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 Industry Information: www.fda.gov/oc/industry	02/03/2015 - 02/19/2015* FEI NUMBER 3011278953

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Kenneth Ryan Orton, Owner

FIRM NAME	STREET ADDRESS
Physician Preferred Medical, LLC,	3300 NW 56th Street Suite 101
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Oklahoma City, OK 73112	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:

The following observations pertain to the preparation of testosterone and estradiol pellets. From November 1, 2014-January 30, 2015 there were approximately (b) (4) lots of Testosterone 99.5% Granulation, (b) (4) lots of testosterone pellets (varying strengths), (b) (4) lots of Estradiol 99.5% Granulation, and (b) (4) lots of estradiol pellets (varying strengths) made.

OBSERVATION 1

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

Specifically,

a) The cleanroom (buffer room) is equipped with a direct flow of unfiltered HVAC air.
b) The ante-room, where gowning and entry into the cleanroom occurs, is not constructed with a supply of HEPA filtered air.
c) Your firm does not have any documentation of smoke studies having been performed in the cleanroom (buffer room).
d) During the certification of the (b) (4) hood (serial number (b) (4)) on 10/30/14, the third party service reported that the HEPA filter needed to be replaced. Your firm failed to replace it until 1/6/15. During the time period between 11/1/14 and 1/5/15, the (b) (4) hood was used during the weighing, melting, granulation, sieving, and packaging (b) (4) lots of granulated testosterone, (b) (4) of granulated estradiol; (b) (4) lots of testosterone pellets (varying strengths); and (b) lots of estradiol pellets (varying strengths).
e) Your firm does not have a scientific rationale for performing environmental monitoring in your cleanrooms and (b) (4) hoods only once every (b) (4) during certification of the rooms.
f) Your firm has not established alert and action limits for environmental monitoring of surfaces and air (viable) in the cleanroom (buffer room). During the last certification in October 2014, the report stated that there were 25cfu (active air) and 5cfu (surface) found in the cleanroom and 9cfu (active air) and 7cfu (surface) found in the ante room.
g) Your firm does not perform any personnel monitoring of employees involved in making the testosterone and estradiol pellets.
h) The cleanroom (buffer room) and ante-room are not equipped with pressure differential indicating magnehelic gauges resulting in a lack of monitoring of pressure differentials during operations. There is no documentation of any monitoring by your firm of the pressure differential between the cleanroom (buffer room) and the ante room (where gowning occurs) and between the ante room and the retail pharmacy. The last room certification dated 10/30/14 reported that the cleanroom

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(buffer room) is +.0025" W.C. positive to the ante-room; the ante-room is +.0290" W.C. positive to the retail pharmacy; and the cleanroom (buffer room) is +.0674" W.C. positive to the retail pharmacy. The pressure differential of the cleanroom (buffer room) does not meet the minimum pressure differential of (b) (4) to the ante-room as noted in the 10/30/14 certification.
i) The exhaust vent for the cleanroom (buffer room) exits (b) (4)
j) Re-certification of the cleanroom (buffer room) did not occur following the relocation of the (b) (4) away from the corner to facilitate cleaning or the addition of the (b) (4)

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.

Specifically, your firm has not validated the sterilization process for any of the drug products that you prepare. Your firm prepares testosterone and estradiol pellets of varying strengths from bulk non-sterile APIs and excipients, places them into non-sterile vials with screw-top lids, and then (b) (4) them. Your firm has no documentation of the qualification of the (b) (4) used (b) (4) or how the (b) (4) for the pellets was developed. Per your Pharmacy Technician, up until a few weeks ago (exact date unknown), your (b) (4) Your firm purchased a new (b) (4) that you started using (date unknown) and the (b) (4)

OBSERVATION 3

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.

Specifically,

a) Lot #06241401-070714Q of Estradiol 18mg pellets made on 7/7/14 failed sterility. Part of the lot had been distributed on 7/7/14 & 7/8/14 and was recalled by your firm on 7/24/14. There is no documentation of an investigation being performed by your firm into the sterility failure and no corrective actions implemented with the exception of having your employees take an "Aseptic Technique Self-Assessment" exam.
b) The last environmental monitoring of your cleanroom (buffer room) by a third party in October 2014, revealed levels of microbiological contamination in your cleanroom (buffer room) that were considered above action level per the report. The report states that viable environmental sampling "requires attention." Counts in the cleanroom (buffer room) were 25CFU for active air. The action limit listed in the report is (b) (4). There is no documentation of an investigation performed by your firm into this failure and how this may impact product. Your Pharmacist stated that after the report you changed the disinfectant used from (b) (4). No additional environmental monitoring was performed after the change in disinfectant to demonstrate that the corrective action was effective.
c) The last certification report for the (b) (4) hoods in the cleanroom dated 10/30/14 states that the hood with serial number

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(b) (4) failed air flow testing. The report states that the "device does not meet the minimum requirement exhaust velocity. Filter needs to be replaced ASAP." Your firm did not change the HEPA filter until 1/6/15. There is no documentation of an investigation by your firm into the failure of the filter or any product impact. From the date of the initial failure in October 2014 until it was changed on 1/6/15, (b) (4) lots of granulated testosterone, (b) (4) of granulated estradiol, (b) (4) lots of testosterone pellets (varying strengths), and (b) (4) lots of estradiol pellets (varying strengths) were produced.

OBSERVATION 4

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Specifically,

a) Your firm has not validated the cleaning/disinfection of the equipment (i.e. (b) (4)) used to make testosterone and estradiol pellets.
b) Your firm is using non-sterile (b) (4) wipes when cleaning and disinfecting the equipment used to prepare the testosterone and estradiol pellets. The non-sterile wipes are used on all equipment used to make the pellets including the (b) (4) .
c) Your firm is using non-sterile (b) (4) to clean the (b) (4)
d) Your firm is not documenting the preparation of or the specific cleaning agents and disinfectants used on processing equipment (b) (4) that operations occur.

OBSERVATION 5

There is a lack of written procedures assigning responsibility, providing cleaning schedules, and describing in sufficient detail the methods, equipment and materials to be used for sanitation.

Specifically,

a) Your firm has not validated the cleaning/disinfection of the cleanroom (buffer room) or (b) (4) hoods where testosterone and estradiol pellets are made.
b) Your firm is using non-sterile (b) (4) wipes when cleaning and disinfecting the cleanroom (buffer room). The non-sterile wipes are used on the floors, walls and ceilings of the cleanroom and the powder hoods.
c) Your firm is using non-sterile (b) (4) on floors, walls, and ceilings in the cleanroom (buffer room) and to clean the (b) (4) hoods.
d) Your firm is not documenting the preparation of or the specific cleaning agents and disinfectants used in the cleanroom (buffer room) (b) (4) that operations occur.

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OBSERVATION 6

Clothing of personnel engaged in the manufacturing and processing of drug products is not appropriate for the duties they perform.

Specifically, the general gowning attire for entry into the cleanroom (buffer room) where testosterone and estradiol pellets are made consists of the following: scrubs worn from outside the facility, a disposable lab coat, a single hair net, a surgical face mask with ties and booties. All are non-sterile. The operators use sterile gloves. The general gowning requirements leave exposed skin around the eyes, forehead, and neck of the person preparing the drug product. Your firm does not have a scientific rationale for your gowning requirements.

OBSERVATION 7

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, your firm packages the testosterone and estradiol pellets into non-sterile/non-depyrogenated 2mL amber glass vials with a screw top lid. Your firm has no documentation to show that this packaging and container/closure system is suitable to protect the drug product from external factors that may affect the quality and sterility of the drug product over time.

OBSERVATION 8

Drug product containers and closures were not sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Specifically, your firm packages the testosterone and estradiol pellets into non-sterile/non-depyrogenated 2mL amber glass vials with a screw top lid that are (b) (4) Your firm does not process the vials and screw-top lids prior to packaging to remove pyrogenic properties. Your firm has not validated the (b) (4) for the pellets and has no documentation to show that the vials and screw-top lids are (b) (4) .

OBSERVATION 9

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,

a. The floor of the cleanroom (buffer room) is constructed of (b) (4)
b. The ceiling of the cleanroom (buffer room) is constructed of (b) (4)

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(b) (4) There is a noticeable lip between the (b) (4) that allows for the collection of production dust and airborne particulates. Also, (b) (4) do not totally enclose the circumference of (b) (4) allowing open access directly into the cleanroom (buffer room) from the adjoining unclassified areas above and about.

OBSERVATION 10

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

Specifically, your firm has not defined all specifications for the release of each lot of drug products prepared by your firm. Your firm has not determined endotoxin limits for your pellet products (testosterone and estradiol), drug release rate, or any other physical quality outside of potency that might affect the quality of the pellets.

OBSERVATION 11

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications and identity and strength of each active ingredient prior to release.

Specifically, your firm does not conduct potency testing for all lots of sterile drug products produced. Your firm only performs potency testing on (b) (4) of pellets (testosterone and estradiol) produced from a lot of granulation.

OBSERVATION 12

There is no written testing program designed to assess the stability characteristics of drug products.

Specifically, your firm does not have a written stability testing program to justify the Beyond Use Date (BUD) of 180 days placed on your testosterone and estradiol pellets. In addition to that, the BUD assigned to some lots of pellets exceeds the expiration date/retest date of the active pharmaceutical ingredient (API) used. For example, the expiration date for lot #(b) (4) of Testosterone, USP (soy) per the Certificate of Analysis from your vendor is 2/28/15. This lot of API was used in lot #11251401 of Testosterone (b) (4). Lot #11251401 was in turn used to make lot #s 120114P (100mg), 120314R (200mg) and 120814S (25mg) of testosterone pellets. The BUD assigned to these lots was 05/15.

OBSERVATION 13

Each batch of drug product required to be free of objectionable microorganisms is not tested through appropriate laboratory testing.

Specifically, your firm does not perform endotoxin testing on (b) (4) of pellets (testosterone or estradiol) made from a new lot of granulation.

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OBSERVATION 14

The master production and control records are deficient in that they do not include complete manufacturing and procedures.

Specifically, your firm does not include in the batch records for the testosterone and estradiol pellets the sterilization (b) (4) to be used or the date of sterilization. A few weeks ago (date unknown) your firm purchased a new (b) (4) that has the capability to (b) (4) Prior to that time your firm has no documentation of the sterilization of any lots of pellets produced. From November 1, 2014-January 14, 2015 your firm made approximately (b) (4) lots of testosterone pellets (varying strengths) and (b) (4) lots of estradiol pellets (varying strengths) for which there is no documentation of the sterilization of the lot.

OBSERVATION 15

Written production and control procedures include batches formulated with the intent to provide less than 100 percent of the labeled or established amount of active ingredient.

Specifically, your firm does not formulate your testosterone and estradiol pellets to provide for 100% of label claim. Your firm formulates the pellets to contain (b) (4) of the active ingredient.

OBSERVATION 16

Routine calibration and checking of electronic equipment is not performed according to a written program designed to assure proper performance.

Specifically,

a) The (b) (4) electronic balance certification last performed on 8/8/14, did not include specific balance identifications and the certification stickers were placed on a sheet of paper instead of on the balances.
b) The (b) (4) electronic balances (models (b) (4)) used to weigh the active pharmaceutical ingredients (testosterone and estradiol); the (b) (4) and the finished product (testosterone and estradiol) pellets are not calibrated within their intended range of use (b) (4) . The latest certification dated 8/8/14 certified them as a "counter scale over 10lbs" and the actual weight used during the certification was not documented.
c) The (b) (4) electronic balances (models (b) (4)) used to weigh the active pharmaceutical ingredients (b) (4) , and the finished product pellets are not checked prior to use to verify they remain accurate following their relocation from the storage table to the (b) (4) hoods or from side to side within the (b) (4) hoods each time a batch of pellets is made.

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OBSERVATION 17

Master production and control records lack a statement of theoretical yield including the maximum and minimum percentages of theoretical yield beyond which investigation is required.

Specifically, batch records for the testosterone and estradiol pellets do not define a minimum and maximum percentage of theoretical yield beyond which an investigation is required. A review of batch records from November 1, 2014-January 31, 2015 showed some actual yields for estradiol pellets to be as follows:

a) 6mg: (b) (4) (lot 12161401-010815B) and (b) (4) (lot 01131501-011515F),
b) 10mg: (b) (4) (lot 10271402-112114O)
c) 12.5mg: (b) (4) (lot 10271401-111014I)
d) 15mg: (b) (4) (lot 10271401-102714D) and (b) (4) (lot 10271402-121014T)
e) 20mg: (b) (4) (lot 12161401-121714V),
f) 22mg: (b) (4) (lot 01131501-011415E) and (b) (4) (lot 10271401- 102814F)
g) 25mg: (b) (4) (lot 10271402-121514U) and (b) (4) (lot 01131501-011315D)

No investigations were performed for any of these lots.

OBSERVATION 18

Equipment used in the manufacture, processing, packing or holding of drug products is not of appropriate design to facilitate operations for its cleaning and maintenance.

Specifically, the work tables used to hold the two (b) (4) hoods in the cleanroom (buffer room) are constructed of (b) (4) that are not easily cleanable.

*** DATES OF INSPECTION:**
02/03/2015(Tue), 02/04/2015(Wed), 02/05/2015(Thu), 02/10/2015(Tue), 02/13/2015(Fri), 02/17/2015(Tue), 02/19/2015(Thu)

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