

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT ADDRESS AND PHONE NUMBER

4040 North Central Expressway, Suite 300
Dallas, TX 75204
(214) 253-5200 Fax: (214) 253-5314
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

07/06/2016 - 07/15/2016

FEI NUMBER

3006031801

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Eddie W. Glover, CEO

FIRM NAME

US Compounding Inc

STREET ADDRESS

1270 Don's Lane

CITY, STATE, ZIP CODE, COUNTRY

Conway, AR 72032

TYPE ESTABLISHMENT INSPECTED

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 WE OBSERVED:

OBSERVATION 1

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

Specifically, your firm has SOP Q9 entitled "ENVIRONMENTAL MONITORING OF THE ASEPTIC PROCESSING ENVIRONMENT AND ANCILLARY CLEAN AREAS" which describes personnel and environmental monitoring. The following deficiencies in the procedure and practices were observed:

- a. Your firm's mold recoveries have shown an increase in isolates in (b) (4) from March to June of 2016, as indicated below. However, your firm has failed to investigate this trend of increasing mold levels or determining a root cause of mold.

Isolates		
	(b) (4)	(b) (4)
March	0	0
April	4	2
May	10	4
June	15	6

Additionally, throughout the inspection, large conglomerates of fuzzy colonies appearing to be mold were observed on environmental monitoring plates sampled from a (b) (4). Your firm's Environmental Monitoring Technician stated that these results do not require attention, as the colony encompassing approximately one fourth of the plate was a single colony forming unit. No investigation was conducted and no action was taken.

- b. (b) (4) surface sampling is conducted (b) (4) which had been (b) (4). For example, on 07/08/2016, I observed operators (b) (4) (b) (4). Moreover, (b) (4).
- c. For the week of 07/04/2016, the only environmental monitoring using (b) (4) plates was conducted on (b) (4) (b) (4), in a cleanroom that had not been utilized for production and subject to (b) (4) cleaning.
- d. Your firm is currently performing environmental monitoring (b) (4) (b) (4) that has (b) (4) (b) (4). Your firm was unable to demonstrate the effectiveness of this method to conduct environmental monitoring.
- e. On 07/08/2016, we observed an operator spraying sanitizing (b) (4) to sanitize their gloves directly above a (b) (4).

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- plate used to assess viable air monitoring.
- f. On 07/13/2016, we observed viable active air sampling performed when no personnel were present (b) (4)
 - g. Your firm performs environmental monitoring for yeast and mold (b) (4) plates) on a (b) (4) basis, and not daily or after every sterile operation. Section 8.4 of this SOP indicates that (b) (4) and (b) (4) plates "shall be taken at the (b) (4) (b) (4) "
 - h. On 07/08/2016, we observed non-viable particulate monitoring with the (b) (4) (b) (4) (b) (4) Additionally, on 07/08/2016 and 07/13/2016, (b) (4) non-viable monitoring occurred (b) (4) when no personnel were present.
 - i. Documentation of environmental monitoring, entitled "Environmental Monitoring Log", fails to indicate when environmental sampling plates were taken, incubated or read. Furthermore, section 8.5.8 of SOP Q9 indicates for incubating (b) (4) growth plates for (b) (4) yet plates are not incubated for a consistent duration. On 07/11/2016, your firm's Environmental Monitoring Technician stated that in the morning he removed and read (b) (4) plates incubated at (b) (4) °C from (b) (4) 2016 (obtained in the late afternoon). Thus, these plates were incubated for approximately (b) (4) days, rather than (b) (4) days.
 - j. On July 13, 2016, we reviewed temperature records that did not include daily temperatures on the weekend when the incubators were actively in use to hold microbiological samples. Incubator (b) (4) # (b) (4) intended for (b) (4) °C, (b) (4) # (b) (4) intended for (b) (4) °C, and (b) (4) # (b) (4) intended for (b) (4) °C storage, do not have temperature records on the weekend. Temperatures for incubators used for Environmental Monitoring Samples and Media Fill units are not complete.

THIS IS A REPEAT OBSERVATION FROM AUGUST 21, 2015

OBSERVATION 2

Aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure.

a. Pressure differentials are routinely not met (with negative pressure occurrences). The table below indicates the average number of minutes per day that pressure differentials were not met or went negative from May and June of 2016:

	Min Pressure Differential Not Achieved (avg. per day)	Min Pressure Differential Went Negative (avg. per day)
Chemical Storage to Hallway (ISO 8 to Unclassified)	45.01	0.02
Glassware Storage to Chemical Storage (ISO 8 to ISO 8)	193.98	20.98
Sterile Prep to Glassware Storage (ISO 8 to ISO 8)	59.34	3.05
Sterile Prep to Chemical Storage (ISO 8 to ISO 8)	4.07	0.64
Sterile Prep to Anteroom (b) (4) (ISO 8 to ISO 7)	17.67	1.39
Anteroom (b) (4) to Anteroom (b) (4) (ISO 7 to ISO 7)	19.93	1.25
Anteroom (b) (4) to Cleanroom (b) (4) (ISO 7 to ISO 7)	12.81	12.90

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Storage (b)(4) to Anteroom (b)(4) (ISO 7 to ISO 7)	15.37	0.67
Storage (b)(4) to Storage (b)(4) (ISO 7 to ISO 7)	35.17	2.66
Cleanroom (b)(4) to Storage (b)(4) (ISO 7 to ISO 7)	19.57	1.84
Cleanroom (b)(4) to Anteroom (b)(4) (ISO 7 to ISO 7)	14.08	13.15
Cleanroom (b)(4) to Quarantine (ISO 7 to Unclassified)	1.93	1.64

Note: During a review of your firm's pressure logs, we observed missing time points. For example, on 05/02/2016, approximately 29% of pressure time point data is missing. On this day, Neostigmine Methylsulfate lot #20160205@1, MIC + B12 lots #20160205@6 and 20160205@8 were aseptically processed.

Furthermore, your firm's SOP Q27 entitled "Parameters for Controlling Pressures in the Cleanrooms" stipulates "Pressure differential shall maintain appropriate minimum specifications"


Examples of processing sterile drug products during pressure excursions include:

1. On 05/11/2016, the pressure differential between ISO 7 Cleanroom (b)(4) and ISO 7 Anteroom (b)(4) went negative from 3:43 to 4:06 pm during the processing of Methylprednisolone Acetate PF 40mg/ml (lot #20161005@9). Your firm's Vice President of Regulatory and Quality stated no investigation into this occurrence was available. This product was distributed on 06/15/2016. Moreover, complete pressure readings from 05/11/2016 and thus during processing were not present in the pressure log. Your firm was unable to explain why various time points are not present in the pressure log.
2. On 07/08/2016, during the duration of processing of Glycopyrrolate 0.2mg/ml 5ml (lot #20160807@1) the pressure differentials between ancillary rooms was lost on four occasions (Glassware Storage to Chemical Storage and Anteroom (b)(4) to Anteroom (b)(4)). Document QF73 which documents excursions in pressure differentials fails to include these losses of pressure differentials. Your firm was unable to reconcile the failure to capture these pressure excursions on document QF73, which is intended to annotate all such events. Firm management indicated this product is intended for distribution.
3. On 06/22/2016, during the processing of Medroxyprogesterone 200mg/ml 100ml amber vial (lot #06212016@46) the pressure differentials between ancillary rooms ISO 8 Chemical Storage to the unclassified Hallway and ISO 8 Chemical Storage to the ISO 8 Hallway simultaneously fell below specification, with the pressure differential between the Chemical Storage to Hallway going negative during aseptic processing. No investigation into these events were available. Firm management indicated this product is intended for distribution.

b. Additionally, your procedure for calibration of differential pressure gauges in cleanrooms does not require a minimum accuracy.

On the most recent calibration dated (b)(4) differential pressure gauges demonstrated inaccuracy (b)(4) from set points of up to (b)(4) inches of water from the (b)(4) gauges.

Your SOP "Q27 v5.0" calls for minimum pressure differentials of (b)(4) between (b)(4) ISO environments) and differentials of (b)(4) inches of water (between (b)(4) ISO environments).

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Your VP of Regulatory stated there is not a procedure speaking to the accuracy needed during calibration of pressure gauges.

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OBSERVATION 3

Buildings used in the manufacture, processing, packing, or holding of a drug product do not have the suitable construction to facilitate cleaning, maintenance, and proper operations.

Specifically, your cleanrooms used for producing sterile human drugs have design elements that do not minimize risk to sterile drug production.

On July 8, 2016, we observed a total of (b) (4) fire sprinklers installed through rough-cut holes in the (b) (4) ceiling tiles of Cleanroom # (b) (4) and (b) (4) such that these holes were not sealed causing the cleanroom to be exposed to an uncontrolled environment.

On July 11, 2016, we observed the following:

- a. Duct work connects the ceiling of Cleanroom # (b) (4) that leads to an un-classified attic and utility area. This ceiling connection had a piece of clear plexi-glass glued over the ceiling opening. Air pressure from the attic opening was observable utilizing a sheet of paper.
- b. Duct work connecting Cleanroom # (b) (4) to the Anteroom # (b) (4) through the ceiling which creates a difficult to clean area. If differential pressures are negative, air would flow into the Cleanroom # (b) (4) from Anteroom # (b) (4). Additionally, with the ductwork in the ceiling, the direction of airflow is upwards towards the ceiling.
- c. Duct work connecting Cleanroom # (b) (4) to Cleanroom # (b) (4) through the ceiling which creates a difficult to clean area.

On (b) (4), report (b) (4) documents smoke studies were performed that show the (b) (4)

as follows:

- a. Video time (b) (4) - Room # (b) (4) - Cleanroom # (b) (4)
- b. Video time (b) (4) - Room # (b) (4) - Cleanroom # (b) (4)
- c. Video time (b) (4) - Room # (b) (4) - Cleanroom # (b) (4)
- d. Video time (b) (4) - Room # (b) (4) - Cleanroom # (b) (4)
- e. Video time (b) (4) - Room # (b) (4) - Cleanroom # (b) (4)
- f. Video time (b) (4) - Room # (b) (4) - Anteroom # (b) (4)

A separate video shows (b) (4) as follows:

- a. Video time (b) (4) (b) (4)
- b. Video time (b) (4) (b) (4)
- c. Video time (b) (4) (b) (4)
- d. Video time (b) (4) (b) (4)

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OBSERVATION 4

The quality control unit lacks the responsibility and authority to reject all drug products.

Specifically, your firm has released human drug products that were tested and showed preservative and API potency values outside of specifications.

- Oxytocin Sublingual Drops - lot #20151808@7 API potency at 82% of labeled strength
Produced on August 18, 2015, BUD 90 days
- Brompheniramine 10mg/ml Injectable - lot #20160504@24 preservative potency at 85% of label strength
Produced on April 5, 2016, BUD 180 days
- Pentosan 250mg Injectable - lot #04062016@1 preservative potency at 84% of label strength
Produced on April 6, 2016, BUD 180 days
- Neostigmine 1mg/mL Injectable - lot 2013103@19 preservative potency at 61% of label strength
Produced on March 31, 2016, BUD 180 days


OBSERVATION 5

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Specifically, your firm manufactures batches of sterile product ranging from (b) (4) to (b) (4) units; however, per SOP QA-007 entitled "Sterile Finished Product Testing (b) (4)" assessed for endotoxin levels. No scientific rationale for sampling on (b) (4) for endotoxin levels was provided.

For example, the following batches (with quantity indicated) have been tested for endotoxin levels using (b) (4) for endotoxin levels:

- Triamcinolone Diacetate PF lot #20162704@1 processed 04/28/16 - (b) (4) units. This product was distributed on 06/13/2016.
- methylPREDNISolone PF lot #20161005@9 processed 05/11/16 - (b) (4) units. This product was distributed on 06/15/2016.
- Triamcinolone Diacetate PF lot #20160905@1 processed 05/09/16 - (b) (4) units. This product was distributed on 07/11/2016.

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OBSERVATION 6

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

Specifically, your firm has not adequately investigated discrepancies of sterile human suspension drug products.

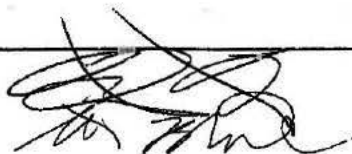
During 2015 and 2016, 22 complaints were received pertaining to Methylprednisolone, Bethamethasone, and Dexamethasone that was difficult to inject through a needle or push through a syringe. Your investigation focused on the (b) (4) sterilization of the product and effect on viscosity. Investigations did not determine if product specifications were adequate with respect to viscosity, solubility of API, or suspension quality.

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