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	03/03/2015 - 03/06/2015
	FEI NUMBER 3011014614

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Curtis M. Boxley, Pharm.D., Pharmacist In Charge

FIRM NAME	STREET ADDRESS
Ionia Pharmacy	15421 Red Hill Ave
CITY, STATE, ZIP CODE, COUNTRY Tustin, CA 92780-7309	TYPE ESTABLISHMENT INSPECTED Producer of Sterile and Non-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,

A. SOP No. 2004 effective 11.10.14 titled "Environmental Testing for Laminar Flow Hood—EnviroTest is deficient in that

a. There is no requirement to conduct personnel fingertip monitoring including forehead, mask, or chest on a daily basis when products are made. In actual practice, fingertip testing is done [redacted (b) (4)]. On 11/21/14, fingertip test of the sterile room technician [redacted (b) (6)] was found with a count of one (1) colony. The firm did not identify the type of colony found. Per SOP # 2182 effective date 10/16/14 titled "Environmental Monitoring of the buffer or clean area and anteroom area" section F states [redacted (b) (4)]

b. Surface monitoring of ISO 5 and ISO 7 areas are performed on a [redacted (b) (4)] basis for viable count instead of a daily basis when products are made. Per the PIC, the firm recently conducts non-viable monitoring but do not maintain any records. Non-viable monitoring is performed [redacted (b) (4)] on a [redacted (b) (4)] per SOP 2182 section C which states "...viable and nonviable air sampling performed at least [redacted (b) (4)]..." The last ISO 5 hood, ISO 7 room, and ISO 8 room certifications were performed on 12/05/14.

c. There is no requirement to use disinfectant neutralizers before taking the environmental monitoring samples in the ISO 5, ISO7 and ISO 8 zones. Per the PIC, the firm cleans these areas [redacted (b) (4)].

B. The ISO 5 hood is deficient in that

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a. The dynamic smoke studies conducted on 12/05/14 and 06/24/14 by a third party vendor were done with the plastic protector down. We also observed that the third party vendor employee did wear sterile gloves with arm skin still exposed during smoke study testing using [redacted] (b) (4). The Pharmacist In Charge (PIC) stated that he does not have record of the hood being cleaned [redacted] (b) (4). According to the technician, the ISO 5 vertical laminar flow hood which has a plastic protector is always in the up position when drug products are made creating a hood opening up to the head of the technician (or about 3/4 of the hood would be open to ISO 7 environment) when he sits down on the stool to work. If the plastic protector is placed down, the opening would open down to about chest level or below (or about 1/3 of the hood would be open to ISO 7 environment) when the technician sits down. On both 03/03/15 and 03/04/15, we observed that the technician was making products with the plastic protector up.

   i. Testosterone Cypionate 200mg/Progesterone 2.5mg per ml lot # 030315F BUD 06/01/15 produced on 03/03/15.

   ii. Papaverine/Phentolamine/Alprostadil 22.5/0.83/8.33 mg lot # 030315CU BUD 08/30/15 produced on 03/04/15.

b. There is no pressure differential monitoring between ISO 5 hood and ISO 7 room to determine whether vertical air flow from the ISO 5 hood (with or without plastic protector down) is greater than ISO 7 room.

OBSERVATION 2

Equipment and utensils are not cleaned at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

Specifically,

A. The firm has not performed cleaning validation or studies to show that their cleaning reagents are effective against bacteria, fungus, yeast, mold, and spores. SOP No. 2034, effective 11/17/14 titled "General Aseptic Procedures Used at a Laminar Airflow Workbench" mentions the use [redacted] (b) (4) for [redacted] (b) (4) cleaning and [redacted] (b) (4) [redacted] (b) (4) was verified as a steril cleaning reagent. None of the cleaning reagents used is sporicidal. This SOP also mentions the use of non-shedding wipes for cleaning. The wipes we observed during the inspection are [redacted] (b) (4) non-sterile wipes). The firm could not verify that the [redacted] (b) (4) located in the ISO 5 hood are sanitized before used for production. There is no sanitization record for the [redacted] (b) (4).

B. On 03/03/15, we observed one [redacted] (b) (4) package containing vials to make Testosterone Cypionate 200mg/Progesterone 2.5mg per ml lot # 030315F BUD 06/01/15 product brought from ISO 7 room into the ISO 5 hood. We observed that the [redacted] (b) (4) package was not cleaned with an appropriate disinfectant prior to being

brought into the ISO 5 hood or was not transferred from ISO 7 area into the ISO 5 hood using aseptic technique transfer or mechanism.

C. The firm's SOP No. 3026 effective 09/03/12 titled "[redacted] (b) (4) – Use, Calibration, Cleaning, and Maintenance" is deficient in that it does not address how the (b) (4) is cleaned. In actual practice, the firm cleans the (b) (4) with [redacted] (b) (4)

OBSERVATION 3

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 for sterile products produced from non-sterile components using [redacted] (b) (4) The (b) (4) has [redacted] (b) (4) . The vials are then incubated at [redacted] (b) (4). The incubator [redacted] (b) (4) the firm uses is not temperature monitored during [redacted] (b) (4) and is only recorded during [redacted] (b) (4) On 03/05/15, we observed that the incubator was reading at 32°C on the digital reading. There is no calibrated thermometer inside the incubator to verify the reading.

This media fill process does not simulate the actual production process with respect to container closure size (actual product sizes are 5ml, 10 mL, and 30 mL) and processing duration. According to the PIC, the media fill process takes about [redacted] (b) (4) to complete, however, the actual production may take up from an [redacted] (b) (4), No challenges or interventions are introduced during the media fill operations. For example,

a. Testosterone Cypionate 200mg/Progesterone 2.5mg per ml, 10 ml vial lot # 030315F takes about [redacted] (b) (4) to produce
b. Testosterone Enanthate 250mg/ml MDV 10ml vial lot # 021215XAA takes about [redacted] (b) (4) to produce
c. Alprostadil 20mcg/ml Bupivacaine 0.5% injection solution, 5 ml vial lot # 030215CY takes about [redacted] (b) (4) to produce
d. Alpha Lipoic Acid 25mg/ml, 30ml vial lot # 012315NAN takes about [redacted] (b) (4) to produce

B. Per the firm's SOP No. 3021 effective 09/03/12 titled [redacted] (b) (4) – Use and Maintenance" page 6 of 6 states that [redacted] (b) (4) "Frequency as Determined by PIC" rather than a specific

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frequency. In actual practice, [redacted] (b) (4) tests were performed by a contract lab on the following days: [redacted] (b) (4) [redacted]. The [redacted] (b) (4) is used to [redacted] (b) (4) stoppers and oil based products such as:

a. Testosterone Cyp 150/Nandrolone 150mg/ml *Sesame Oil* 10 ml, lot 021115XAH, BUD 05/12/15
b. Testosterone Cyp 200/Progesterone 2.5mg/ml *Sesame Oil*, lot 030315F, BUD 06/01/15

OBSERVATION 4

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

Specifically, S.O.P. 2175 Revision 5 titled "Sterile Gowning Procedure" is deficient in that

A. Non-sterile gowns, facemasks, and booties are allowed to be worn in the ISO 7 and ISO 8 zones. In actual practice, these non-sterile items and sterile gloves are also worn while working in the ISO 5 and ISO 7 environment. On 03/03/2015 we observed a pharmacy technician walking between the ISO 7 and ISO 8 zone of the pharmacy with non-sterile gowning. We observed exposed facial skin during product manipulation (Testosterone Cypionate 200mg/Progesterone 2.5mg per ml lot # 030315F with BUD 06/01/15) in the ISO 5 zone. The ISO 5 hood is located in the ISO 7 area. We also noticed that the technician did not change the sterile gloves when he walked out of the ISO 7 area into ISO 8 and back into ISO 7 to work on production in ISO 5 hood.

B. Employees working in the sterile area is not required to wear sterile goggles.

OBSERVATION 5

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 a [redacted] (b) (4) to crimp the caps after placing the rubber stoppers onto the product vials. The firm does not perform any leak test on the vials containing the product. All products produced go through the [redacted] (b) (4) crimping process.

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OBSERVATION 6

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

Specifically, according to the PIC the firm performs sterility and endotoxin testing on finished sterile drug products filled from [redacted] (b) (4). The firm does not conduct any endotoxin testing for products made under individual "patient-specific" prescriptions. For example,

A. Alpha Lipoic Acid 25mg/ml 30ml lot # 0122915NAJ, BUD 03/15/15
B. Testosterone Cypionate 200mg/Progesterone 2.5mg per ml lot # 030315F BUD 06/01/15 produced on 03/03/15.
C. Papaverine/Phentolamine/Alprostadil 22.5/0.83/8.33 mg lot # 030315CU BUD 08/30/15 produced on 03/04/15.

OBSERVATION 7

Each lot of a component that is liable to microbiological contamination that is objectionable in view of its intended use is not subjected to microbiological tests before use.

Specifically, the firm uses [redacted] (b) (4) (per the PIC) to [redacted] (b) (4) [redacted] (b) (4) process. The PIC could not confirm if the [redacted] (b) (4) used for [redacted] (b) (4) is sterile or not. The [redacted] (b) (4) Certificate of Conformance does not state that [redacted] (b) (4) is sterile. Per the PIC, the firm does not use sterilizing [redacted] (b) (4). Examples of [redacted] (b) (4) products using [redacted] (b) (4) include:

A. Human Chorionic Gonadotropin 12,000 Units [redacted] (b) (4) Multi-Dose Vial Injection Solution 10mL, lot # AL-112114NAZ, BUD 05/23/15, date made 11/24/14, quantity made [redacted] (b) (4)

B. Human Chorionic Gonadotropin 5,000 Units/Cyanocobalamine 5,000 mcg [redacted] (b) (4) Multi-Dose Vial Injection Solution Units per vial, lot # AL-022015XC, BUD 08/19/15, date made 02/20/15, quantity made [redacted] (b) (4)

C. Papaverine 30mg/Phentolamine 1mg/Alprostadil 10mcg [redacted] (b) (4) Injection 5ml, lot # AL-121214NAZ, BUD 06/10/14, date made 12/12/14, quantity made [redacted] (b) (4)

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OBSERVATION 8

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

Specifically, the firm has not performed any reconstitution studies on any of the (b) (4) products it produces such as Papaverine/Phentolamine/Alprostadil 22.5-0.83-8.33 MDV 5ml, lot 030315CU, BUD 08/30/15, date made 03/04/15.

OBSERVATION 9

Results of stability testing are not used in determining appropriate storage conditions.

Specifically,

A. The firm does not have stability procedure and does not conduct stability studies to support the BUD's assigned on sterile drug products. Per the PIC, they rely on literature such as (b) (4) to assign product BUD's. For example, the following products were assigned with BUD's without any supportive stability studies:

   a. Alpha Lipoic Acid 200mg/ml MDV 30ml, lot 060414AAK, BUD 09/02/14, date made 06/04/14. Per the PIC, the firm assigned a 90 day BUD based on (b) (4) literature which states "Beyond Use Date after compounding is estimated to be 90 days." The following information was also noted in this (b) (4) literature which the firm did not adhere to

      i. "The Beyond Use Date assigned to this formulation is valid only if (b) (4) Chemicals/Bases, Equipment and Closure System specified in procedure are utilized." Closure System describes "20 mm Sterile Amber Glass Serum Bottle ((b) (4) ' – the formula worksheet had no reference to which container and closure were used.

      ii. "According to USP guidelines, in the absence of passing a sterility test the storage periods for compounded sterile preparations (high risk) cannot exceed...cold temperature...not for more than 3 days" – this product was labed as "Store in refrigerator-Protect From Light"

   b. Testosterone Cypionate 150mg/Nandrolone 150mg per ml, 10 ml, lot 021115XAH, BUD 05/12/15, date made 02/12/15. Per the PIC, the firm assigned a 90 day BUD based on (b) (4) literature which states "Beyond Use Date after compounding is estimated to be 90 days." The following information was also noted in this (b) (4) literature which the firm did not adhere to

      i. "According to USP guidelines, in the absence of passing a sterility test the storage periods for

compounded sterile preparations (high risk) cannot exceed...controlled room temperature...not more than 24 hours" – this product was labeled as "Store at Room Temperature Protect From Light"

c. Papaverine/Phentolamine/Alprostadil 22.5-0.83-8.33 MDV 5ml, lot 030315CU, BUD 08/30/15, date made 03/04/15. Per the PIC, the firm assigned a 180 day BUD based on (b) (4) literature which states "Frozen at – 23°C, Beyond Use Date is 180 days." The following information was also noted in this (b) (4) literature which the firm did not adhere to

   i. "According to USP guidelines, in the absence of passing a sterility test the storage periods for compounded sterile preparations (high risk) cannot exceed...cold temperature...not more than 3 days" "Refrigerate at 4°C, Beyond Use Date is 30 days" – this product did not have a label associated with the formula worksheet and per the PIC is supposed to be stored frozen.

B. The firm does not have temperature study or procedure on how refrigerated or frozen drug products are shipped. The firm does not have product stability data to determine acceptable storage temperatures and shelf life of products for the temperature ranges. The firm does not have shipping validations studies to show that the ice pack is sufficient to keep products within an acceptable temperature range and there is no verification from customers to report if the products received were out of the acceptable temperature conditions. Finished products are packaged with an ice pack for pickup and delivery by common carriers. On 03/03/15, we observed the following products were being shipped to various locations:

a. Sermorelin 9mg/GHRP2(5.4mg)/GHRP6(5.4mg) Multi-Dose Vial (b) (4) Injection 9ml, lot AL-110714B, BUD 05/06/15, quantity made (b) Keep Refrigerated → (x 9ml vials were shipped to (b) (4) under Rx # (b) (4) on 03/03/15 and (x 9ml vials were shipped to (b) (4) under Rx # (b) (4) on 03/03/15.

b. Trimix Papaverine/Phentolamine/Alprostadil 30-1-1 MDV 5ml, lot AL-011915XA, BUD 07/18/15, quantity made (b) Frozen → (x 5ml vials were shipped to (b) under Rx # (b) (4) on 03/03/15.

OBSERVATION 10

Batch production and control records do not include complete information relating to the production and control of each batch.

Specifically, the firm does not always have complete information on formula worksheets. For example,

A. Alpha Lipoic Acid 25mg/ml, lot 012315NAN, Rx # (b) (4) BUD 03/09/15, date made 01/26/15

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a. Product label is missing
b. Individual ingredient manufacturer, lot #, and expiration dates are missing
c. (b) (4) Used Mfr, lot, and Exp are missing
d. Visual inspection, (b) (4), and vials found with particulates/impurities do not have initials

B. Alpha Lipoic Acid 25mg/ml, lot 012915NAJ, Rx # (b) (4) BUD 03/15/15, date made 01/29/15

a. Product label is missing
b. (b) (4) is stated to be (b) (4) with (b) (4) but (b) (4) lot # and expiration date is missing
c. (b) (4) used did not have lot # and expiration date listed

C. Papaverine/Phentolamine/Alprostadil 22.5-0.83-8.33 MDV, lot 030315CU, Rx # (b) (4) BUD 08/30/15, date made 03/04/15

a. Product label is missing
b. (b) (4) result was not circled as pass/fail/NA
c. pH information is not filled in

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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."