DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
550 W. Jackson Blvd., Suite 1500 Chicago, IL 60661-4716 (312) 353-5863 Fax:(312) 596-4187 Industry Information: www.fda.gov/oc/industry	06/30/2014 - 07/21/2014* FEI NUMBER 3003381432

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Matthew G. Marks, Director of Operations

FIRM NAME	STREET ADDRESS
Martin Avenue Pharmacy, Inc.	1247 Rickert Dr
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Naperville, IL 60540-1008	Producer of sterile drugs

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

During a field examination of drug products at your facility the following was observed:

Specifically,

On 6/30/2014 I observed a vial of sterile injectable human drug product Bi-Mix (30mg Papaverine/1 mg Phentolamine/1 ml) (b) (6) with a black particle in it.

PRODUCTION SYSTEM

OBSERVATION 2

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

Specifically,

(a) During the production of the sterile human drug product Acetylcysteine (Preservative Free) 20% Inhalation Solution lot 07022014@43 on 7/2/2014, I observed the Pharmacist In Charge produce the lot with the following deficient aseptic practices:

- He used non-sterile (b) (4) in ways that could contaminate the lot.
  - When he sprayed the main compartment of the ISO 5 (b) (4) with (b) (4) the open beaker of bulk product solution in the (b) (4) was close to underneath the slight overhang in the clear plastic separating the (b) (4) with the potential for (b) (4) to drip into the open beaker of product solution.
  - He sprayed his gloves and immediately brought the open beaker of bulk product solution into the main part

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of the [redacted] - with his wet gloves right above the open beaker.
  - One of the times he sprayed the [redacted] with [redacted] he did so above and approximately three to six inches in front of the open vials of product.
- To retrieve open inhalation vials, he reached into the bag, brought each open vial out separately and put it into the foam vial holder. In doing so he repeatedly touched the open ends of the vials and put his gloves over the open vials as he placed [redacted] vials into the foam vial tray.
- He filled the open vials with his gloves directly over the syringes (with [redacted] attached) he used for filling and the open vials. He did this until all [redacted] vials in the tray were filled. His gloves were over the open product vials the entire time, and sometimes his arms were over them as well.
- He opened one of the [redacted] that he used for filling by [redacted] packaging directly over the open product vials.
- To retrieve the vial caps, he reached into the bag then brought each cap out and screwed it onto each vial separately. During this process I saw his gloves touch nearby open vials, and twice I saw his gloves touch the interior (product side) of a cap. The capping occurred above the open product vials roughly half of the time.
- He repeated the above process on [redacted] more vials, during which I saw him open a syringe package and a [redacted] package over open, empty vials.
- During filling he used sterile syringes that were not labeled as non-pyrogenic.

(b) The [redacted] used to sterilize most sterile human and animal drug products are not [redacted] tested after use.

(c) The firm does not conduct media fills.

(d) The firm has no evidence that the [redacted] and [redacted] used to sterilize containers, closures, and human drug products are effective or validated.

OBSERVATION 3

Time limits are not established when appropriate for the completion of each production phase to assure the quality of the drug product.

Specifically,

(a) On 7/2/2014, while observing the production of the sterile human drug product Acetylcysteine (Preservative Free) 20% Inhalation Solution lot 07022014@43, I observed the use of [redacted] from a [redacted] bag that had been left open in the horizontal flow ISO 5 hood since 7/1/2014.

~~(b) The firm has no evidence to support the hold times for stock solutions which have not been sterilized but are used in the production of sterile human drug products. For example, [redacted] lot 05282014@16 was produced on 5/28/2014 and has a Beyond Use Date (BUD) of 11/24/2014. [redacted] is not sterilized after it is produced~~

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~~but it is used to produce sterile drugs, such as Cyanocobalamin 1000mcg/ml Injectable Solution.~~

~~(c)~~ (b) The firm has no established time limits for the exposure of the sterile human drug product Acetylcysteine (Preservative Free) 20% Inhalation Solution to air and light, even though the Formula Worksheet for the product states that "Acetylcysteine is not compatible with oxygen" and to "Protect from light." When I observed lot 07022014@43 of this product produced on 7/2/2014 it was exposed to air and light for approximately two to three hours.

OBSERVATION 4

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

Specifically,

No record is made when visual inspections of sterile human and animal drug products are conducted. Furthermore, Formula Worksheets for such products do not include conducting visual inspections as production steps.

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 5

The control systems necessary to prevent contamination or mix-ups are deficient.

Specifically,

The control systems necessary to prevent contamination during aseptic processing are deficient as follows:

(a) During the production of the sterile human drug product Acetylcysteine (Preservative Free) 20% Inhalation Solution lot 07022014@43 on 7/2/2014, I observed the Pharmacist In Charge produce the lot with the following deficient sanitization practices:

- He used [redacted] (b) (4), both as a spray and soaked low-lint non-sterile "shop towels", to sanitize the horizontal flow ISO 5 hood in which bulk formulation (prior to [redacted] (b) (4) and filling) occurred. He did not sanitize the HEPA filter guards.
- When sanitizing the [redacted] (b) (4) of the vertical flow ISO 5 [redacted] (b) (4) into which materials used in sterile filtration and filling are introduced into the [redacted] (b) (4) he used [redacted] (b) (4) spray and dried with low-lint non-

sterile shop towels with no pause to allow for contact time. He did not sanitize the HEPA filter guards.

- He insufficiently sanitized some of the equipment that he introduced into the left side of the vertical flow ISO 5 (b) (4) with a (b) (4) spray:
  - He did not sanitize a foam vial tray and a dry, low-lint, non-sterile shop towel.
  - He sprayed packaged sterile (b) (4) only on the plastic side, not the paper backing that is peeled off to open the package.
  - He sprayed a bottle of (b) (4) then wiped it with a dry, low-lint, non-sterile shop towel.
  - He did not completely spray a bag of sterilized empty inhalation vials.
- He used (b) (4) both as a spray and soaked low-lint non-sterile shop towels, to sanitize the main compartment of the vertical flow ISO 5 (b) (4) in which (b) (4) and filling occurred. The (b) (4) (b) (4) were sprayed but not the arms. He did not sanitize the HEPA filter guards.
- After filling and capping was complete he sprayed the bottom of the ISO 5 (b) (4) and the (b) (4) with non-sterile (b) (4) then dried them with a dry, low-lint, non-sterile shop towel without allowing significant contact time.

(b) The only other sanitization that the ISO 5 (b) (4) undergoes is the (b) (4) use of (b) (4) which are not labeled as sporicidal or sterile.

(c) The ISO 5 hoods, ISO 5 (b) (4), and Class 10,000 clean room the firm uses to produce sterile human and animal drug products are not environmentally monitored for microbial contamination or particles during production. Environmental monitoring of these areas occur approximately once ever (b) (4) and only when the areas are not in use. The most recent environmental monitoring of these areas occurred 4/24/2014, although they were used to produce sterile drug products as recently as 7/2/2014.

(d) Personnel who produce sterile human and animal drug products are not monitored for microbial contamination.

(e) Although the contractor that the firm has hired to evaluate its ISO 5 hoods and Class 10,000 clean room has conducted static smoke pattern testing, no dynamic smoke pattern testing has been conducted.

(f) The firm's Class 10,000 clean room has a sink with faucets for municipal tap water and "purified" water and a drain open to the environment approximately three feet to the side of the ISO 5 vertical flow biosafety hood that it sometimes uses to process sterile human and animal drug products prior to sterilization.

(g) Records are not kept for the cleaning, sanitizing, and inspection of the facilities used in the production of sterile human and animal drugs.

- No record is made of the use of (b) (4) once per (b) (4) to clean and sanitize inside the ISO 5 (b) (4) that the firm uses to fill sterile human and animal drugs.
- No record is made of the periodic inspection of the (b) (4) inside the ISO 5 (b) (4) that the firm uses to fill sterile human and animal drugs.
- No record is made of the cleaning of the Class 10,000 clean room, which the firm uses to produce sterile human and

animal drugs, by the firm's contract cleaning crew (b) time per week.
- No record is made of the sanitizing that the firm conducts in its (b) (4) ISO 5 hoods before and after they are used to produce sterile human and animal drugs.

OBSERVATION 6

Equipment for adequate control over micro-organisms is not provided when appropriate for the manufacture, processing, packing or holding of a drug product.

Specifically,

The firm's Class 10,000 clean room, in which it produces sterile human and animal drugs, is not designed to adequately protect the ISO 5 areas from turbulent air flow as both return vents are located on the ceiling of the room.

OBSERVATION 7

Equipment surfaces that contact components and in-process materials are reactive, additive or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

Specifically,

On 7/2/2014 I observed the use of a metal spatula to weigh (b) (4) USP for use in the sterile human drug product Acetylcysteine (Preservative Free) 20% Inhalation Solution lot 07022014@43, even though the Formula Worksheet for the product states that (b) (4) is not compatible with***metals".

OBSERVATION 8

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

Specifically,

(a) The firm rinses sterilized glass beakers and stir bars used to produce bulk product solutions with "purified water". This water is produced at room temperature from municipal tap water in a stagnant system consisting of a (b) (4) (b) (4) The firm has not tested the water to determine its purity, bioburden, or pyrogen levels.

(b) After this rinse the beakers are dried with low-lint, non-sterile "shop towels". The firm has not tested the towels to

determine their bioburden or pyrogen levels.

(c) On 6/30/2014 I observed white residues on the HEPA filter guards on the ISO 5 vertical laminar flow biosafety cabinet and the ISO 5 horizontal laminar flow hood. Both are used in the production of sterile human and animal drugs.

(d) On 6/30/2014 I observed cracking on the clear plastic sides and top of the ISO 5 horizontal laminar flow hood, which is used in the production of sterile human and animal drugs.

MATERIALS SYSTEM

OBSERVATION 9

There was a failure to handle and store drug product containers at all times in a manner to prevent contamination.

Specifically,

After treating plastic inhalation vials and eye dropper bottles with [redacted] (b) (4) to sterilize them the firm places them into non-sterile plastic bags for storage until they are filled with sterile human drug product.

OBSERVATION 10

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,

The firm has no evidence that its procedures sterilize and remove pyrogens from the containers and closures into which it fills sterile human and animal drug products. The firm's (b) sterilization procedures are (b) (4) [redacted] (b) (4) [redacted]

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OBSERVATION 11

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,

On 7/2/2014 I observed the sterile human drug product Acetylcysteine (Preservative Free) 20% Inhalation Solution lot 07022014@43 filled at 3ml into a 7 ml vial with air in the headspace even though the Formula Worksheet for the product states that "Acetylcysteine is not compatible with oxygen".

OBSERVATION 12

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,

The firm does not test any of the non-sterile components it uses to produce sterile human and animal drug products. Instead it relies on the Certificates of Analysis sent with these components, but it has not taken steps to establish the reliability of these Certificates of Analysis. In addition, no record is made when each Certificate of Analysis is reviewed.

LABORATORY CONTROL SYSTEM

OBSERVATION 13

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

Specifically,

None of the firm's sterile human and animal drug products has been tested for pyrogens or sterility in the three months prior to the start of this inspection, during which over (b) lots of human and animal sterile drug products were produced. In the

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twelve months prior to the start of this inspection five lots of sterile human drug products were tested for sterility and none for pyrogens.

OBSERVATION 14

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,

None of the firm's sterile human and animal drug products has been tested for potency in the three months prior to the start of this inspection, during which over (b) lots of sterile human and animal drug products were produced. In the twelve months prior to the start of this inspection five lots of sterile human drug products were tested for potency.

OBSERVATION 15

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

Specifically,

The firm has conducted no stability testing to support the Beyond Use Dates (BUD) assigned to its sterile human and animal drug products. For example:

- The human drug product Hyaluronidase Injectable Solution (Preservative Free) 150 U/ml lot 05232014@32 was produced 5/23/2014 and has a BUD of 11/19/2014.
- The human drug product Methylcobalamin (Preservative Free) 25mg/ml Injectable lot 04092014@14 was produced 4/9/2014 and has a BUD of 10/6/2014.
- The animal drug product Prednisolone Acetate 50mg/ml Injectable lot 05082014@23 was produced 5/8/2014 and has a BUD of 11/4/2014.
- The animal drug product Penicillin G/Procaine/Streptomycin/Chlorpheniramine/Hyoscyamine Injectable Suspension lot 06262014@20 was produced 6/26/2014 and has a BUD of 12/23/2014.

*** DATES OF INSPECTION:**
06/30/2014(Mon), 07/01/2014(Tue), 07/02/2014(Wed), 07/03/2014(Thu), 07/04/2014(Fri), 07/07/2014(Mon), 07/08/2014(Tue), 07/11/2014(Fri), 07/14/2014(Mon), 07/21/2014(Mon)

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