1270 Don's Lane
Conway, AR 72032

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VIA ELECTRONIC MAIL

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.
FOLLOW UP TO 2019 INSPECTIONAL OBSERVATIONS

LCDR Diehl:

US Compounding, Inc. ("USC") would like to take this opportunity to update the U.S. Food and Drug Administration ("FDA") on the commitments made in its March 1, 2019 response and April 11, 2019 supplemental response to the inspectional observations listed on the Agency's February 7, 2019 Form 483 ("Form 483"). As USC identified in its prior responses, USC is committed to ongoing corrective actions and process improvement projects to ensure that it meets FDA's updated 503B Outsourcing Facility expectations set forth in the Agency's December 2018 FDA Guidance for Industry[1]. The purpose of this letter is to provide the Agency with a comprehensive update on the corrective actions USC completed and to reaffirm USC's commitment to executing the remaining corrective actions outlined in its prior Form 483 responses. With that background, USC provides the following updates for FDA's review.

Follow Up to Response to Observation 2B:

In response to Observation 2B, USC committed to executing a feasibility study and method development study to create a specific, accurate and sensitive test method for recovering and quantifying potential testosterone residue with swabs. As stated in USC's prior responses, USC's initial focus was on developing a proof of concept, feasibility and qualifying liquid chromatography-mass spectrometry/mass spectroscopy quantitative analytical method for detection of testosterone concentration and from surfaces using swab recoveries. The third-party contract lab that USC engaged for developing this testing methodology has now developed and qualified the testosterone analytical liquid chromatography-mass

[1] Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, Revised Draft Guidance, December 2018.

spectrometry/mass spectroscopy ("LC-MS/MS") method. This testing method includes a limit of quantitation ("LOQ") and limit of detection ("LOD").

As part of this process, the third-party contract lab completed the scope of work for the LC-MS/MS analytical method development and feasibility. Specifically, the suitably sensitive LC-MS/MS method establishes LOD and LOQ thresholds for testosterone at 0.1 ppm for LOD and 0.3 ppm for LOQ. These thresholds are based on six replicate injections of standard solution (0.1 ppm and 0.3 ppm, respectively) that have a LOQ mean signal to noise ("S/N"), ≥ 3 and a LOQ mean ("S/N") ≥ 10. These thresholds are also based on the percent relative standard deviation ("%RSD") of < 10% for all peak areas measured at LOQ. The completed experiments are provided as Exhibit 1.

The third-party contract lab also qualified that the LC-MS/MS analytical method developed is suitable for quantifying residual levels of testosterone recovered when swabbing different surface types. Three coupon types (Stainless Steel, Borosilicate Glass, and Formica) were used to represent the surfaces of the compounding and filling operation at USC. The base line cleaning detection limit used in this method verification was established as 5 µg/swab for a 16 $inch^2$ area = 0.3125 µg/$inch^2$ (48 ng/cm^2). After the baseline detection limit was established, the LC-MS/MS method was evaluated using the following criteria: Specificity, Linearity, LOQ, LOD, System Precision, and Accuracy prior to executing swab recoveries on the three different surfaces. The results of the third-party contract labs method evaluation are outlined by category in the following table:

Table 1: Method Evaluation Results

Evaluation Parameter	Acceptance Criteria	Actual Measurement
Specificity	No significant interference from the diluent, blank swab, swabbed blank coupons, and detergents at the retention time of the Testosterone, Testosterone Cypionate and Testosterone Propionate peaks.	No interference was observed from the peaks due to the diluent, blank swab, swabbed blank coupons, and detergents at the retention time of the Testosterone peaks.
Linearity	The correlation coefficient must be ≥ 0.98 from a range of 0.3 ppm to 15 ppm for Testosterone standard and from a range of 0.1 ppm – 20 ppm for Testosterone Cypionate and Testosterone Propionate	Testosterone: r = 0.99799 (refer to Figure 3) Testosterone Cypionate: r = 0.99774 (refer to Figure 4) Testosterone Propionate: r = 0.99959 (refer to Figure 5)
LOQ	The average signal to noise ratio (S/N) of the Testosterone standard peak at 0.3 ppm must be ≥ 10 & %RSD of peak areas NMT 10% (n=6).	Mean S/N: 11.8; RSD: 1.40%

LOD	The average S/N ratio of the Testosterone standard peak at 0.1 ppm must be ≥ 3 (n=6).	Mean S/N: 3.8

The fully executed assay verification and swab recovery summary report is attached as Exhibit 2. Importantly, the executed swab recoveries were between 70 -130% for each of the three materials (Stainless Steel, Borosilicate Glass, & Formica) at all three spiking levels (80%,100%, and 150%), which meets the acceptance criteria for accuracy.

As a next step, USC is planning to execute an in-situ study during actual compounding and filling of testosterone compounded drug product. This study will be executed using swabs to recover and quantify potential testosterone residue throughout the process. USC will update FDA once it has more information relating to the in-situ study.

Finally, to confirm powder containment hood performance, USC had dynamic smoke studies performed on all hoods, and those smoke studies confirmed the hoods' airflow performance and containment. The powder containment smoke study protocol is attached as Exhibit 3. The certification documentation for each powder containment hood is attached as Exhibit 4. Video documentation of the smoke study for each powder containment hood is attached as Exhibit 5.

Follow Up to Response to Observation 3:

As a follow up to USC's prior responses to Observation 3, the first phase of deploying Everbuild® Everflex® 565 Clean Room Silicone for cleanroom ceiling tiles was completed on April 6, 2019. The ceiling tiles in Cleanroom 2 were replaced, seated, sealed and caulked with Everbuild® Everflex® 565 Clean Room Silicone. After these ceiling tiles were replaced, USC recertified the cleanroom. The Controlled Environment Performance Test and Certification Report is attached as Exhibit 6. Finally, USC anticipates replacing ceiling tiles, using the above caulking material, in Cleanroom 1 and the anterooms in October 2019. USC will update FDA as to the progress of the October 2019 ceiling tile replacement when more information becomes available.

Follow Up to Response to Observation 4A:

As a follow up to USC's prior responses to Observation 4A, USC successfully re-executed dynamic media fills under the most challenging and stressful compounding conditions possible on February 25, 2019.

USC's February 25, 2019 media fills were conducted in the following manner so that they replicate the most challenging and stressful compounding conditions. During this media fill, a total of 3,681 3mL syringes were filled with 1mL tryptic soy broth media. Three planned interventions were executed during the media fill with a total of thirteen people present in the room (the maximum amount of people that can currently occupy a cleanroom during operation

at USC's compounding area). To add to the total dynamic conditions, three additional ISO 5 hoods in Cleanrooms 1 and 2 were in operation to simulate daily production activities such as filtration, homogenization, and packaging. Moreover, simulated material transfer, batch record recording, finished product reconciliation, and environmental monitoring were performed in Cleanrooms 1 and 2 throughout the entire day while the media fill was performed.

Importantly, there were not any environmental monitoring or personnel action level excursions associated with this media fill batch. All syringes from the media fill were incubated at 22.5°C for period of seven days. A visual inspection that was performed and documented by USC's quality unit followed the incubation. The visual inspection demonstrated that no visual turbidity or growth was detected. The media fill was incubated further at 32.5°C for another seven days, followed by a second USC quality unit visual inspection. No visual turbidity or growth was detected during the second visual inspection. As a result, USC concluded that this media fill was successfully completed as all of the syringes compounded during this simulation met USC's required acceptance criteria. As such, USC believes that it addressed FDA's concerns in this observation.

Follow Up to Response to Observation 4B:

As a follow up to USC's prior responses to Observation 4B, USC previously committed that it would re-execute smoke studies under extreme dynamic conditions for critical aseptic operations performed in ISO 5 hoods per an approved protocol. The objective of the re-executed smoke studies was to generate additional scientific data demonstrating that all critical aseptic operations performed in USC's ISO 5 hood maintained adequate laminar airflow during dynamic simulated operational working conditions (i.e., USC's goal was to ensure there was not any air from the ISO 7 controlled environment that entered the ISO 5 controlled environment).

In order to generate this data, USC engaged a third-party contract service (AirSafe, LLC) to execute smoke studies on March 19 and 20, 2019. USC Operational and Quality Leadership were present during the smoke studies for observational oversight and real-time communication with the third-party vendor. The smoke studies material for Cleanroom 1 is included as Exhibit 7. Please note that these smoke studies cover aseptic operations for the aseptic processing and fill of solutions under dynamic and un-dynamic conditions. As such, Cleanroom 1 successfully passed USC's smoke studies protocol.

However, during the March 2019 execution of approved protocol smoke studies for Cleanroom 2's aseptic processing, homogenization and filling of suspensions, USC determined that the turbulence caused by the homogenization process and beaker manipulation could potentially introduce ISO 7 air into the ISO 5 environment. As a result, USC suspended production of all sterile compounded suspension products until suitable corrective actions could be identified and implemented as Cleanroom 2 is where suspension products are compounded.

Since the March 2019 smoke studies, USC took the necessary actions to resume sterile compounded product suspension production. USC began the process of sourcing Vertical

Laminar Flow Hoods ("VLFH") as a primary engineering control to eliminate all turbulent air movement around a beaker during the dynamic homogenization process for suspension products. As part of the sourcing process and installation of the VLFH, USC completed a number of activities, which include:

- Drafting and approving additional smoke study protocols that specifically address the VLFH. This protocol is attached as Exhibit 8.
- Reviewing and updating Standard Operating Procedures as well as the Media Fill Master Validation Plan to reflect the introduction of the VLFH. An example SOP is attached as Exhibit 9. Refer to the attached Exhibit 10 for the updated Media Fill Master Validation Plan.
- Creating and approving process media fill batch records for suspensions in VLFH. An example of an updated batch record is attached as Exhibit 11.
- Updated and approved Compounded Sterile Drug Product ("CSDP") Master Batch records to reflect the change from horizontal laminar airflow to vertical laminar airflow. An example of an updated CSDP Master Batch record is attached as Exhibit 12.
- Training aseptic operations and environmental monitoring staff on operation of the VLFH and the principles of aseptic technique as it pertains to vertical laminar airflow as opposed to horizontal. An example of the training provided is attached as Exhibit 13.
- Installing three VLFHs in Cleanroom 2, executing installation and operational qualification ("lOQ") and certification. The Installation and Operational Qualification documentation is attached as Exhibit 14. The device certification for each VLFH is attached as Exhibit 15.

On April 9, 2019, USC executed protocol smoke studies performed by a third-party contract service for Cleanroom 2 to ensure that the turbulence issue was addressed. Again, USC Operational and Quality Leadership were present during these smoke studies for real-time observation of the smoke visualization patterns. USC's internal visual results, along with the third-party contract personnel's results, concluded that the smoke visualization patterns in Cleanroom 2 did meet the pre-defined acceptance criteria named in USC's smoke study protocol. This included dynamic suspension product homogenization, aseptic vial filling, and solution product filtration across all three VFLH at the same time. The smoke study video documentation for Cleanroom 2 is attached as Exhibit 16.

Additionally, USC conducted suspension process media fills, 6 in total, 2 in each hood, to ensure performance of the new VLFH. As part of media fill process, USC produced 12,732 units of suspension injectables with a 1mL fill volume in a 2mL vial and another 529 units of suspension injectables with a 100mL fill volume in a 100mL vial across all three VLFH. These media fills were performed over a period of three days (April 22-24, 2019) and used to qualify technicians for aseptically filling in VFLH. Please note that dynamic conditions were present for suspension product homogenization, aseptic vial filling and common aseptic interventions during these media fills.

Importantly, no environmental monitoring or personnel action level excursions were associated with the executed media fills. Each media fill lot was incubated at 22.5°C for period of seven days followed by a visual inspection executed by the USC quality unit. No visual turbidity or growth was detected. Each lot of media was then incubated at 32.5°C for an additional seven days and followed by a visual inspection by the quality unit. No visual turbidity or growth was detected after this second incubation. As a result, all suspension process media fills received passing results from USC's quality unit, and therefore supported USC's decision to resume compounding suspension drug products, which is outlined in more detail in response to Observation 5A.

Follow Up to Response to Observation 5A:

As a follow up to USC's prior responses to Observation 5A, USC committed to initiating process performance qualifications ("PPQ") for its compounded suspension drugs to ensure their quality. In support of this commitment, USC drafted and executed PPQ protocols for its current product portfolio of compounded suspension drug products. This original protocol is attached as Exhibit 17. An amendment to the protocol concerning preservative free products was made at a later date and is also attached as Exhibit 18. USC executed PPQ batches in triplicate to confirm that the compounding, autoclave sterilization, homogenization process and aseptic fill processes are in a state of control. Additionally, to show homogeneity of active ingredients in the CSDP across the aseptic fill, samples from the beginning, middle, and end of the aseptic fill underwent full release testing to ensure predefined release testing criteria were met. The PPQ batches were initiated and completed for each of following CSDP suspensions:

- Triamcinolone Diacetate 40mg/mL (NDC – 62295320507)
- Triamcinolone Diacetate PF 40mg/mL (NDC – 62295320602)
- Triamcinolone Diacetate 80mg/mL (NDC – 62295320807)
- Triamcinolone Acetonide PF 50mg/mL (NDC – 62295331702)
- Methylprednisolone Acetate + Lidocaine 40mg/1%/mL (62295312107)
- Methylprednisolone Acetate + Lidocaine 80mg/1%/mL (62295312207)
- Methylprednisolone Acetate PF 80mg/mL (62295311901)
- Betamethasone Combo 7mg/mL (62295328407)
- Betamethasone Combo PF 6mg/mL (62295301802)

After successful completion of PPQ activities, USC resumed production and dispensing of the above listed compounded suspension drug products. Supporting documentation is provided as Exhibit 19 (A-I).

Follow Up to Response to Observation 5B:

To update USC's previous responses to Observation 5B, USC would like to provide the following information. All homogenizers have gone through the comprehensive installation, operational, performance qualification processes described in the initial response. The executed protocols for these homogenizers were provided as an exhibit to USC's April 2019 supplemental Form 483 response and are reincorporated here as Exhibit 20 (A-K) for ease of reference.

Further, the initial assessment for suspension quality attributes has been completed. Analytical proof of concept (feasibility) methodology, design of experiments and qualification for particle size distribution of the compounded suspension drug product Methylprednisolone Acetate + Lidocaine 80mg/1%/mL particle size distribution, have been completed. Methylprednisolone Acetate + Lidocaine 80mg/1%/mL was chosen as a potential worst case scenario particle size as it has the highest active pharmaceutical ingredient concentration out of all suspension in USC's compounding processes (therefore representing the highest risk profile). Completed particle size activities for suspension quality attributes are included as Exhibit 21 (A-F). To further evaluate the Methylprednisolone Acetate + Lidocaine 80mg/1%/mL particle, a formal protocol will be initiated to perform particle size analysis on retain samples of this compounded suspension drug product. Additionally, the next compounded suspension that will undergo these activities is compounded suspension drug product, Betamethasone Combo PF 6mg/mL.

Follow Up to Response to Observation 8:

To update USC's prior responses to Observation 8, USC would like to provide the following information. USC successfully installed and qualified the fourier-transform infrared ("FTIR") spectroscopy instrument that USC will use to perform identity analysis. FTIR installation and qualification documentation is attached as Exhibit 22. Associated standard operating procedures are attached as Exhibit 23. An example of an executed active pharmaceutical identification data packet is provided as Exhibit 24. As such, USC believes that it has addressed FDA's concerns in this observation.

Follow Up to Response to Observation 9:

To update USC's prior responses to Observation 9, USC would like to provide the following information. As of April 1, 2019, USC ceased compounding 503A patient-specific human drug compounding. As evidence of that cessation, USC provides its final summary of its 503A patient specific human compounding history as Exhibit 25.

In closing, USC would like to assure FDA that it continues to take its professional responsibilities very seriously and will continue to update the Agency regarding its corrective actions in the manner outlined throughout this response.

Respectfully,

Ronald E Antes II
Director of Quality
US Compounding, Inc.