DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, TX 75204 (214)253-5200 Fax:(214)253-5314	1/23/2019-2/7/2019* FEI NUMBER 3006031801

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Bradford S. Powell, General Manager Aseptic Operations

FIRM NAME	STREET ADDRESS
US Compounding Inc	1270 Dons Ln
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Conway, AR 72032-4753	Outsourcing Facility

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

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

****THIS IS A REPEAT OBSERVATION FROM 08/21/2015 & 07/15/2016****

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

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, ISO7, and ISO 5). Your firm's 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. The following mycological contaminants (primarily soil borne microbes) were identified in your firm's Sterile Suite Area where sterile drug products are produced in 2018:

Epicoccum nigrum
Pestalotiopsis vismiae
Phoma novae-verbascicola
Cladosporium cladosporioides / herbarum / phaenocomae
Cladosporium halotolerans

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Curvularia geniculata / senegalensis
Exophiala dermatitidis
Aspergillus creber / puulaauensis
Aspergillus austroafricanus / fructus / griseoaurantiacus / protuberus / tabacinus / versicolor
Alternaria alternata
Pithomyces sacchari
Curvularia geniculata / senegalensis
Ustilago cynodontis
Microsphaeropsis arundinis
Curvularia variabilis
Curvularia lunata
Periconia epilithographicola
Nigrospora sphaerica
Myrothecium cinctum
Arthrinium phaeospermum
Chaetomium globosum

B. Your firm failed to conduct (b) (4) 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 (b) (4) 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, (b) (4) 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. For example, but are not limited to:

Sampling Dates	Lot Number	Drug Name
(b) (4)	20182612@4P	EPHEDRINE SULFATE PF 5ML SYRINGE

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		5MG/ML INJECTABLE
(b) (4)	20182612@5P	EPHEDRINE SULFATE PF 5ML SYRINGE 5MG/ML INJECTABLE
	20182612@3P	EPHEDRINE SULFATE PF 10ML SYRINGE 5MG/ML INJECTABLE
	20181812@2	EPHEDRINE SULFATE PF 10ML SYRINGE 5MG/ML INJECTABLE
	20181012@3	EPHEDRINE SULFATE PF 5ML SYRINGE 5MG/ML INJECTABLE
	20181012@4	METHYLPREDNISOLONE ACE/LIDO 10ML VIAL 80MG/1% /ML INJECTABLE
	20180412@8	TRIAMCINOLONE ACETONIDE PF 2ML VIAL 50MG/ML INJECTABLE
	20180312@9	SUCCINYLCHOLINE CHLORIDE PF 10ML SYRINGE RT 20MG/ML INJECTABLE
	20180312@1	PE/LIDO SULFITE-FREE OPHTHALMIC PF 1ML VIAL 1.5%/1% INJECTABLE

C. Your firm failed to justify the reduction of environmental monitoring frequencies of yeast and mold ((b) (4) plates) from (b) (4) to (b) (4) 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 (b) (4) to (b) (4) in 2017 (11% to 39% increase). This trend was also observed in (b) (4) of 2016; in (b) (4) 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 (b) (4) 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).

D. Your firm's written procedure, QA-008: "*EM during Aseptic Operations and Post Process Personnel Monitoring*" states only (b) (4)

(b) (4) . However, (b) (4) is not representative of your firm's most challenging and/or stressful conditions. For example, on 01/24/2019, I observed surface sampling conducted (b) (4) 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.

OBSERVATION 2

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

Specifically,

A. Your firm failed to clean as recommended by your firm's 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).
B. Your firm failed to establish cleaning procedures to prevent cross-contamination of testosterone to other drug products.
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.

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 (b) (4) 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.

OBSERVATION 4

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

Specifically,

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 (b) (4) (b) (4) . However, your media fills are performed under (b) (4) of the LAFH (ISO 5) (b) (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. (b) (4) (b) (4)), 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 ISO 7 environment into ISO 5 environment) in your firm's smoke study titled, "(b) (4) *Airflow Visualization*".

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.

Specifically,

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A. Your firm does not have any process validations for the aseptic production of your firm's suspension products. Including, but are not limited to:
   1. Methylprednisolone 80mg/mL PF Sterile Injectable
   2. Methylprednisolone/Lidocaine 40mg/1%/mL Sterile Injectable
   3. Methylprednisolone/Lidocaine 80mg/1%/mL Sterile Injectable
   4. Betamethasone 7mg/mL Combo 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
   9. (b) (4) /Lidocaine 150mg/mL 150mg/1%/mL Sterile Injectable
   10. Dexamethasone Acetate 8mg/mL Sterile Injectable
   11. Dexamethasone Acetate 16mg/mL Sterile Injectable
   12. Dexamethasone Acetate Sodium Phosphate Combo 8mg/4mg/mL Sterile Injectable

B. Your firm's equipment validation, VAL009, for the (b) (4) EQ ID: (b) (4) , is deficient. For example, but are not limited to, the report does not address the max/min volumes the (b) (4) is able to process; process times are not defined; calibration and maintenance programs are not defined. The (b) (4) is used during the production of your firm's sterile suspension drug products.

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 been already distributed.

****THIS IS A REPEAT OBSERVATION FROM 07/15/2016****

Specifically, your firm failed to investigate and appropriately determine if batches can be released for Sterility and Potency final release out-of-specifications. For example, but are not limited to:

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.

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 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. In addition, the investigation did not identify the microorganisms.

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 firm's batch record for Lot #20181307@7 documents (b) (4) syringes of Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes was produced. Your firm's distribution records and investigation report, USC-1399, document (b) (4) syringes of this lot was distributed to the end user for pediatric patients use.

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 (b) (4) 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 (b) (4) containing morphine oral solution:

- (b) (4) for Lot #20181804@9 and Lot #20182009@6 "supported brown particles consistent with biological material, possibly fungus or mold".
- (b) (4) Lot 20182008@7, may be due to a defect in the syringe material.

In addition, your firm identified the organism for Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes, Lot #20182009@6, was found to be *Aureobasidium pullulans,* a yeast-like fungus.

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Your firm's distribution records documents Morphine Sulfate 0.5mg/mL Oral 1mL Dose Syringes, Lot # 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.

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 ((b) (4)%).

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.

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 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 testing (e.g. identity, 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.

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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,

****THIS IS A REPEAT OBSERVATION FROM 07/15/2016****

Your firm relies on the supplier's COA is used 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.

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). Specifically,

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 35 mL Oral Bottle
    2. Acetaminophen Oral 240mg/7.5ml Oral syringe
    3. Magic Mouthwash – Lidocaine + Diphenhydramine + Antacid 5 mL Oral Syringe
    4. Promethazine Topical Gel 25ml/ml 1 mL Topical Syringe
    5. Simethicone 120 mg/1.8 mL Oral Syringe
    6. Multivitamin + Iron 1 mL Oral Syringe

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7. Multivitamin Oral 0.5 mL Oral Syringe

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 5 mg/5 mL Single Use Syringe
   2. Glycopyyrolate 1 mg/5 mL Single Use Syringe
   3. Succinylcholine 200 mg/10 mL Single Use Syringe
   4. GI Cocktail - Antacid:Lidocaine 3:1 40 mL Syringe
   5. LET Gel 4%/0.1%/0.5% 3 mL Single Use Syringe

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 (b) (6) Praziquantel – 5 mL, 20 mg/mL Suspension
   2. Rx (b) (6) Progesterone 20 mg/0.5 mL Cream
   3. Rx (b) (6) Acyclovir + Lidocaine – 5 gm, 5%/1% Lip Balm

D. Storage and Handling instructions are not included on some labels. Examples of product labels that do not contain this information include:
   1. Rx (b) (6) Progesterone 20 mg/0.5 mL Cream

***DATES OF INSPECTION**

1/23/2019(Wed), 1/24/2019(Thu), 1/25/2019(Fri), 1/28/2019(Mon), 1/29/2019(Tue), 1/30/2019(Wed), 1/31/2019(Thu), 2/01/2019(Fri), 2/04/2019(Mon), 2/05/2019(Tue), 2/06/2019(Wed), 2/07/2019(Thu)

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