DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
19701 Fairchild Irvine, CA 92612 (949) 608-2900 Fax:(949) 608-4417 Industry Information: www.fda.gov/oc/industry	01/12/2015 - 01/16/2015* FEI NUMBER 3005084110

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Tanaz (nmi) Kohan, Pharm.D., Pharmacist In Charge

FIRM NAME	STREET ADDRESS
Advanced Physician Solutions, Inc.	7225 Fulton Ave
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
N Hollywood, CA 91605-4111	Producer of Sterile Drug Products

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, the following deficiencies were observed in (b) (4) separate production areas: (b) (4) ISO 5 hood is for (b) (4) referred to by the Pharmacist In Charge (PIC) as for (b) (4) use and the (b) (4) is ISO 5 (b) (4) referred to by the PIC as for (b) (4) use located within a non-controlled room. (Note: There are (b) (4) ISO 5 hoods within ISO 7 area with an ISO 8 anteroom, however, (b) (4)).

A. For ISO 5 hood,

a. The firm's procedure titled "Environmental Monitoring of the Clean Room Facility" dated 09/14/2014 section 1.d. states "in situ air pattern analysis via smoke studies shall be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic condition." However, the firm has not conducted any static or dynamic smoke studies.

b. There is an air conditioning (AC) unit installed (b) (4) ISO 7 clean room across from (b) (4) ISO 5 hood units. The AC unit supplies air to the ISO 7 room. There is no evidence that there is a HEPA filter inside the AC unit. In addition, no return air vent was observed in the ~~room~~ ISO 7 room.
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c. The ISO 5 hood is (b) (4) which is in violation of the firm's SOP titled "Equipment" section 1.a.i. which states "(b) (4) ." The pressure differential for ISO 5 hood is not recoded. Per the PIC, only ISO 7 and 8 are on (b) (4) On 01/12/15, we noticed that ISO 5 and 7

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rooms were not clean per the PIC but there was no label indicating the status of cleaning. Pressure differential is not recorded continously for ISO 5, ISO 7 or ISO 8 zones. The pressure differential between ISO 5 and ISO 7 is noted when the ISO 5 hood is turned on, however, there is no documentation of the pressure differential. The pressure differential between ISO 7, ISO 8 and unclasssified zones is recorded (b) (4)

d. Firm's SOP titled "Environmental Monitoring of the Clean Room Facility" section 4.b. states "Sites of surface sampling should (b) (4) [redacted] In actual practice,

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i. The firm does not perform viable active air monitoring during production ~~OK~~ in ISO 5 hood such as Medroxyprogesterone Acetate, Testosterone Cypionate, Triamcinolone Acetonide, Sodium Hyaluronate, and Methylprednisolone Acetate. Viable monitoring using (b) (4) for the ISO 5 zone is conducted (b) (4) [redacted]. Settling plates are used (b) (4) [redacted]

ii. Per the firm's (b) (4) certification of ISO 5, the firm contracts a third party to perform non-viable air monitoring approximately (b) (4). The latest certification on ISO 5 hood was conducted on 09/26/14. The firm does not recertify the ISO 5 hood (b) (4) [redacted].

iii. The firm conducts personnel monitoring on finger tips only. The compounders are monitored every (b) (4) [redacted]. No other areas such as forehead, mask, or chest are monitored for the operators.

B. The ISO 5 (b) (4) used for production is located in a non-classified area with the following deficiencies observed.

a. The vent directly above the ISO 5 (b) (4) has a filter that was observed to be dark and dirty. The PIC did not know when the filter was last changed.

b. The (b) (4) has incoming and return vents sharing the same pipe. The incoming air and return air appear to share the same plastic pipe and there is no HEPA filter on the return air path. The PIC did not know if incoming and exiting air shared the same pipe or not.

c. There are (b) (4) of the ISO 5 (b) (4) . The (b) (4) . Air flows freely from inside the (b) (4) to the outside unclassified room, without any filter. During the inspection, we felt air coming out of these (b) (4) from the ISO 5 (b) (4) The ISO 5 (b) (4) per the PIC. ISO 5 (b) (4) is certifed (b) (4) The ISO 5 (b) (4) was last certified on 09/26/14.

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OBSERVATION 2

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

Specifically,

A. The firm performs media fill studies using (b) (4) (b) (4) media-fill challenge (b) (4) The (b) (4) has a vial containing (b) (4)

The vials are incubated at (b) (4) .

This media fill process does not simulate the actual production process with respect to container closure type (actual products have vials and syringes), container closure size (actual product size ranges from 10 mL, 30 mL, and 100 mL), and processing duration. According to the PIC, the media fill process takes about (b) (4) to complete, however, the actual production may take up to (b) (4) No challenges or interventions are introduced during the media fill operations.

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B. Per the PIC, a (b) (4) is conducted (b) (4). However, the firm has no documentation to show that (b) (4) is conducted after (b) (4)

C. Per the firm's SOP titled "Equipment" section 5.c. "(b) (4) or similar product will be used to verify (b) (4) effectiveness. This test will done every (b) (4) ". The (b) (4) is used to verify effectiveness of (b) (4). The firm had results from a contract laboratory of (b) (4) (b) (4) test for the validation runs conducted on 4/7/14 and 7/25/14. However, there were no records of the actual operating conditions including (b) (4). Under normal conditions, the firm uses (b) (4) for product sterilization. The (b) (4) are printed and attached to the production logs.

The following products are sterilized using (b) (4):

a. Triamcinolone Acetonide Injection Suspension, 80 mg/mL (10/30/100 mL vials)
b. Medroxy Progesterone Acetate Injection Suspension 150 mg/mL (10/30/100 mL vials)
c. Methylprednisolone Acetate Injection Suspension 100 mg/mL (10/30/100 mL vials)

D. The firm had results from a contract laboratory for (b) (4) test conducted on 7/25/14 and 10/29/14. However, there were no records of the actual operating conditions such as (b) (4) used during the (b) (4), which is a (b) (4). The following products are sterilized using (b) (4)

a. Hydroxyprogesterone Caproate Oil Injection Solution 250mg/mL (10mL vials)
b. Testosterone Cypionate Oil Injection Solution 200 mg/mL (10/30/100 mL vials)

Under normal conditions, the (b) (4) is conducted at (b) (4)

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OBSERVATION 3

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

Specifically,

A. The firm has not performed cleaning validation to determine if their cleaning procedure is effective when the ISO 5 hood is (b) (4) The procedure "Cleaning and Maintenance of the Clean Room Facility" does not detail the level of cleaning needed when the ISO 5 hood is (b) (4) . The firm also uses the same procedure to clean the ISO 5 (b) (4)

B. Per SOP titled "Equipment" dated 09/14/2014 section 12.b. (b) (4) will be used at regular intervals". However, the SOP does not define what a regular interval is.

   a. Per the PIC, sporicidal agent ((b) (4)) is used to clean ISO 5 hood, metal shelves in ISO 7 zone, and ISO 8 sink once every (b) (4) . However, there is no documented record for the cleaning with sporicidal agent.

   b. Per the PIC and SOP titled "Equipment" dated 09/14/2014, the firm cleans ISO 5 hood, metal shelves in ISO 7 zone, and ISO 8 sink with sterile (b) (4) (b) (4) There are records to document the cleaning, however, the cleaning agent used (b) (4)) is not documented.

C. Per the PIC, non-sterile cleaning wipes are used for cleaning and sanitizing ISO 5 hood and ISO 5 (b) (4) , with sterile sporicidal agent and/or sterile (b) (4)

D. There are no disinfectant efficacy studies conducted to show that sterile sporocidal ((b) (4) and sterile (b) (4) are effective in cleaning equipment used in the production of sterile drugs.

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OBSERVATION 4

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

Specifically,

A. The firm does not have any written procedures for disinfectant neutrallizton and does not perform any disinfectant neutralization before taking the enviromental monitoring samples in the ISO 5, ISO7 and ISO 8 zones.

B. The firm uses (b) (4) titled "(b) (4) " for sterility testing which requires the vials to be incubated at (b) (4) . On 01/13/15, we observed the following oil based products incubated in Incubator #(b) (4) :

   a. Hydroxyprogesterone lot # 1/6/15 1.1 (04/06/15 or 90 days expiration)
   b. Estradiol Cypionate Oil Injection solution lot # 1/5/15 0.23 (exp 04/05/15 or 90 days expiration)

C. The firm uses (b) (4) test for sterility testing of non oil based drug products. The test requires (b) (4) On 01/12/15, we observed the following (b) (4) product syringes were incubated for sterility testing in Incubator # (b) (4)

   a. Methylcobalamine injection solution lot # MC12/30/14 3.84 (exp 01/13/15 or 14 days expiration)
   b. Cyanocobalamin lot # 1/9/15 3.77 (04/09/15 or 90 days expiration)

The firm does not have an incubator set at (b) (4) incubation as required by the test. Further, it should be noted that the sterile (b) (4) product is (b) (4) for sterility testing using the (b) (4) The following products were observed in Incubator (b) (4)

   a. Methylcobalamine injection solution lot # MC12/30/14 3.84 (exp 01/13/15 or 14 days expiration)

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b. Cyanocobalamin lot # 1/9/153.77 (04/09/15 or 90 days expiration)

D. Per the PIC, there has never been a sterility failure since she joined the firm in Feb of 2014.

OBSERVATION 5

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically, As per SOP 9.100, version 1.0 titled "Required Garb For Clean Room Facility Access" during production:

A. Non-sterile gowns are allowed to be worn while working in ISO 5 and ISO 7 zones.

B. Per the PIC: nose, lips, and chin are covered with a sterile face mask, eye area is coverd with goggles wiped with (b) (4) using non-sterile wipes, and hair nets are sterile and disposable; however the facial skin of the operators is not fully covered. During this inspection, we did not observe any drug compounding activities.

OBSERVATION 6

Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

Specifically, the firm uses an (b) (4) The firm does not perform any leak test on the vials containing the product.

OBSERVATION 7

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

Specifically, for all sterile products that are tested in-house only sterility test is performed. However, no endotoxin testing is performed. No endotoxin testing was conducted for the following products with Beyond Use Date of 90 days.

A. Cyanocabalamin 2000 mcg/ml, Lot# CY 12/19/14 6.06, BUD 3/19/2015

B. Nandrolone Decanoate 200 mg/ml, Lot# NA 1/8/15 1.76, BUD 4/8/2015
C. Hydroprogesterone Caproate 250 mg/ml, Lot# HC 1/9/15 3.6, BUD 4/9/2015
D. Estradiol Cypionate 5 mg/ml, Lot# ES 1/5/15 7.84, BUD 4/5/2015

OBSERVATION 8

Drug products do not bear an expiration date determined by appropriate stability data to assure they meet applicable standards of identity, strength, quality and purity at the time of use.

Specifically, the firm has no stability study to show that preservatives used in multidose vials (MVD) are effective to keep products sterile up to 28 days after the multidose drug vial is punctured. Per the PIC, the 28 day expiration dating is assigned based on pharmacy regulations and is not based on any stability or preservative antimicrobial effectiveness testing. For example, the following are multidose drug products ~~compounded~~ produced by the firm. SMK 1/16/15

A. Medroxy Progesterone Acetate Injection Suspension (Paraben Free) 150 mg/mL: 10, 30, and 100ml MDV's contain (b) (4) as preservatives.

B. Testosterone Cypionate Oil Injection Solution 200 mg/Ml: 10, 30, and 100ml MDV's contain (b) (4) as preservatives.

C. Methylprednisolone Acetate Injection Suspension 100 mg/Ml: 10, 30, and 100ml MDV's contain (b) (4) as preservatives.

OBSERVATION 9

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

Specifically, on 01/12/15 we observed a microwave and a toaster oven for cooking food in the operation room. There were also boxes of cereal (one Honey Maid brand and one Cheerios brand) and two refrigerators used for food storage. All these were in a close proximity to the production equipment (b) (4) and Incubator (b) (4) In addition, there was a sink in the operation room for (b) (4) . The operation room is located (b) (4) the ISO 5 (b) (4) is located and there is no door separating the two rooms.

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OBSERVATION 10

Records of the calibration checks and inspections of automatic, mechanical or electronic equipment, including computers or related systems are not maintained.

Specifically, there are no records available for the calibration of critical equipment that are essential to the production. For example,

SMK 1/16/15 (b) (4)

A. There is one (b) (4) refrigerator with freezer in the compounding room where the ISO 5 (b) (4) is located. The thermometers that are used to record temperatures for firm's refrigerator and freezer do not have unique identifiers and are not calibrated. The following materials were stored in the refrigerator:
   a. Hydroxocobalamin, USP (b) (4) Lot# (b) (4)
   b. Alprostadil, USP, (b) (4) Lot# (b) (4)
   c. Sodium Hyaluronate, (b) (4) Lot# (b) (4)
   d. Vitamin D3 Liquid, (b) (4), Lot# (b) (4)

   The following material was stored in freezer:
   a. Hyaluronidase, (b) (4), Lot# (b) (4)

B. The temperature monitoring devices used for the following (b) (4), and incubators, are not calibrated.
   a. (b) (4)
   b. (b) (4)
   c. (b) (4)
   d. (b) (4)
   e. (b) (4) S/N information not accessible
   f. (b) (4) and S/N information not accessible

C. According to the PIC, standard weights are used for (b) (4) verification of the balances however, the weight standards have never been calibrated. The balances are used to weigh raw material used in drug production.

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D. The balances had stickers showing the previous calibration was conducted in January 2014. However, no records were available to show the calibration of the following balances.
   a. Balance (b) (4) (max (b) (4) weight capacity)
   b. Balance (b) (4) (max (b) (4) weight capacity)

E. There are no records of the pH meter calibration. The pH meter is used to measure the pH of the following drug products:
   a. Cyanocobalamin Injection Solution lot # CY1/7/15 8.15
   b. Triamcinolone Acetonide Suspending Vehicle lot # TV 9/29/14 9.76

*** DATES OF INSPECTION:**
01/12/2015(Mon), 01/13/2015(Tue), 01/14/2015(Wed), 01/16/2015(Fri)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."