compounding. Immediately after compounding, and as a condition of release, each compounded sterile preparation is inspected for visible particulates or other foreign matter. USP<797> does not require the use of a lighted white or black background for evidence of visible particulates or other foreign matter. Other sterile compounding standards, such as the ASHP Guidelines on Compounding Sterile Preparations (2013), do not mention (or otherwise recommend) the contrasting background inspection as necessary for adequate inspection of single dose compounded sterile preparations. There are also no such requirements under state pharmacy law. BioScrip NY policy CLIN-PH214, General Compounding Procedures [See Attachment H] describes the final check of all compounded sterile products, stating that the pharmacist is responsible for a final inspection of the finished compounded preparation for the presence of:

a. Particulate matter
b. Container integrity
c. Signs of preparation deterioration
d. Color changes, cloudiness of the solution, presence of foreign matter
e. Correct ingredients and correct volume of additives
f. Final container volume
g. Accuracy of prescription label affixed to container

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

**OBSERVATION 9**

**There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expirations dates.**

***Investigator Allegations:*** *Your firm has not tested for sterility or potency over the assigned Beyond Use Date (BUD) for any sterile injectable, all of which are preservative free. For example, your firm has not conducted any testing to support the BUDs such as 14 days refrigerated for Vancomycin or 7 days room temperature for Fluorouracil. You have no data to show that the sterility and potency will be maintained over the time period of the BUD.*

**BioScrip NY Response:** BioScrip NY objects to Observation 9 because FDA holds the pharmacy to a standard that is inapplicable to a compounding pharmacy under FDCA Section 503A. Observation 9 copies verbatim 21 C.F.R. § 211.166(a). (Specifically, that section of 21 C.F.R. part 211 requires: "There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates.") FDA's cGMP regulations are inapplicable because Section 503A pharmacies are exempt from cGMP.

Notwithstanding the inapplicability of FDA's cGMP, BioScrip NY has in place appropriate procedures and policies to determine beyond use dating and/or expiry dates for preparations it compounds. USP<797> establishes the Beyond Use Dates (BUD) for the sterility of compounded preparations in the subsections for low-, medium-, and high-risk products. There is no requirement for sterility testing of low- or medium-risk compounded preparations when the BUD assigned the sterile preparation is within the allowable limits set forth in USP<797>. BioScrip NY's sterile compounded preparations do not exceed the allowed sterility dating for low- and medium-risk compounded sterile preparations. Furthermore, BioScrip NY does not perform any high-risk compounding. For all of these reasons, this Observation is not applicable to BioScrip NY's compounding operations, and is thus incorrect.

Stability determination per USP General Chapter <797> requires that, "compounding personnel refer to applicable publications to obtain relevant stability, compatibility, and degradation information regarding the drug or its congeners. When assigning a beyond-use date, compounding personnel should consult and apply drug-specific and general stability documentation and literature where available, and they should consider the nature of the drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy". BioScrip NY policy,

**Mr. Ronald M. Pace**
**FDA, New York District Office**
**October 10, 2014**

CLIN-PH207, Storage Dating for Infusion Prescriptions [See Attachment U] requires that compounded sterile preparation stability dating be derived from the package insert or published, peer-reviewed data, such as the data from Micromedex Trissel 2 IV Compatibility software available and used by BioScrip NY. No further testing of drug stability is required. If stability data are not known, the preparation must be compounded for immediate use, via a system that allows drug dilution at the time of administration or other home mix method, per USP<797>.

**Conclusion**

Based on the foregoing, BioScrip NY respectfully asserts that FDA's Observations are based on an inspection where FDA applied an inapplicable and incorrect standard to BioScrip NY's facilities, operations, personnel and procedures. BioScrip NY is a compounding pharmacy acting in accordance with FDCA Section 503A. Thus, FDA's Form 483 Observations concerning alleged cGMP violations are inappropriately issued and should be rescinded, or in the alternative, amended to reflect the correct standard to which BioScrip NY should be held, for all of the reasons set forth in this Response.

Respectfully submitted,

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

cc: James A. Liubicich, Investigator
Karla Palmer
Kathryn Stalmack

Attachments

# ATTACHMENT INDEX

**BioScrip Pharmacy (NY), Inc.**

**Response to FDA Form 483**

**Issued September 19, 2014**

**FEI No. 3011022663**

| |
|---|
| **Attachment A**<br>CLIN-PH305, ISO Class 7 Clean Rooms: Routine and Preventive Maintenance |
| **Attachment B**<br>BioScrip and ENV Services Service Agreement 110113 |
| **Attachment C**<br>CETA Certification Guide for Sterile Compounding Facilities, CAG-003-2006-11, Revised January 31, 2012 |
| **Attachment D**<br>CETA Certification Matrix for Sterile Compounding Facilities (Secondary Engineering Controls) CAG-008-2010, January 31, 2012 |
| **Attachment E**<br>ACHC Certificate of Accreditation, Infusion Pharmacy Services BioScrip Pharmacy (NY), Inc. December 19, 2013-December 18, 2016 |
| **Attachment F**<br>ACHC Letter (09/19/2013 – "Accreditation Commission for Health Infusion Pharmacy Accreditation Includes USP 797" |
| **Attachment G**<br>CLIN-PH005 – Pharmacy Checklist |
| **Attachment H**<br>CLIN-PH214, General Compounding Procedures |
| **Attachment I**<br>Photo of Clean Room Operator Garb |
| **Attachment J**<br>CLIN-PH007, Infusion Pharmacy Gap Analysis |
| **Attachment K**<br>CLIN-PH 303, ISO Class 5 (Class 100) Clean Bench Rooms: Routine and Preventive Maintenance |
| **Attachment L**<br>CLIN-PH307, Environmental Monitoring of the Clean Room |
| **Attachment M**<br>CLIN-PH300, Validation Testing of Aseptic Technique |
| **Attachment N**<br>CLIN-PH301, Testing of Products Dispensed to the Patient Environment |
| **Attachment O**<br>Competency Policy and Assessments |

# ATTACHMENT INDEX

**BioScrip Pharmacy (NY), Inc.**

**Response to FDA Form 483**

**Issued September 19, 2014**

**FEI No. 3011022663**

| |
|---|
| **Attachment P**<br>CLIN-PH 212, Preparing to Compound Sterile Preparations |
| **Attachment Q**<br>CLIN-PH304, ISO Class 5 (Class 100) Clean Rooms: Cleaning |
| **Attachment R**<br>CLIN-PH306, ISO Class 7 (Class 10,00) Clean Rooms: Cleaning |
| **Attachment S**<br>Connecticut Clean Room CR-9300 Nonwoven Wipers |
| **Attachment T**<br>CLIN-PH300, Validation Testing of Aseptic Technique |
| **Attachment U**<br>CLIN-PH207, Storage Dating for Infusion Prescriptions |