US Compounding
PHARMACY

1270 Don's Lane
Conway, AR 72032

March 1, 2019

VIA EMAIL

LCDR John W. Diehl,
Director, Compliance Branch
ORA/OPQ – Division 2
Department of Health and Human Services
Food and Drug Administration
Dallas District Office
4040 North Central Expressway, Room 950
Dallas, TX 75204

RE: US COMPOUNDING, INC.
RESPONSE TO INSPECTIONAL OBSERVATIONS IN FEBRUARY 7, 2019 FORM 483

LCDR Diehl:

US Compounding, Inc. ("*USC*") would like to take this opportunity to respond to the inspectional observations listed on the FDA Form 483 issued by your office on February 7, 2019. During the most recent inspection, USC engaged cooperatively and constructively with the Food and Drug Administration ("*FDA*"). USC would now like to provide FDA with further assurance that USC is committed to providing the highest quality compounded preparations.

As an initial matter, USC would like to emphasize at the outset that it takes the FDA process and its professional responsibilities very seriously. USC understands the importance of FDA's observations, and patient safety and well-being remain our primary concerns. For example, as evidence of that understanding, USC is closing its 503A patient specific human compounding operations after evaluating the challenges of separating 503A and 503B operations under FDA's recently published guidance. This substantive shift in operations will ensure that USC's Quality Unit has direct and sufficient authority over all drugs compounded for human use. Further, USC is commissioning additional process validations to bolster its quality and compliance programs. USC believes that these actions, and the other actions outlined below, demonstrate USC's commitment to fulfilling its professional responsibilities and meeting FDA's expectations. As such, USC provides the following responses to FDA's Form 483 observations:

FDA Observation 1:
Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, your firm has written procedures which describes personnel and environmental monitoring. The following deficiencies in the procedures and practices were observed:

FDA Observation 1(A):

Your firm failed to conduct investigations related to all mold recoveries in 2018. According to your firm's 2018 Environmental Monitoring Trend Draft Report, 21 colony forming units (CFUs) counts for mold were identified in your firm's Sterile Suite (ISO 8, ISO 7, and ISO 5). Your firms' QA Department documents 18 Environmental Control Alert/Action Notification Reports for Environmental Monitoring excursions related to mold. However, your firm only investigated 50% of these excursions. Your firm's Director of QA/QC did not provide scientific justification as to why an investigation was not performed on all notifications.

USC Response to Observation 1(A) [1]:

USC acknowledges the importance of written procedures for personnel and environmental monitoring. However, before describing the actions taken to address Observation 1(A), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC objects that this observation is a repeat observation since all fungal recoveries within the critical ISO 7, ISO 7 buffer and ISO 5 space received immediate attention and were thoroughly investigated. Specifically, this investigation included an analysis of each excursion's root cause and appropriate corrective action prior to Lot disposition. Further, all microbial environmental monitoring recoveries (both bacterial and fungal) are tracked and trended on a quarterly basis. The *2018 EM Trending Report* is provided as Exhibit 1A-1. USC provides more detail in support of this position below.

For clarification, *all* actionable environmental monitoring recoveries inside the ISO 7 or ISO 5 classified areas of the Sterile Suite were fully investigated and product impact was considered *prior to disposition* of any Lot(s) being processed on the date of recovery under SOP QA-014 *Routine Environmental Monitoring Program*, Exhibit 1A-2. Both SOPs, SOP QA-008 *Environmental Monitoring during Aseptic Operations and Post Process Personnel Monitoring*, Exhibit 1A-3, and SOP QA-014 *Routine Environmental Monitoring Program*, require investigation. Importantly, one CFU recovery of mold inside the ISO 7 or ISO 5 classified areas of the Sterile Suite is considered actionable – thus *all* mold recoveries in these spaces resulted in an investigation to determine the root cause of the recovery and the potential product impact *prior to Lot disposition*. Moreover, out of an abundance of caution, USC discards all Lots in process in cases where there is fungal recovery within the ISO 7 buffer area or ISO 5 laminar airflow workbench ("LAFW"). As such, no units of any Lot with a fungal recovery in the ISO 7 buffer room or ISO 5 LAFW were released for distribution. Thus, all mold and fungal recoveries within ISO 7 and ISO 5 classified areas are investigated and immediate corrective actions are taken to prevent those Lots from being released.

Further, USC excursions that are recovered in the ISO 8 classified areas (i.e. areas outside the ISO 7 buffer/ante areas or the ISO 5 laminar flow hoods) are not subject to the same investigation as ISO 7 and ISO 5 recoveries as the ISO 8 area is the preparation area where USC sanitizes materials used during compounding. Importantly, USC uses a number of controls and processes to prevent contaminants in the ISO 8 area from entering the ISO 7 and ISO 5 areas. Those controls and processes include engineering controls, process controls, quality review and oversight, and a routine environmental monitoring program to ensure that actionable recoveries are identified and immediately corrected. USC's facilities are the primary safeguard for its sterile suites as there are always at least three, and as many as five, closed doorways of cascading differential pressures negative to the ISO 7 buffer areas. USC's facility diagram is provided as Exhibit 1A-4. As such, the presence of materials in the ISO 8 area prior to their sanitization with a sporicidal agent is the most likely root cause for the excursions identified in the observation and is addressed by the controls and processes described above, which eliminates the need to conduct the same investigation as ISO 7 and ISO 5 recoveries.

[1] USC objects that this observation and all of its subparts are repeat observations.

Nevertheless, out of an abundance of caution, USC implemented a number of corrective actions aimed at addressing FDA's concerns in this observation. USC updated the following environmental monitoring procedures to clarify USC's investigation process as well as its cleaning, disinfection, and sterilization requirements:

- SOP QA-008 *EM during Aseptic Operations and Post Process Personnel Monitoring*, Exhibit 1A-3
- SOP QA-014 *Routine Environmental Monitoring Program*, Exhibit 1A-2

Additionally, in an effort to make USC's compliance program even more robust, USC created a new position in 2019 that is solely dedicated to ensuring that environmental monitoring is performed according to USC's SOPs. Importantly, this quality person is required to investigate all deviations related to environmental monitoring thoroughly and in a timely manner. Finally, USC now requires an additional two layers of cleaning upon an action level mold recovery, which is incorporated into SOP QA-018 *USC Facility Cleaning* (Exhibit 1A-5) to further mitigate any potential mold or fungus recovery in any of the ISO classified suites. As such, USC believes that the above explanation and corrective actions address the concerns identified in this observation.

FDA Observation 1(B):
Your firm failed to conduct 16 surface samples as outlined in your firm's written procedure, QA-014 "Routine Environmental Monitoring Program." Section 7.4.1 and 7.4.2 states the frequency of testing in the ISO 7 area should occur daily as outlined in Appendix 1. For example, on 01/24/2019, I observed the environmental and personnel monitoring plate readings for Media Fills Lot 20192101@1 and Lot 20192101@2. During my review of your firm's documentation, 16 surface samples were not collected for material flow. In addition, during my review of your firm's environmental monitoring documentation, surface samples were not collected during the aseptic production of the following Lots listed below.

Sampling Dates	*Lot Number*	*Drug Name*
12/27/2018	*20182612@4P*	*Ephedrine sulfate PF 5mL Syringe 5mg/mL Injectable*
12/27/2018	*20182612@5P*	*Ephedrine sulfate PF 5mL Syringe 5mg/mL Injectable*
12/26/2018	*20182612@3P*	*Ephedrine sulfate PF 10mL Syringe 5mg/mL Injectable*
12/19/2018	*20181812@2*	*Ephedrine sulfate PF 10mL Syringe 5mg/mL Injectable*
12/11/2018	*20181012@3*	*Ephedrine sulfate PF 5mL Syringe 5mg/mL Injectable*
12/11/2018	*20181012@4*	*Methylprednisolone Ace/Lido 10mL Vial 80mg/1%/mL Injectable*
12/05/2018	*20180412@8*	*Triamcinolone acetonide PF 2mL Vial 50mg/mL Injectable*
12/04/2018	*20180312@9*	*Succinylcholine chloride PF 10mL Syringe RT 20mg/mL Injectable*
12/03/2018	*20180312@1*	*PE/Lido sulfite-free Ophthalmic PF 1ml Vial 1.5%/1% Injectable*

USC Response to Observation 1(B)[2]:

USC acknowledges the importance of written procedures for personnel and environmental monitoring. However, before describing the actions taken to address Observation 1(B), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC objects that this observation is a repeat observation since USC believes it appropriately collected surface samples during each of the described Lot numbers. USC's SOP QA-014 *Routine Environmental Monitoring Program*, Version

[2] USC objects that this observation and all of its subparts are repeat observations.

7, lists sampling for "Material Flow" rooms that did not occur during the aseptic processing of the listed Lot numbers. However, the rooms identified for "Material Flow" (122, 123 and 124) were decommissioned in 2017. These rooms are in the process of being recommissioned, and USC's SOP was updated in anticipation of that activity. Importantly, these three "Material Flow" rooms have not been commissioned as aseptic processing areas and were not used in the aseptic processing of the Lots described in this observation or any other Lot. As such, environmental monitoring sampling for these rooms has not begun. Nevertheless, once these rooms are recommissioned as aseptic processing areas, USC will start environmental monitoring sampling in those rooms.

Moreover, USC conducted routine environmental testing for the Lots identified in this observation. Specifically, Exhibit 1B-1 details the routine environmental monitoring documentation for the commissioned aseptic processing areas in use during these two Media Fill Lots (including surface samples). Additionally, Exhibit 1B-2 includes the individually executed batch records for each compounded drug preparation Lot. This information is summarized in Exhibit 1B-3 and shows that not less than fifty (50) environmental samples were taken and reviewed for each Lot. Importantly, each of these sample locations has established action and alert thresholds to monitor control of the aseptic production environment.

Nevertheless, out of an abundance of caution, USC updated its SOP QA-014 *Routine Environmental Monitoring Program* (Exhibit 1A-2) to clarify when areas are decommissioned. Specifically, this SOP now includes a definition of decommissioned areas and their applicable environmental monitoring requirements. As such, USC believes that the above explanation and corrective actions address the concerns identified in this observation.

FDA Observation 1(C):
Your firm failed to justify the reduction of environmental monitoring frequencies of yeast and mold (SDA plates) from a daily to a weekly basis after aseptic operations per your firm's written procedure, QA-008: "EM during Aseptic Operations and Post Process Personnel Monitoring". Furthermore, your firm's 2017 Environmental Monitoring Trend Report states mold isolates increased from Quarter 1 to Quarter 2 in 2017 (11% to 39% increase). This trend was also observed in Quarter 2 of 2016; in Quarter 3 of 2017, the highest identified microbial isolate was mold (37%). In addition, your firm's 2018 Environmental Monitoring Trend Draft Report states mold recoveries were reduced by more than 50% from Quarter 2 in 2017, which may be attributed to process improvements regarding material flow. However, your firm's EM sampling records are deficient as addressed in Observation 1(B).

USC Response to Observation 1(C) [3]:

USC acknowledges the importance of written procedures for personnel and environmental monitoring. However, before describing the actions taken to address Observation 1(C), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC objects that this observation is a repeat observation as USC has always conducted environmental monitoring on a weekly basis to support production. Additionally, Observation 1(C) should reference SOP QA-014 *Routine EM Program* instead of SOP QA-008 *EM during Aseptic Operations and Post Process Personnel Monitoring* as SOP QA-014 more specifically addresses SDA plate usage. USC provides more detail regarding these matters below.

[3] USC objects that this observation and all of its subparts are repeat observations.

In 2016, USC clarified that there were conflicting statements within SOP QA-014, version 00, effective August 17, 2016, where one section required SDA sampling to occur weekly and another section erroneously stated that it should occur daily. USC corrected this typographical error in the procedure in its 2016 response to FDA. As such, SDA monitoring has always occurred on a weekly basis for routine production, and USC did not decrease sampling with FDA plates from daily to weekly.

Moreover, USC's quarterly trending of environmental and personnel monitoring shows that mold or fungal recoveries represent a very small percentage of overall isolates, and the majority of those mold or fungal isolates are obtained from TSA plates, not SDA plates. In 2017, there were a total of 20,813 samples taken, with 3,529 being SDA plates. Total recoveries across all plate/sampling types and sampling locations was 6.69%. The overall contamination recovery rate (CRR) for mold or fungal isolates was an extremely low percentage—0.31% (65 CFU / 20,813 samples). For 2017, 47 of the 65 CFU recovered (72.31%) were recovered on TSA plates.

The trend of low mold and fungal recoveries continued throughout 2018. For 2018, a total of 23,557 samples were taken, with 3,082 being SDA plates. Total recovery percentage for the year across all plate/sampling types and sampling locations was 3.56%. The overall CCR for mold was 0.085% (20 CFU / 23,557 samples taken). Thus, the mold or fungal CRR in 2018 was 4-fold lower compared to 2017. In 2018, 14 of the 20 CFU recovered (70.00%) were recovered from TSA plates. This data is contained in Exhibit 1A-2, *QA-014 Routine Environmental Monitoring Program*, and Exhibit 1C-1, *2017 Environmental Trending Report*.

USC recognizes there were periodic slight increases in mold or fungal isolates in some quarterly trending. However, these trends were always investigated prior to disposition of individual Lots, and USC determined that all of these slight increases were likely related to seasonal environmental changes or material movement and appropriate corrective actions were implemented. Additionally, in all cases of mold or fungal recoveries within the ISO 7 buffer area or ISO 5 hoods, the Lot at issue was destroyed out of an abundance of caution. As such, USC believes that the above explanation and corrective actions address FDA's concerns in this observation.

FDA Observation 1(D)[4]*:*
Your firm's written procedure, QA-008: "EM during Aseptic Operations and Post Process Personnel Monitoring'' states only one viable contact surface sample is taken at the center of each ISO 5 hood. However, this sample is not representative of your firm's most challenging and/or stressful conditions. For example, on 01/24/2019, I observed surface sampling conducted in the center of the LAFH (ISO 5), EQ ID 0083 and LAFH (ISO 5), EQ ID 0085; however, the individuals that performs aseptic operations (commonly referred to as the aseptic filler and the aseptic personnel assistant) worked predominately on the far right and far left sides of the ISO 5 workbench.

USC Response to Observation 1(D):

USC acknowledges the importance of written procedures for personnel and environmental monitoring. However, before describing the actions taken to address Observation 1(D), USC would like to provide more detailed insight into the issues underlying the observation. As an initial matter, USC objects that this observation is a repeat observation as USC believes that its sampling does address the highest risk conditions during compounding. USC provides detail in support of this position below.

[4] USC objects that this observation and all of its subparts are repeat observations.

USC believes its sampling addresses the highest risk conditions that occur during USC aseptic operations. As an initial matter, the aseptic filler is continuously within the ISO 5 LAFW during aseptic filling of syringes. The second person involved in the syringe fill manipulation (the aseptic personnel assistant) only intermittently enters the ISO 5 controlled area during syringe fills. The aseptic personnel assistant enters the ISO 5 area when necessary for insertion and removal of unfilled/filled devices. Additionally, the closest location to open product and highest risk during the fill process material(s) and finished product flow is at the fill manifold block located toward the center of the hood. Specifically, the overall aseptic fill activity flow is as follows:

- unfilled syringes are opened at the right side and flow to the fill manifold in the center of the hood where each syringe is filled,
- filled syringes move from the fill manifold (center) to the left for capping,
- syringe caps then flow from the right toward the fill manifold at center of the hood.

Therefore, the greatest risk for any potential contamination is concentrated toward the center of the hood where there is the most open compound. This risk serves as USC's scientific rationale for its sampling locations during fill operations because USC is sampling where there is the greatest potential for contamination.

Moreover, as an added environmental monitoring safeguard, USC positions passive air "settling" plates in each hood for passive viable air sampling during each aseptic processing Lot. Active viable and non-viable air sampling in each ISO 5 hood also occurs during each aseptic processing Lot. These sampling points are part of the environmental monitoring quality control data reviewed for each Lot of sterile compounded drug product and provide at least four samples across the entire ISO 5 space. Importantly, in assessing environmental monitoring trends since 2014, there have been zero mold recoveries from ISO 5 laminar flow hood surfaces, which includes results from the passive air "settling" plates.

Nevertheless, out of an abundance of caution, USC is evaluating its ISO 5 surface sampling requirements to determine whether USC should broaden its surface sampling areas during its ongoing trending. Additionally, USC updated its ISO 5 surface sampling requirements to require that a collection of samples is taken directly in front of the aseptic filler where the highest workflow occurs, SOP QA-008 EM during *Aseptic Operations and Post Process Personnel Monitoring*, version 14, section 7.6.3 (Exhibit 1A-3).

Therefore, USC believes that the above explanation and corrective actions address the concerns identified in this observation.

FDA Observation 2:
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

FDA Observation 2(A):
Your firm failed to clean as recommended by your firms' 503B Operations Manager after your firm received an out-of-specification for EM excursions in your firm's Sterile Prep Room (ISO 8) for 14 CFU (i.e. 11 CFU for bacteria and 3 CFU for mold contamination). Your firm prepares materials such as excipients and APIs in the Sterile Prep Room (ISO 8).

USC Response to Observation 2(A):

USC understands the importance of an effective and robust cleaning program that prevents microbial contamination of the sterile compounding and aseptic packaging areas. However, before describing the actions taken to address Observation 2(A), USC would like to provide more detailed insight into the issues underlying the observation. As an initial matter, USC did clean in accordance with its 503B Operations Manager's directions after receiving out-of-specification results. On December 12, 2018, a routine environmental monitoring sample recovered two CFU of mold in the ISO 8 area of the sterile suite: one CFU in the ISO 8 entry (Room 116), and one CFU in Glassware Storage (Room 118) after five days of incubation. On December 19, 2018, USC's Director of Pharmacy acknowledged the microbial recoveries and alerted operations management and sterile staff for immediate corrective action via email (Exhibit 2A-1). On that same day, a sporicidal clean was performed per the 503B Operations Manager's directions in the affected and adjacent areas: Rooms 116, 117, and 118. USC recognizes that a deviation should have been formally documented to reflect a change from the routine daily cleaning procedure.

As such, out of an abundance of caution, USC updated SOP QA-018 *USC Facility Cleaning* (Exhibit 1A-5) to require better documentation and cleaning whenever microbial or fungal environmental monitoring action limits are triggered. The associated cleaning forms were also updated for the sterile suite to indicate whether the cleaning is daily or an "additional cleaning" due to an environmental monitoring action or alert level being triggered. Revised SOP QA-018, *USC Facility Cleaning*, Exhibit 1A-5. USC therefore believes that the above explanation and corrective actions address the concerns identified in this observation.

FDA Observation 2(B):
Your firm failed to establish cleaning procedures to prevent cross-contamination of testosterone to other drug products.

USC Response to Observation 2(B):

USC acknowledges the importance of cleaning procedures to prevent-cross contamination. However, before describing the actions taken to address Observation 2(B), USC would like to provide more detailed insight into the issues underlying the observation.

USC recognizes testosterone as a challenging and hazardous drug. In order to prevent cross-contamination of testosterone, USC's cleaning disinfection program uses a four agent, three-tiered system comprising sporicidal disinfectant, a quaternary ammonium agent or phenolic agent based on a rotational schedule, and a final 70% isopropyl alcohol wipe for cleaning disinfection. Additionally, surfaces and materials in the sterile suite undergo regularly scheduled daily, weekly and monthly cleaning. Additional cleaning outside of these regular intervals is performed under SOP QA-018 *USC Facility Cleaning*, Exhibit 1A-5. To bolster this cleaning program, USC is undertaking a feasibility study and method development to create a specific, accurate and sensitive test method for recovering and quantifying potential testosterone residue with swabs. USC will also validate this method for in situ testing. Importantly, this analysis will serve as a worst-case chemical contaminant baseline and a more effective means for evaluating USC's controls for the use of testosterone. The proof of concept study is scheduled to be initiated by March 11, 2019 and completed in April 2019. USC will update the Agency regarding the progress of this study as information becomes available. As such, USC believes that this information and analysis will address FDA's concerns identified in this observation.

FDA Observation 2(C):
Your firm has not established a cleaning validation to assure your cleaning process removes chemical and microbial residues on the equipment used in your aseptic operations.

USC Response to Observation 2(C):

USC acknowledges the importance of cleaning procedures to remove chemical and microbial residues. However, before describing the actions taken to address Observation 2(C), USC would like to provide more detailed insight into the issues underlying the observation.

USC recognizes the need to perform and document a prospective validation of both chemical and microbial residue cleaning effectiveness. USC's cleaning disinfection program uses a four agent, three-tiered system comprising sporicidal disinfectant, a quaternary ammonium agent or phenolic agent based on a rotational schedule, and a final 70% isopropyl alcohol wipe for cleaning disinfection. Surfaces and materials in the sterile suite undergo regularly scheduled daily, weekly and monthly cleaning. Additional cleaning is performed under SOP QA-018 *USC Facility Cleaning*, Exhibit 1A-5.

Nevertheless, out of an abundance of caution, USC is initiating additional cleaning validation for chemical and microbial effectiveness. As an initial matter, prior to the FDA inspection, USC had initiated contract discussions with qualified outside laboratories, negotiating vendor statements of work, and evaluating analytical methodologies for chemical and microbial cleaning effectiveness. (Exhibit 2C-1, Exhibit 2C-2). Once these discussions are finalized, the chemical cleaning validation will be implemented in a phased approach: 1) Method Feasibility, 2) Qualification, and 3) Validation. Additionally, the microbial cleaning will be executed in accordance with USP <1072>. USC anticipates starting the validations by March 11, 2019. As such, USC will update the Agency to the status of these projects as more information becomes available.

FDA Observation 3:
Aseptic processing areas are deficient in that ceilings are not smooth and/or hard surfaces that are easily cleanable.

Specifically, your firm failed to ensure the material used to caulk and seal the ceiling tiles, located in your firm's Sterile Suite, is cleanroom grade or suitable for cleanrooms that are used for aseptic filling operations. On 11/05/2018, your firm replaced 1 ceiling tile and resealed 42 ceiling tiles in your firm's Sterile Suite (ISO 8 and ISO 7 areas), where sterile drug products are produced. The caulking is not smooth.

USC Response to Observation 3:

USC recognizes the importance of easily cleanable surfaces in the clean room. USC believes that its current cleaning processes and documentation demonstrate that the surfaces identified in this observation are adequately cleaned. Nevertheless, in deference to the Agency, USC will implement the following corrective actions to address FDA's concerns:

1. USC will remove the existing silicone sealant know as American Sealants, Inc (ASI) 505 using Everbuild® Silicone Eater, see Exhibit 3-1, throughout the sterile production suite. This will ensure removal of all seen and unseen unevenness, including the specific locations in FDA's observations.
2. USC will reseal all ceiling tiles in the sterile suite using cleanroom FDA approved Everbuild® Everflex® 565 Clean Room Silicone, see Exhibit 3-2.

3. To further ensure the new sealant is installed with a smooth surface, USC will hire a qualified professional contract firm to perform the work listed above under the immediate oversight and approval of USC's facilities management.

As such, USC believes that this information and analysis will address FDA's concerns identified in this observation.

FDA Observation 4:
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

FDA Observation 4(A):
Your firm's Media fills do not simulate the most challenging and/or stressful conditions. For example, but not limited to, according to your firm's Director of Pharmacy, aseptic operations may occur simultaneously in all three (3) LAFH (ISO 5): EQ ID 0083; EQ ID 0084; EQ ID 0085 located in Cleanroom #1. However, your media fills are performed under two (2) of the LAFH (ISO 5 (EQ ID 0083 and EQ ID 0085).

USC Response to Observation 4(A):

USC understands and recognizes the need for media fills to be performed under the most challenging and stressful circumstances likely to be encountered during compounding. However, USC believes that its media fills replicate the most challenging and stressful circumstances that occur during its compounding processes. At maximum operation capacity, USC operates all three hoods (0083, 0084, and 0085) in a staggered manner. The term "simultaneous" used by USC's Director of Pharmacy refers to the overall duration of single shift—at no point in the compounding process are all three hoods used at the same time for the same activities. Rather, only two hoods are used in the exact same manner at the exact same time. Specifically, two hoods will be used for aseptic packaging and the third hood may be used for filtration of the product to be packaged. As such, USC performed a media fill during the inspection that replicated these conditions—two hoods were in use for aseptic fill simulation (EQIDs 0083 and 0085) while a third hood, EQID 0084, was used for filter sterilization just prior to the start of aseptic filling. This staggered compounding typically occurs during production (Lot 20192101@1) and reflects the most challenging scenario that occurs at USC.

Nevertheless, out of an abundance of caution, USC is taking a number of corrective actions to address the media fill issues identified in this observation. To address this observation, USC performed another media fill under conditions that mimic a full capacity production of sterile drug products (even though this is not ever a process that occurs at USC). This media fill involved all hoods being simultaneously used in the same manner for most challenging work at the same time. This media fill performed on February 25, 2019 under approved batch record, Media Fill 1mL in the 3mL syringe, Lot 20192502@1. The seven-day read is scheduled for March 6, 2019 and the final fourteen-day read is scheduled for March 13, 2019.

In addition, USC updated SOP ST-004 *Media Fills*, (Exhibit 4A-1), the *Media Fill Master Validation Plan* (Exhibit 4A-2), and the Media Fill 1ml in 3mL syringe master batch record (Exhibit 4A-3) to reflect this new process. These updates include the following:

- a definition for required conditions and acceptance criteria,
- documentation of activities performed in conjunction with media fills,
- number of personnel present,

- activities per hood, and
- performance and documentation of planned and unplanned interventions.

As such, USC believes that this information and analysis will address FDA's concerns in this observation.

FDA Observation 4(B):
Your firm did not conduct any dynamic smoke studies from 10/19/2015 through 11/07/2018. The airflow studies performed in November 2018 were deficient in determining if the air movement from the HEPA filters within the ISO 5 classified area, where sterile drug products are manipulated, was unidirectional.

1. *In addition, your firm's aseptic processing assistant, who primarily moves into ISO 5 from the ISO 7 area multiple times during routine aseptic processing (approx. 2 times/min), did not move (static conditions) during the dynamic smoke studies.*
2. *In addition, I observed turbulent air movement, including the potential influx of air (from the ISO 7 environment into the ISO 5 environment) in your firm's smoke study titled, "Homogenization Process: Static Airflow Visualization".*

USC Response to Observation 4(B):

USC acknowledges the importance of dynamic smoke studies. However, before describing the actions taken to address Observation 4(B), USC would like to provide more detailed insight into the observation itself. As an initial matter, the qualified third-party vendor that performed the Controlled Environment Performance Test and created the Certification Report stated that the operational testing was performed under *dynamic conditions* and that all actual operating personnel are present and performing actual or simulated operations. Specifically, the report detailed that eleven (11) clean room staff plus one (1) EM technician and one (1) Certification Engineer technician were present across each cleanroom under testing, which exceeds normal dynamic operations by one (1) person.

Additionally, USC's compounding processes reflected dynamic conditions during the smoke study. During the testing, compounding processes flowed in the normal high-volume sequences to simulate aseptic filling in two of three hoods per room followed by repeat activities with one of the three hoods used sequentially. The Vendor's *Air Flow Smoke Test Report* (Exhibit 4B-1) documented a status of "Acceptable" with the following statement:

> "*Airflow pattern testing was performed using visual smoke source within the horizontal clean benches. The first air was seen sweeping across the critical work zone (direct compounding area) with little to no reflux or turbulence being observed*."

In addition to the Air Flow Smoke Test, the Certification Report (Exhibit 4B-1) also documented "Acceptable" statuses for measured Air Change Rate, HEPA Filter Integrity (Rooms), Room Pressurization, Particle Count Classification (Rooms), and Viable Surface and Air Environmental Sampling. Importantly, there are no deficiencies in the report. The only recommendations were for rooms to settle for a short period upon entry for pressures, and to use caution when entering the compounding rooms while the compounding process is taking place, which is USC's standard practice. Thus, all Primary Engineering Controls and Facility Engineering Controls received a final status of "Acceptable" by the air testing service provider who was qualified and certified for this activity.

Nevertheless, USC is evaluating its current airflow smoke studies to determine how it can better address FDA's concerns in this observation. As part of this effort, USC scheduled to re-execute airflow smoke studies under extreme dynamic conditions according to the attached the protocol (Exhibit 4B-2). This protocol defines USC's expectations for dynamic conditions as well as common interventions to aseptic processing activities performed during the smoke studies. As such, USC believes that this information addresses FDA's concerns in this observation, and USC will update the Agency regarding the results of the re-executed airflow smoke studies.

FDA Observation 5:
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include validation of the aseptic and sterilization process.

FDA Observation 5(A):
Your firm does not have any process validations for the aseptic production of your firm's suspension products.

USC Response to Observation 5(A):

USC acknowledges the importance of process validations for injectable suspensions. However, before describing the actions taken to address Observation 5(A), USC would like to provide more detailed insight into the observation itself. As an initial matter, the sterilization and aseptic processes for injectable suspensions are qualified through process simulation media fills, which were successfully completed at least twice each year in 2016, 2017, and 2018. This media fill process qualification for injectable suspensions includes the homogenization process in the ISO 5 LAFW for the maximum duration and the aseptic fill in the ISO 5 environment as outlined in SOP ST-004 *Media Fills* (Exhibit 4A-1), and the *Media Fill Master Validation Plan* (Exhibit 4A-2).

Nevertheless, in deference to the Agency, USC is implementing a number of actions to further address FDA's concerns in this observation. As part of these actions, USC will initiate process validations to further ensure compounded suspension drug quality. Process performance qualification protocols will be written, approved, and executed for the following suspension products:

1. Methylprednisolone acetate 80mg/mL PF Sterile Injectable
2. Methylprednisolone acetate/Lidocaine HCl 40mg/1%/mL Sterile Injectable
3. Methylprednisolone acetate/Lidocaine HCl 80mg/1%/mL Sterile Injectable
4. Betamethasone Combo 7mg/mL Sterile Injectable
5. Triamcinolone acetonide PF 50mg/mL Sterile Injectable
6. Triamcinolone diacetate 40mg/mL PF Sterile Injectable
7. Triamcinolone diacetate 40mg/mL Sterile Injectable
8. Triamcinolone diacetate 80 mg/mL Sterile Injectable

As part of this process, USC will generate individual process performance qualification protocols for each of these suspensions. Under this approach, USC will document the compounding conditions, including operating parameters, processing limits, and component (raw material) inputs. This documentation will also include in-process release testing to ensure quality suspension compounds meet USC's acceptance criteria. USC intends to start these process validations the week of March 11, 2019 and will update the Agency on the status of these validations as more information becomes available.

Please note that the remaining four compounded injectable suspensions identified in this observation have not been compounded since as early as 2016 and are now removed from USC's product portfolio. Specifically, those compounds are as follows:

1. Medroxyprogesterone acetate/Lidocaine HCl 150mg/mL 150mg/l %/mL Sterile Injectable: Last compounded June 12, 2016.
2. Dexamethasone acetate 8mg/mL Sterile Injectable: Last compound July 19, 2017.
3. Dexamethasone acetate 16mg/mL Sterile Injectable: Last Compounded September 23, 2016.
4. Dexamethasone Combo (acetate/sodium phosphate) 8mg/4mg/mL Sterile Injectable: Last compounded December 5, 2017.

These formulations were also removed from the relevant SOPs. As such, USC believes that this information and analysis will address FDA's concerns identified in this observation.

FDA Observation 5(B):
Your firm's equipment validation, VAL009, for the Homogenizer, EQ ID: LUMAC 0225, is deficient. For example, but are not limited to, the report does not address the min/max volumes the Homogenizer is able to process; process times are not defined; calibration and maintenance programs are not defined. The Homogenizer is used during the production of your firm's sterile suspension rug products.

USC Response to Observation 5(B):

USC recognizes the importance of equipment validation. In deference to FDA, all homogenizers will go through a more extensive installation qualification, operational qualification, and performance qualification. This qualification process will include minimum and maximum process volumes, process performance against process times as well performance verification requirements, including suspension quality specifications, and required maintenance. As part of this process, a measurable quality attributes will be scientifically determined including analytical particle size distribution, which is under development with a qualified third-party vendor. This process will be initiated the week of March 11, 2019. Additionally, USC will re-assess the maintenance and calibration program for all equipment associated with the compounding processes to ensure that a robust Performance Verification and Preventive Maintenance (PM) program is in place. Lastly, USC will formalize a Master Validation Plan that will govern selection, procurement, qualification, use and maintenance of all compounding equipment. As such, USC believes that this information and analysis will address FDA's concerns in this observation.

FDA Observation 6:
There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed.

Specifically, your firm failed to investigate and appropriately determine if batches can be released for Sterility and Potency final release out-of-specifications.

FDA Observation 6(A):
On 12/27/2018, Investigation, USC-1455, was created to document the personnel monitoring (PM) failure (5 CFUs) identified as Staphylococcus hominis, of an aseptic filler during the production of Ephedrine 10mg/mL Sterile Injectable, Lot #20181812@2, expiration date 06/16/2019. Your firm's investigation documents only ½ of this Lot produced was destroyed. The investigation is deficient and does not provide any scientifically sound justification as to why the entire Lot was not destroyed.

USC Response to Observation 6(A) [5]:

USC acknowledges the importance of investigating sterility and potency out-of-specification results. However, before describing the actions taken to address Observation 6(A), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC disputes that this is a repeat observation as this Lot was compounded in 2018, USC thoroughly investigated the out-of-specification recoveries in this Lot, and there was a scientifically sound justification for why the entire Lot was not destroyed. USC provides more detail supporting this position below.

For clarification, this Lot was aseptically filled by two qualified operators in separate ISO 5 laminar flow hoods. The units were segregated by aseptic operator through the entire process, including during the subsequent investigation. One operator had a personnel excursion and the other operator's post-processing suit, mask, and gloved fingertip samples yielded no recoveries. USC completed an internal investigation as required under SOP QA-008 *Environmental Monitoring during Aseptic Operations and Post Process Personnel Monitoring* (Exhibit 1A-3) and SOP QA-017 *Deviation and Investigation System* (Exhibit 6A-1). This investigation included the following:

- a review of the routine and aseptic fill environmental monitoring for the week of December 12, 2018 through December 17, 2018;
- a review of all cleaning logs documenting cleaning for the month of December 2018;
- a review of temperature, humidity and differential pressures for the week of December 12, 2018 through December 17, 2018;
- a review of training for all personnel involved in aseptic processing;
- personnel interviews;
- video review of the actual aseptic fill of Lot 20181812@2; and
- the actionable isolate was identified by a qualified third-party laboratory.

These actions demonstrate that USC conducted a thorough investigation prior to Lot disposition and that this observation is not a repeat observation.

Additionally, USC's Quality program testing and destruction practices provide further support for its decision to release half of this Lot and destroy the other half. The batch record and associated documentation for Lot 20181812@2 demonstrate that the portion of this Lot that was released met all of USC's release criteria, which includes testing for sterility, endotoxin, and potency. Additionally, the units filled by the operator with the personnel monitoring excursion were dispositioned for destruction and deemed not eligible for release. As such, USC's Quality Unit performed an investigation and believes it had sufficient scientific justification based on fill location and time segregation supporting release of the units filled by the operator with no recoveries. Additionally, this lot was presented and reviewed by the material review board who dispositioned for release.

Nevertheless, out of an abundance of caution and in deference to the Agency, USC executed a voluntary recall to all customers on January 29, 2019 (Recall Letter, Exhibit 6A-2). As of February 19, 2019, 100% of the ten consignees have returned product to USC (Exhibit 6A-3). No adverse events were reported and there is no evidence of any quality defect in the voluntarily recalled units. USC also updated its procedures to ensure that future similar cases are handled in an appropriate manner to ensure patient

[5] USC objects that this observation and all of its subparts are repeat observations.

safety. As part of this update to improve the process, scientifically sound rationale, investigations, and product impact assessments will be scrutinized by the Material Review Board (SOP QA-011 *Material Review Board*, Exhibit 6A-4) to ensure the most probable root cause for the microbial recovery. Lastly, USC will continue to apply this strategy as part of USC's process for determining if medication should be destroyed when there are any microbial recovery personnel excursions in the ISO 5 area. As such, USC believes that these actions address FDA's concerns in this observation.

FDA Observation 6(B):
On 07/16/2018 Investigation, USC-1245, was created to document the PM failure (Too Numerous to Count; TNTC) of an aseptic personnel operator during the production of Succinylcholine PF 20mg/mL Sterile Injectable, Lot #20181107@4, expiration date 11/08/2018. Your firms' investigation documents only ½ of this Lot produced was destroyed. The investigation is deficient and does not provide any scientifically sound justification as to why the entire Lot was not destroyed. In addition, the investigation did not identify the microorganisms.

USC Response to Observation 6(B) [6]:

USC acknowledges the importance of investigating sterility and potency final release out-of-specification results. However, before describing the actions taken to address Observation 6(B), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC disputes that this is a repeat observation as this lot was compounded in 2018, USC thoroughly investigated the out-of-specification recoveries in this Lot, and there was a scientifically sound justification for why the entire Lot was not destroyed. The named Succinylcholine product, Lot 20181107@4, was aseptically filled by two qualified operators in separate ISO 5 laminar flow hoods. The units were segregated by aseptic operator through the entire process, including during the subsequent investigation. One operator had a personnel excursion and the other operator's post-processing suit, mask, and gloved fingertip samples yielded no recoveries. The 888 syringes filled by the operator with an actionable recovery from the mask were dispositioned for destruction and the remaining 895 syringes filled by the operator with no actionable recoveries were dispositioned for release. This disposition occurred *after* a completed investigation into the recoveries, which included a thorough review of the production, cleaning, facility control, personnel training, and routine environmental monitoring involved in this Lot. Importantly, the investigation did identify the microorganism for the actionable recovery as *Paenibacillus lautus*, a spreader known to confound enumeration. Moreover, the released portion of this Lot passed potency, endotoxin, and sterility testing. Additionally, this lot was presented and reviewed by the material review board who dispositioned for release. Based on this investigation and testing, USC's Material Review Board determined that the physical separation of aseptic processing was a sound scientific justification to support release of the units identified in this observation. As such, USC believes that this information and process improvements address FDA's concerns in this observation.

FDA Observation 6(C):
On 11/12/2018, Investigation, USC-1399, was created to document a consumer complaint related to particulate matter found in your firm's drug product, Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes, Lot #20181307@7, EXP 01/09/2019. Your firms' batch record for Lot #20181307@7 documents 933 syringes of Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes was [sic] produced. Your firms' distribution records and investigation report, USC-1399, document 933 syringes of this Lot was distributed to the end user for pediatric patients use.

[6] USC objects that this observation and all of its subparts are repeat observations.

After the initiation of this investigation, your firm found particulate matter in your retain samples for previous Lots for morphine oral solution. Your firm used an outside microscopy contract laboratory who conducted the analysis of 3 syringes containing morphine oral solution. On 12/06/2018, your firm received a confirmatory report from the outside microscopy contract laboratory who conducted the analysis of 3 lots containing morphine oral solution:

- *Two (2) samples for Lot #20181804@9 and Lot 320192009@6 "supported brown particles consistent with biological material, possibly fungus or mold".*
- *The 3rd sample, Lot 20182008@7, may be due to a defect in the syringe material.*

In addition, your firm identified the organism for the Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes, Lot #20182009@6, was found to be Aureobasidium pullulans, a yeast-like fungus. Your firm's distribution records documents [sic] Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes, Lto # 20181804@9 and Lot # 20182008@7, were distributed to end users.

To date, your investigation does not address if the end users were notified of your firm's findings.

USC Response to Observation 6(C)[7]:

USC is committed to fully investigating all product and customer complaints to ensure that any potential risks to patient safety are thoroughly evaluated and appropriately addressed. However, before describing the actions taken to address Observation 6(C), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC disputes that this is a repeat observation as the Lot at issue was compounded in 2018, USC thoroughly investigated the customer complaint for this Lot, and USC was in regular communication with the customer throughout the investigation. USC provides more detail in support of this position below.

On November 12, 2018, USC received a customer complaint regarding visible particulate in one syringe of non-sterile oral morphine sulfate (Lot 20181307@7). Importantly, this Lot was only distributed to one customer. This customer confirmed to USC that it quarantined all of the remaining medication in this Lot and would not use the medication when it reported the complaint to USC. Additionally, the customer was advised by FDA not to return suspect units to USC in case FDA wanted to perform testing.

After receiving the complaint, USC immediately responded by initiating an investigation that included regular communication with the customer. As part of this investigation, USC inspected retained samples for the Lot at issue and all other distributed Lots. USC also commissioned investigative testing to determine the most probable root cause of this customer complaint and assess any potential impact to patient safety. Importantly, out of an abundance of caution, USC ceased further distribution of any Lot of this product until this complaint was fully investigated and resolved. Because the investigation involved a DEA Schedule II narcotic not widely accepted for analysis at the specialized contract testing laboratories and USC required microbial assays with specified incubation times, the duration and timeline of the investigation extended beyond the typical target closure of 60 days set forth in SOP QA-013 *Handling Product Quality Complaints*, Section 6.14 (Exhibit 6C-1). USC communicated these steps to the customer and updated the customer regarding this process multiple times via phone and email (Exhibit 6C-2).

[7] USC objects that this observation and all of its subparts are repeat observations.

Importantly, USC visually inspected retained samples for the complaint Lot and found no anomalies. The retained samples were all originally visually inspected as part of routine production and no defects were identified. USC also visually re-inspected all other retained samples of previously distributed Lots and all units of undistributed Lots as another investigational tool. This investigational visual inspection identified a small number of units with potential particulates. Please note that some of these retained samples were beyond the labeled beyond-use-date during this inspection. As a result, USC sent these samples to a qualified third-party analytical testing laboratory for material identification. On December 6, 2018, the analytical laboratory issued its identification report, which concluded that some of the particulates could be microbial. Upon receiving these results, USC initiated further investigational testing by a qualified third-party microbiological testing laboratory using USP <61/62> on the remaining retained samples.

On January 16, 2019, the USP <61/62> testing results were made available to USC. Importantly, the investigational testing results showed that all distributed Lots were within acceptable quality limits, including microbial limits for non-sterile oral products per USP <1111> as tested by USP <61/62>. Results are provided as Exhibit 6C-3. The retained samples for the Lot at issue (Lot 20181307@7) indicated that testing for this Lot was with the established USP microbial limits established in USP. However, one of the tested Lots, which was not dispositioned for release by Quality and therefore not distributed to customers, contained a yeast-like fungus. After receiving these results, USC conducted a Lot impact assessment and evaluated whether any distributed Lots of this medication were within expiry. USC determined that all medications within all distributed Lots were expired as the longest beyond-use-date was January 9, 2019. As such, there was no current, urgent risk to patient safety because there were *zero* units in distribution within their labeled beyond-use-date.

In response to this investigation (which is ongoing), USC will implement a number of corrective and preventative actions before resuming production of non-sterile oral morphine sulfate. Corrective actions that will be implemented include improved:

- in-process filtration and environmental monitoring,
- hold time studies for intermediate holding vessels, and
- compendial bioburden limit testing for oral nonsterile products.

When USC resumes compounding this formulation, release testing will include strength, pH, visual inspection, antimicrobial content, and USP <61/62> microbial analysis. Additionally, as outlined in SOP QA-013 *Handling Product Quality Complaints*, Section 6.17.4 (Exhibit 6C-1), the customer will receive communication regarding the investigation conclusion. As such, USC believes that this information and analysis address FDA's concerns identified in this observation.

FDA Observation 6(D):
On 04/13/2018, Investigation, USC-1117, was created to document the initial potency failure (126%) for Triamcinolone Diacetate 80mg/mL Sterile Injectable Lot #20180304@3, expiration date 09/30/2018. Your firm's Director of QA/QC documents the contract lab performed a retest with an average passing result. The investigation is deficient in that it did not contain the original failure (126%) or the individual retest results; only the average passing result was reported (97.9%).

USC Response to Observation 6(D) [8]:

USC acknowledges the importance of investigating sterility and potency out-of-specification results and its responsibility to adequately oversee the services performed by contract testing laboratories. However, before describing the actions taken to address Observation 6(D), USC would like to provide more detailed insight into the observation itself. As an initial matter, USC disputes that this observation is a repeat observation as USC thoroughly investigated the testing results for this Lot. For clarification, the initial out-of-specification result from the contract analytical testing laboratory was invalidated by the contract-testing laboratory. After the invalidation, the contract-testing laboratory duplicated the retest with medication from the original container, and the average result was reported to USC.

However, in an effort to improve USC's oversight of analytical testing services, SOP QA-010 *Quality Hold, Storage, and Review & Disposition of GMP Compounded Product* (Exhibit 6D-1) and SOP QA-00*Vendor Oversight* (Exhibit 6D-2) were revised to include more specific requirements for what needs to be included in all third-party contract-testing laboratory data. Additionally, quality agreements will be executed with each qualified contract-testing laboratory to specifically detail how out-of-specification results should be handled and that all testing data is reported on the certificate of analysis. As such, USC believes that this information and analysis address FDA's concerns in this observation.

FDA Observation 7:
The written stability program for drug products does not include reliable, meaningful and specific test methods.

Specifically, your firm failed to test preservative content at expiry to verify the preservative system is effective and protects the product over its shelf life under expected conditions of use.

USC Response to Observation 7:

USC acknowledges the importance of reliable, meaningful, and specific test methods. USC testing of finished products is governed by SOP QA-007 *Sterile Finished Preparation Testing*. USC currently has potency over time and end-point sterility analyses to support the beyond-use-date for all of its sterile preparations. These analyses evaluate the potency and stability of each sterile compounded drug product over the respective labeled beyond-use-dates. Additionally, since 2016, USC has been conducting formal full stability studies for each medication that it offers as an added safeguard for its beyond-use-dating practices. As part of that process, USC initiates a stability study for one medication per month and determines the order of drugs to be studied by sales volume (i.e. products with the highest sales volume are studied first). Specifically, USC initiated stability testing on its sterile drug products packaged in multi-dose containers prior to the FDA inspection. The approved protocol for these drugs requires that an assessment of antimicrobial effectiveness at the beginning and end of the study.

As such, USC expects to finish formal stability studies for all current sterile compounded drug product by the end of 2019. USC acknowledges the importance of these assessments and will update the Agency on the progress of these stability studies as more information becomes available.

FDA Observation 8:
Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without performing at least one specific identity test on each

[8] USC objects that this observation and all of its subparts are repeat observations.

component and establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically, your firm relies on your vendor supplier's Certificate of Analysis (COAs) for the use of drug components, without conducting any addition [sic] testing (e.g. identify, potency, sterility, and endotoxin) prior to use in your firm's aseptic operations. In addition, your firm does not have a quality agreement with each supplier.

USC Response to Observation 8:

USC acknowledges the importance of establishing an adequate quality release process for raw material components used in the manufacture of finished products. However, before describing the actions taken to address Observation 8, USC would like to provide more detailed insight into the observation itself.

In addition to qualifying vendors, USC inspects incoming components upon arrival. As part of this process, each shipment of incoming components is quarantined from use until the material is inspected and released by the USC Quality Department. *See* SOP QA-035 *Receiving, Quarantine, and Quality Release of Incoming Raw Materials and Components* (Exhibit 8-1). As noted in FDA's observation, the USC Quality Department reviews the supplier's Certificate of Analysis to determine whether the component is acceptable for release and use in production.

Nevertheless, USC acknowledges the expectations for testing components outlined in FDA's December 2018 revised *Good Manufacturing Practices – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*. USC's actions to meet the expectations in this recently published Guidance document are as follows. USC is implementing identity testing using four tier-transform infrared spectroscopy ("FTIR") on components that are not approved drug products. The FTIR instrument was purchased prior to this inspection and was delivered to USC on February 26, 2019. The installation, operational, and performance qualifications are scheduled to begin the first week of March 2019. The identification test method will be qualified and is anticipated to be implemented by April 2019.

Further, USC will also continue to establish the reliability of supplier Certificates of Analysis through meaningful vendor oversight (SOP QA-004, Exhibit 6D-2). Going forward, Quality Agreements will be required for all component vendors to ensure they are qualified. On-site audits will also be required for component vendors on a risk-based schedule. Further, the qualification analysis will include verification testing at least annually for active pharmaceutical ingredients and every two (2) years for other components.

As such, USC believes that this information and analysis will address FDA's concerns identified in this observation.

FDA Observation 9

The quality control unit lacks the responsibility and authority to approve and reject all components, drug product containers, closures and drug products.

Specifically, your firm relies on the supplier's COA is used [sic] in lieu of conducting any specific tests on drug components to establish the identity, purity, strength, and quality of these components which are used in the production of non-sterile drug products. In addition, your firm does not have a Quality Agreement with these vendors. Furthermore, testing and release of drug product for distribution do not include appropriate

laboratory determination of satisfactory conformance to the final specifications, identity, and strength of each active ingredient prior to release.

USC Response to Observation 9 [9]:

USC acknowledges the importance of the quality unit having appropriate authority to approve and reject components. However, before describing the actions taken to address Observation 9, USC would like to provide more detailed insight into the observation itself. As an initial matter, USC objects that this observation is a repeat observation as the Agency's expectations regarding the segregation of 503A and 503B operations dramatically changed in 2018. As such, new Agency expectations cannot serve as the basis for concluding this is a repeat observation. Additionally, USC recognizes FDA's Guidance for Industry *Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, which was finalized in May 2018. After this Guidance was published, USC immediately conducted an assessment of its registered facility for compliance. Recognizing that the registered facility's design did not comply with FDA's new expectations for segregating 503A and 503B operations, USC initiated two activities: (1) a Quality Risk Assessment to internally segregate 503A and 503B activities to the largest extent possible in the registered facility (Exhibit 9-1, USC-1267-QRA) and (2) building a new facility to house 503B operations and physically segregate it from 503A. **Nevertheless, after evaluating the challenges of segregating these operations, USC decided that it will cease its 503A patient specific human drug compounding operations by April 1, 2019.**

Further, USC disputes that this is a repeat observation and that the quality control unit lacks sufficient authority because this conclusion is based on FDA's belief that USC does not apply 503B's requirements to the non-sterile compounded medications it dispenses via valid prescriptions for individually identified human patients. Importantly, the FDA Guidance for Industry governing this issue was not finalized during the previous inspection, which occurred in 2016. Additionally, USC-1267-QRA outlines the company's interim plan to apply cGMPs to 503B products, taking the conservative approach of applying cGMP procedures to all sterile drug products, regardless of whether the intended end-user was an individually identified patient (503A) or a facility for administration to a patient (503B). As part of this interim plan, USC's Quality Risk Assessment assessed factors such as the batch size, number of recipients, and clinical risk as determined by the supervising pharmacist (e.g. pediatric use, narrow therapeutic index). As such, USC believes it has acted in good faith and taken all reasonable steps to balance continuity of patient care with regulatory compliance for prescription dispensing activities, and this good faith effort is documented in SOP QA-010 *Quality Hold, Storage, Disposition, and Release of GMP Compounded Product* (Exhibit 6D-1) where USC requires that all non-patient specific human sterile drug products and non-sterile drug products intended for distribution are subject to approval or rejection by the quality control unit. Moreover, part of this issue will be moot as USC will cease its 503A patient specific human drug compounding operations in April 2019.

Additionally, USC acknowledges the FDA Draft Guidance for Industry *Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, December 2018, which incorporates new expectations for 503B facilities, such as quality agreements with vendors. Importantly, this is a December 2018 draft guidance that for the first time addresses the Agency's current thinking on the cGMPs applicable to non-sterile compounded drug products distributed by outsourcing facilities. As such, USC has been working to address these new expectations since they were published in December 2018. Specifically, in response to this revised draft guidance, USC initiated a

[9] USC objects that this observation and all of its subparts are repeat observations.

comprehensive gap assessment for compliance and is working to meet FDA's recently published expectations for:

- specific tests on drug components used to prepare non-sterile compounded drugs,
- Quality Agreements with those vendors, and
- release testing specifications for each Lot of non-sterile compounded drug product.

As such, USC believes that this information and analysis address FDA's concerns in this observation.

FDA Observation 10:
The labels of your outsourcing facility's drug products are deficient.

The labels of some of your outsourcing facility's drug products do not include information required by section 503B(a)(10)(A).

FDA Observation 10(A):
The proportion or quantity of each inactive ingredient is not included on some labels. Examples of product labels that do not contain this information include:

1. *GI Cocktail – Belladonna Alkaloids:Antacid:Lidocaine 35mL Oral Bottle*
2. *Acetaminophen Oral 24mg/7.5mL Oral Syringe*
3. *Magic Mouthwash – Lidocaine + Diphenhydramine + Antacid 5mL Oral Syringe*
4. *Promethazine Topical Gel 25mg/mL 1mL Topical Syringe*
5. *Simethicone 120mg/1.8mL Oral Syringe*
6. *Multivitamin + Iron 1mL Oral Syringe*
7. *Multivitamin Oral 0.5mL Oral Syringe*

USC Response to Observation 10(A):

USC acknowledges the importance of appropriate labeling. However, before describing the actions taken to address Observation 10(A), USC would like to provide more detailed insight into the observation itself. As an initial matter, the proportion or quantity of each active pharmaceutical ingredient is appropriately quantified in each of the examples listed in this observation. Additionally, most of the examples are non-sterile drug products that are compounded using FDA approved finished drug products. The source NDC numbers are listed below:

1. GI Cocktail – Belladonna Alkaloids:Antacid:Lidocaine 35mL Oral Bottle
    a. 51927-1831 (active pharmaceutical ingredient)
    b. 57896-629 (approved drug product)
    c. 38779-0082 (active pharmaceutical ingredient)
2. Acetaminophen Oral 24mg/7.5mL Oral Syringe
    a. 50580-296 (approved drug product)
    b. 0113-0212 (approved drug product)
3. Magic Mouthwash – Lidocaine + Diphenhydramine + Antacid 5mL Oral Syringe
    a. 38779-0082 (active pharmaceutical ingredient)
    b. 0603-0823 (approved drug product)
    c. 57896-629 (approved drug product)
4. Promethazine Topical Gel 25mg/mL 1mL Topical Syringe

   a. 51927-9018 (active pharmaceutical ingredient)
5. Simethicone 120mg/1.8mL Oral Syringe
   a. 0536-2220 (approved drug product)
6. Multivitamin + Iron 1mL Oral Syringe
   a. 00087-405 (approved drug product)
7. Multivitamin Oral 0.5mL Oral Syringe
   a. 00087-402 (approved drug product)

The manufacturer labeling for the finished approved drug products used to compound the medications listed in this observation does not quantify the inactive ingredients. As the FDA finished approved products do not label inactive ingredients, USC has no way of quantifying these inactive ingredients itself. As such, FDA is enforcing an expectation that can never be met given FDA's current labeling requirements for manufacturers. USC therefore believes that its current practices adequately address FDA's concerns in this observation.

FDA Observation 10(B):
The dosage form of the drug is not included on some labels. Examples of product labels that do not contain this information include:

1. *Neostigmine 5mg/5mL Single Use Syringe*
2. *Glycopyrrolate 1mg/5mL Single Use Syringe*
3. *Succinylcholine 200mg/10mL Single Use Syringe*
4. *GI Cocktail – Antacid:Lidocaine 3:1 40mL Syringes*
5. *LET Gel 4%/0.1%/0.5% 3mL Single Use Syringe*

USC Response to Observation 10(B):

USC acknowledges the importance of appropriate labeling. However, before describing the actions taken to address Observation 10(B), USC would like to provide more detailed insight into the observation itself. USC notes that the label for the fifth product listed in this observation, LET Gel 4%/0.1%/0.5%, contains the same dosage form as reported to FDA through the Structured Product Labeling system. A copy of the label and a screenshot from its SPL submission is included in Exhibit 10B-1. As a result, USC believes the existing label for this medication meets FDA's expectations. However, in deference to FDA, the medication labels identified as 1-4 in the above observation were corrected to include the dosage form of the drug (Exhibit 10B-1). Additionally, USC updated SOP PC-010 *Finished Product Label Requirements and Compliance* (Exhibit 10B-2) to clarify all information that must be included on a label. Finally, USC initiated a comprehensive review of all human compounded drug product labels to ensure there are no additional labels missing required information. As such, USC believes that this information and these actions address FDA's concerns in this observation.

FDA Observation 10(C):
The required statements, "This is a compounded drug" and "Not for resale" are not included on some labels. Examples of product labels that do not contain this information include:

1. *Rx 587841 Praziquantel – 5mL, 20mg/mL Suspension*
2. *Rx 537458 Progesterone 20mg/0.5mL Cream*
3. *Rx 562508 Acyclovir + Lidocaine – 5gm, 5%/1% Lip Balm*

USC Response to Observation 10(C):

USC acknowledges the importance of appropriate labeling and acknowledges that all human drug compounded product labels are required to contain certain information. The products listed in this observation are only dispensed pursuant to prescriptions for identified individual patients, and the labels have been corrected to include these two required elements – a statement that "this is a compounded drug" and a statement the drug is "not for resale" (Exhibit 10C). To ensure the Quality Unit has sufficient authority and oversight on all human drug compounded products (including labeling), USC will discontinue dispensing human prescriptions to individual patients by April 1, 2019. As such, USC believes that this information and these actions address FDA's concerns in this observation.

FDA Observation 10(D):
Storage and Handling Instructions are not included on some labels. Examples of product labels that do not contain this information include:

1. *Rx 537458 Progesterone 20mg/0.5mL Cream*

USC Response to Observation 10(D):

USC acknowledges the importance of appropriate labeling and acknowledges that all human drug compounded product labels are required to contain certain information. The product listed in this observation is only dispensed pursuant to prescriptions for identified individual patients, and the label has been corrected to include storage and handling instructions (See Exhibit 10C). To ensure the Quality Unit has sufficient authority and oversight on all human drug compounded products (including labeling), USC will discontinue dispensing human prescriptions to individual patients by April 1, 2019. As such, USC believes that this information and these actions address FDA's concerns in this observation.

In closing, USC wants to reiterate and emphasize that it is committed to patient safety and to meeting Agency expectations for compliance and quality as it relates 503B Facilities. USC intends to provide the updates it committed to in its responses to FDA's observations and to implementing those changes as quickly as possible. If FDA would like to further discuss the Form 483 or USC's responses, please contact us. Thank you for your attention to this matter.

Respectfully,

Ron E Antes II
Director of QA/QC
US Compounding, Inc.