DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
60 Eighth Street NE Atlanta, GA 30309 (404) 253-1161 Fax:(404) 253-1202 Industry Information: www.fda.gov/oc/industry	03/18/2013 - 03/25/2013
	FEI NUMBER 3010078549

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Chalmas Craig Stewart, Pharmacist and Owner

FIRM NAME	STREET ADDRESS
Stewart Compounding Pharmacy	101 Broadfoot Avenue
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Fayetteville, NC 28305	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

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

Specifically,

A. The firm has not performed any sterility or endotoxin testing on the Human Chorionic Gonadotropin/Vitamin B12 Injection products (pre-filled syringes or vials) produced from November 2012 to present.

B. The firm has not conducted any sterility testing for Cyanocobalamin (Vitamin B12) Injection produced in 2012 to present and only one of the lots have been tested for endotoxins.

C. The firm does not routinely perform sterility or endotoxin testing on their sterile injectable products even though expiration dates for these products range from 7 to 180 days.

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. There is no assurance that the Human Chorionic Gonadotropin (HCG)/Vitamin B12 injectable product is sterile and pyrogen free when dispensed and throughout the assigned expiration date of 90 days as evidenced by the following:

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EMPLOYEE(S) SIGNATURE

Penny H. McCarver, Investigator
Viviana Matta, Investigator

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1. The sterilization process([redacted]) for the Mannitol Powder, USP (non-sterile) used in the formulation of the HCG/Mannitol bulk powder mixture has not been validated and the firm has no scientific justification to support that this process will sterilize the Mannitol .

2. Aseptic filling processes for this product including the dilution of the HCG/Mannitol (bulk powder mixture) with Vitamin B12 (multi-use vials) and the preparation of the pre-filled syringes are both conducted outside the clean room in an unclassified area of the general pharmacy as reported to us by the pharmacist. The HCG/Vitamin B12 (Cyanocobalamin) injectable finished product is not sterile filtered or terminally sterilized using an autoclave.

4. The finished products (vials or pre-filled syringes) have never been tested for sterility or endotoxins.

5. There are no formulation worksheets for the transfer of the HCG/Mannitol (bulk powder mixture) to smaller vials, the dilution of the vials with Vitamin B12, or the preparation of the pre-filled syringes.

B. Sterilization cycles executed utilizing the (b) (4) [redacted] for sterile ophthalmic products and instruments used during aseptic processing have not been validated to assure that the cycles are capable of producing sterile products/instruments. For example, Medroxyprogesterone Acetate 1% Ophthalmic Suspension and Cyclosporin 0.05% Suspension products are sterilized utilizing this (b) sterilizer [redacted] (b) [redacted]). Instruments sterilized include small items used during aseptic processing such as spatulas. The sterilization cycle for the instruments is (b) (4) [redacted] as specified in SOP 8.010, "Sterilization and Depyrogenation". The firm has no documentation that the instruments have been sterilized under these conditions.

OBSERVATION 3

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

Specifically,

There is little assurance that the Human Chorionic Gonadotropin with Vitamin B12 injectable process produces a homogeneous mixture of the HCG/Mannitol and has consistent potency throughout the lot. For example:

The HCG/Mannitol bulk powder mixture, Lot 191275741, failed potency with a result of 229% (Specification: (b) (4) [redacted]) on 1/18/13. The pharmacist stated that he adjusted the patient's dosage based on the potency to assure they received the same amount (125 units). When I reviewed prescriptions filled with this lot from 1/18/13-2/22/13 I noted that the usual dosage was listed (0.125 mL = 125 units) in some cases and others stated only inject one pre-filled syringe. The pharmacist recanted this statement the next day and stated that he actually diluted this lot with double the amount of Vitamin B12 for those

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prescriptions filled from 1/18/13-2/22/13 to assure the correct dosage was received.

This lot of the bulk powder mixture was tested again on 2/22/13 and failed potency with a result of 37.6% (Specification (b) (b)). The pharmacist said that he adjusted the patient's dosage based on the potency to assure they received the same amount (125 units) which I verified.

This HCG/Mannitol lot was later remixed with 200 mg Vitamin B12 (because it would impart color) in order to achieve better mixing of the HCG/Mannitol and dilute it to normal potency. However, the firm has no formula worksheet or other documentation showing this remixing occurred. This lot was then assigned the new lot number of HCG62012, the lot was retested, and potency results on 3/8/13 were found to be 92.8%.

OBSERVATION 4

The written stability testing program is not followed.

Specifically,

SOP 9.050, "Beyond-Use Dating (BUD) of Compounded Preparations" requires that expiration dates shall be assigned based on current drug stability information and sterility considerations. The procedure also requires that a reliable method for determining expiration dates shall be established, including laboratory testing of product stability, pyrogenicity, and chemical content when necessary. There is no stability data including sterility data to support the current expiration dates of up to 180 days assigned to sterile products filled on site for further use in solutions or sold as finished products.

OBSERVATION 5

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

Specifically,

A. The firm failed to (b) (4) the following products as required by the Formula Worksheets:

Cyanocobalamin Injection- Lot 02052013+8348@3, Lot 02282013+8961@5, and Lot 02282013+8957@3.

Hydroxyprogesterone Caproate Oil Injection Solution- Lot 02072013+8450@1, Lot 02282013+8965@7, and Lot 01152013+7778@5.

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Papaverine/Phentolamine/Prostadil Injection- Lot 02282013+8967@8

Vancomycin Opthalmic Solution- Lot 02272013+8927@6

Atropine Sulfate Solution- Lot 02272013+8931@8

Heparin/Lidocaine/Sodium Bicarbonate Injection- Lot 01252013+8055@4

B. The firm used expired (b) (4) for the following products:

Papaverine/Phentolamine Injection- Lot 02072013+8455@4 (produced 2/7/13; (b) (4) expired 1/12).

Heparin/Lidocaine/Sodium Bicarbonate Injection- Lot 02072013+8453@3 (produced 2/7/13; [redacted] expired 10/11).

C. Hydroxyprogesterone Caproate Oil Injection Solution, Lot 03072013+9187@2, was (b) (4) using an (b) (4) [redacted]; however, the firm's procedures state that this (b) should not be used with benzyl alcohol or benzyl benzoate which are both used in the formulation of this product.

D. There is no (b) (4) performed to assure the integrity of the (b) (4) as described in SOP 4.210, "Use and Maintenance of the (b) (4) [redacted]". The aseptic operator stated that he verifies the integrity of the (b) (4) [redacted]

E. The (b) (4) [redacted] used for the sterilization of sterile ophthalmic products and instruments used during aseptic processing has not been qualified to ensure adequate heat distribution and penetration.

F. The (b) (4) [redacted] used for the incubation of environmental monitoring samples and biological indicators (used to verify sterilization cycles in the (b) (4) [redacted]) has not been qualified. Additionally, the thermometer used in this incubator has not been calibrated to ensure its accuracy.

G. Biological indicators are not used to monitor sterilization processes in the [redacted] (b) [redacted] used for the sterilization of sterile ophthalmic products and instruments utilized during aseptic processing. The aseptic technician stated that he has only used the (b) chemical indicators to verify the sterilization cycles. Additionally, the formulation worksheets for Medroxyprogesterone Acetate 1% Ophthalmic Suspension (Lots 31412LAY1100, 91312LAYB, 61212LAY500, & 01282013+8116@19) and Cyclosporin 0.05% Suspension (Lot 04262012+1249@3) document that only

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(b) chemical indicators were used to verify the sterilization cycle.

H. There is no documentation that the sterile products have been 100% visually inspected for particulate matter, container/closure defects, etc. prior to distribution and there are no written procedures established describing the requirements or acceptance criteria for the visual inspection.

I. There is no antimicrobial effectiveness testing data for any of the firm's sterile drug products containing preservatives including Cyanocobalamin (Vitamin B12) 1000mcg/ml Injectable Solution, Hydroxyprogesterone Caproate 250mg/ml (Sesame Seed Oil) Injectable, Nalbuphine HCL 20mg/ml Injectable Solution, Cyanocobalamin 1000mcg/Pyridoxine 100mg/ml Injectable Solution, Medroxyprogesterone Acetate 1% Ophthalmic Solution, and Testosterone Cypionate 100mg/ml Injectable Suspension.

J. There are no written procedures describing the environmental monitoring program for the clean room area including the ISO 5 flow hood or personnel monitoring. The only documentation that any environmental monitoring/personnel monitoring has been conducted are handwritten logs(dated 2/28/11-2/5/13) with the test date, prepared by initials, media lot number, incubation temperature, colony forming units found, and a comment section (which states only fingertip, surface, hood surface, buffer room, or anteroom). Neither the pharmacist or the aseptic technician could describe the environmental monitoring program requirements, identify/locate the type of media that had been used for the previous sampling, identify/locate the media that is currently to be used, or tell me the length of time the samples were incubated. Additionally, there is no documentation of any environmental monitoring/personnel monitoring conducted after 2/5/13.

K. The unidirectional flow of air in the ISO 5 air flow hood has not been confirmed through visual mechanisms (such as smoke studies) under dynamic conditions to ensure adequacy for use

L. There was no sampling conducted of viable particles in the clean room including the ISO 5 air flow hood during the (b) (4) recertification of this area until January 2013. The recertification conducted in July 2012 did not include sampling/testing of viable particulates.

M. There is no sampling conducted for viable/non viable particulates during aseptic processing in the ISO 5 air flow hood.

N. The only documentation provided describing the firm's media fills was a formual worksheet entitled, "Media-Fill Test For High Risk CSP Solution", that describes the filling of sterile vials with a syringe for controls/samples. The worksheet also states that all vials should be incubated (b) (4) [redacted]. However, the media fill test result log (7/25/12-2/5/13) documents that the incubation temperature was 35°C. The media fills conducted to qualify compounding technicians and aseptic operations are also deficient in that they do not support routine processing operations or evaluate worst case activities that could provide a challenge to manual aseptic operations and present a risk to product

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sterility (i.e. interventions or representative container/closure systems used, etc.). This includes the most recent media fill for the current aseptic technician performed 2/5/13 (Lot 02052013+8348@3). Additionally, the formual worksheet states that if the samples exhibit microbial growth the test must be repeated until passed. There are no written procedures describing the requirements for media fills.

O. There is no formulation worksheet (i.e. instructions) for the repackaging of the Avastin Injectable product into 0.1 mL syringes.

OBSERVATION 6

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

Specifically,

A. Sterilization and depyrogenation cycles (b) (4) [redacted] executed in the (b) (4) [redacted] have not been validated to ensure cycles are capable of producing sterile/pyrogen-free vials, rubber stoppers, and glassware used in aseptic processing. The firm also has no data to support that the rubber stoppers remain integral after processing them in the (b) (4) [redacted] under the above listed conditions. The non-sterile vials and rubber stoppers used for the HCG/Vitamin B12 sterile injectable products and the Hydroxyprogesterone sterile injectable products utilize this sterilization/depyrogenation process. Additionally this process is used for all glassware including graduated cylinders, glass mortar/pestle, and beakers used during aseptic processing.

B. The (b) (4) [redacted] used to sterilize/depyrogenate glass vials and rubber stoppers has not been qualified to ensure adequate heat distribution and penetration. Additionally, the thermometer used with this (b) [redacted] has not been calibrated to ensure its accuracy.

C. The aseptic technician stated that he has used the (b) (4) [redacted] to sterilize/depyrogenate glass vials/rubber stoppers used in aseptic processing since 2/18/13 but this has not been documented.

D. The aseptic technician stated to me that since 2/18/13 he has been placing biological indicator strips in the (b) (4) [redacted] (b) (4) [redacted] to verify that the glass vials/rubber stoppers were depyrogenated. He stated that if the strip remained purple this indicated that the vials/stoppers were depyrogenated. However, the biological indicator strips that he showed me were labeled for use as a (b) [redacted] biological indicator (Geobacillus stearothermophilus) and had expired in November 2012.

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E. The rubber stoppers that have been sterilized/depyrogenated are stored in the Class 7 area of the clean room wrapped in foil for an undetermined amount of time before use in aseptic processes. Additionally, the glassware (beakers, graduated cylinders, etc.) used in aseptic processing that have been sterilzed/depyrogenated is stored wrapped in aluminum foil on a shelf in an unclassified area of the general pharmacy for an undetermined amount of time.

OBSERVATION 7

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

Specifically,

A. There are no cleaning/maintenance records documenting cleaning/sanitization performed in the clean room area since 2/18/13 as required by SOP 3.020, "Cleaning and Maintenance of the Clean Room Facility" . The aseptic technician and the pharmacist stated that aseptic processing was conducted in the clean room during this time period.

B. Cleaning/sanitization records for the clean room document that only (b) (4) and (b) (4) (b) (4) have been used since May 2012 for the daily and monthly cleaning. SOP 3.020, "Cleaning and Maintenance of the Clean Room Facility" requires the use of diluted (b) (4) for daily cleaning and (b) (4) for monthly cleaning but there are no contact times specified except when bleach is used. Additionally, the cleaning/sanitization records since May 2012 do not include any signatures or dates of the review of these records; the SOP states that the pharmacist in charge or supervisor shall supervise and document that all personnel responsible for cleaning and maintenance of the clean room facility shall comply with this procedure.

OBSERVATION 8

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

Specifically,

SOP 9.100, "Required Garb For Clean Room Facility Access", that describes the requirements for operators working in the ISO 7 and ISO 5 clean room areas includes a single pair of sterile gloves, a non-shedding disposable labcoat (non-sterile), a single pair of non-sterile shoe covers, a single hair net, and a single ear-loop face mask.

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OBSERVATION 9

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

Specifically,

The magnahelic gauges for the clean area read 0.02 inches of water for the differential pressure between the buffer area/anteroom and 0.005 inches of water between the anteroom/hallway (outside of the clean room area) on each day of the inspection. There are no procedures specifying the required temperature, humidity, or pressure in the clean room other than the monitoring records/logs. The monitoring records for April 2012-July 2012 show that only the buffer/anteroom pressure was documented and the requirement is listed as > 0.02 inches of water. The monitoring records for August 2012 show that the requirement for both areas is > 0.2 inches of water (documented readings for buffer/anteroom were 0.03 and readings for the anteroom/hallway were 0.01). The monitoring records for September 2012-November 2012 show that the requirement for both areas has been changed (handwritten on the form) to < 0.2 inches of water with actual readings of 0.03 for the buffer/anteroom and 0.01 for the anteroom/hallway. The monitoring records for December 2012-February 15, 2013 show the requirement for both areas is > 0.2 inches of water with actual readings of 0.020-.025 for the buffer/anteroom and 0.01 for the anteroom/hallway. There is no documentation of the clean room temperature or differential pressures since February 18, 2013.

OBSERVATION 10

Aseptic processing areas are deficient in that floors are not smooth and/or hard surfaces that are easily cleanable.

Specifically,

The floor in the clean room area (ISO Class 5 and 7) has grooves/pockets which would be difficult to adequately clean.