Inspections, Compliance, Enforcement, and Criminal Investigations

Infupharma, LLC 7/30/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Florida District
555 Winderley Place, Suite 200
Maitland, Florida 32751
Telephone: 407-475-4700
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VIA HAND-DELIVERY

WARNING LETTER

FLA-12-37

July 30, 2012

Dr. Michel Rizo
Owner and Director of Pharmacy
Infupharma, LLC
2013 Harding Street
Hollywood, FL 33020

Dear Dr. Rizo:

During our July 18 through September 27, 2011 inspection of your pharmaceutical manufacturing and compounding facility, located at 2013 Harding Street in Hollywood, Florida, investigator(s) from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your manufactured drug product(s) to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP. In addition, the inspection disclosed that manufactured drug products are also adulterated within the meaning of Section 501(a)(1) of the Act [21 U.SC. § 351(a)(1)] and that your compounded and manufactured sterile drug products are adulterated within the meaning of Section 501(a)(2)(A) of the Act [21 U.S.C. § 351(a)(2)(A)].

Our investigators found that your firm has a contract with another pharmacy to repack Avastin from sterile injectable single-use vials into sterile injectable 1 mL single-use syringes and to repack human chorionic gonadotropin (HCG) multi-use vials into single-use syringes for further distribution. FDA does not consider your practice of repackaging and distributing Avastin and HCG without prescriptions for resale to other entities to constitute the regular course of a pharmacy's business of dispensing and selling drugs at retail.

FDA regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labeling of the product and pursuant to valid prescriptions, to be within the practice of pharmacy. Processing and repacking (including repackaging) of approved drugs without valid prescriptions or for resale by other pharmacies or entities, however, exceed the traditional practice of pharmacy. Consequently, your firm is subject to the CGMP requirements for finished pharmaceuticals as described in Section 501(a)

(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)] and Title 21 Code of Federal Regulations Parts 210 and 211 (21 CFR 210 & 211).

In addition, your firm's repackaged Avastin syringes and repackaged HCG syringes for weight loss are unapproved new drugs marketed in the United States in violation of Section 505 of the Act [21 U.S.C. § 355]. The HCG products are also misbranded in violation of Section 502(a) of the Act [21 U.S.C. § 352(a)] in that their product brochures contain false and misleading claims.

We have reviewed your firm's response of October 10, 2011 and note that it lacks sufficient corrective actions.

ADULTERATION CHARGES

As you were made aware during the course of the inspection, FDA laboratory analysis confirmed the presence of Streptococcus mitis/oralis, as well as other microorganisms, in samples of Avastin collected during the outbreak investigation. These findings demonstrate that the affected lots of Avastin prefilled syringes are adulterated within the meaning of Section 501(a)(1) of the Act [21 U.S.C. § 351(a)(1)] in that the products consist in whole or in part of a filthy, putrid or decomposed substance.

Based on these findings and the findings from the inspection, your products are also adulterated within the meaning of Section 501(a)(2)(A) of the Act [21 U.S.C. § 351(a)(2)(A)] in that they were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health.

In addition, the inspection revealed numerous significant violations of the CGMP regulations for finished pharmaceuticals. These CGMP violations cause the sterile injectable drugs manufactured by your firm—specifically, Avastin and HCG—to be adulterated within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of the referenced drug products do not conform with the CGMP regulations.

CGMP violations

The specific CGMP violations observed during the inspection include, but are not limited to the following:

1. Your firm has not established appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113 (b)].

For example:

a) Between September 23, 2010, and July 11, 2011, you routinely used single-dose **(b)(4)**-mL or **(b)(4)**-mL vials of Avastin for intravenous infusion to manufacture multiple lots of **(b)(4)**-mL syringes of Avastin for intraocular injection. Some of these lots were found to be contaminated with *Streptococcus spp*. Some of the vials were used over a period of days or weeks following the initial puncture of the vials. However, the manufacturer's package insert for Avastin states: *"discard any unused portion left in a vial, as the product contains no preservatives."* There is no assurance of continued sterile integrity for extended periods in storage once the stopper has been breached and the drug product exposed to the outside environment.

b) You did not validate the aseptic repackaging processes for Avastin and HCG injectables through adequate periodic media fills performed by all manufacturing personnel in accordance with a written program. Your failure to have all personnel that process sterile drug products qualified by participation in a media fill could allow personnel with poor aseptic technique to potentially contaminate drug products.

We acknowledge your written response of October 10, 2011. However, this response is inadequate in that it does not address your firm's practice of repackaging the Avastin product from the same bulk vial for extended periods of time after the initial puncture.

We also acknowledge the commitment in your response to conduct media fills on a regular schedule. However, the schedule provided with the response indicates that your firm would not perform a new media fill to address this deviation for **(b)(4)**. This does not address the original violation. The effectiveness of your aseptic process and qualification of each of your employees should be demonstrated before any further production takes place.

2 Your firm has not established separate or defined areas or such other control systems as are necessary to prevent contamination or mix-ups during the course of your aseptic processing [21 C.F.R. § 211.42(c)(10)].

For example:

a) You did not perform environmental monitoring of your clean rooms and Class 5 Laminar Flow Workbenches (LAF) adequately and with the frequency stated in your written program. It is essential that control of environmental conditions be maintained through timely monitoring to provide assurance of aseptic conditions during your repacking operations.

b) On July 20, 2011, FDA investigators observed an excessive amount of supplies and components in cartons in the Class 7 buffer area where the Class 5 LAFs and Biological Safety Cabinet are located. On September 19, 2011, investigators observed several electrical cords and surge protectors on the floor underneath the Class 5 LAFs where they would impede proper cleaning and sanitization of the floors. Inadequate sanitization of the Class 7 buffer area and excessive materials can result in increased levels of microbial contamination in the room environment. In addition, personnel activities in the room could also allow for the transfer of the contaminants into the drug product.

We note your commitment, indicated in the October 10, 2011, response, to conduct environmental monitoring every **(b)(4)**. However your firm has not justified that this monitoring schedule will ensure that you are able to properly evaluate the environmental conditions in your facilities. The effectiveness of your environmental controls should be established before any further production of drug products takes place. In addition, your response does not address the issue of excessive stored materials in the class 7 buffer area.

3. You failed to ensure that each person engaged in the manufacture, processing, packing or holding of drug product has the education, training and experience, or any combination thereof, to enable that person to perform their assigned functions [21 C.F.R. § 211.25(a)].

For example:

a) Your firm did not conduct any gloved fingertip sampling of your firm's employees although your firm's SOP "Sterile Admixture Quality Control" required all processing personnel to complete and pass the test upon hire and then either **(b)(4)** or **(b)(4)** thereafter, depending on the sterile drug products being processed. Routine gloved fingertip sampling of personnel performing aseptic manipulations should be conducted to determine if the employees conducting these critical operations are maintaining their gloves in acceptable condition to protect the drug product from contamination.

b) On July 19, 2011, during a mock demonstration of the repackaging process of Avastin injectable in the Class 5 Biological Safety Cabinet, an FDA investigator observed an employee wearing non-sterile gloves when handling sterile supplies and products.

c) In preparation for and during your firm's demonstration of aseptic processes on September 19, 2011, FDA investigators observed you incorrectly don protective clothing, wear a gown which exposed approximately one inch of skin on the wrist area between your gloves and the gown sleeves, and frequently lean your head and torso inside the LAF which could cause your product to become contaminated.

The immediate corrective actions described in the response appear to be satisfactory. The implementation of these corrective actions will be verified during the next scheduled inspection.

We note the statement in your response that your firm had hired a Quality Assurance director who will "*be an integral part in implementatio*n *and continued compliance with the steps we are taking*." We expect that this person will play a role in assuring appropriate training for your firm's personnel and will be qualified to do so. However, you failed to provide us with any information regarding the individual's identity, qualifying education, and/or experience (i.e., curriculum vitae). Please include this information in your written response to the Warning Letter.

4. Your firm failed to conduct appropriate laboratory testing on each batch of drug product purporting to be sterile and/or pyrogen-free to determine conformance to such requirements [21 C.F.R. § 211.167(a)]. Your firm did not conduct any finished product testing, including conformity with microbiological specifications, prior to releasing syringes of Avastin sterile injectable products (SIPs) repacked for intraocular injection from single-use vials of Avastin for

infusion.

We note that your firm's revised procedures (SOPs 9.003 and 9.005), included with your response, are general in nature and do not address endotoxin testing or incubation times. Your finished sterile drug products must meet the requirements of current good manufacturing practices for finished pharmaceuticals. Please revise your procedures to ensure that endotoxin tests and incubation times for sterility tests are appropriate and meet the requirements for drug products. Furthermore, your firm's release procedures should be revised to ensure that endotoxin and sterility test results are reviewed before release and distribution of your sterile drug products.

5. Your firm did not perform routine calibration, maintenance, and checking of automatic, mechanical, and electronic equipment used in the manufacture, processing, packing or holding of a drug product according to a written program designed to assure proper performance [21 C.F.R. § 211.68(a)].

For example:

a) The incubator used for the incubation of media fills and environmental monitoring samples had not been qualified, maintained, or cleaned according to a written program.

b) All thermometers used in the refrigerator, incubator, autoclave, and manufacturing processes lacked calibrations against a **(b)(4)** thermometer. The temperatures of your refrigerator and freezer used to store components and finished drug products must be accurately controlled. Temperatures should be monitored daily.

c) The magnehelic gauges used to measure differential pressure between areas in the clean room lacked calibration records.
We acknowledge the corrective actions described in your response, including the purchase of a new incubator and recalibration of the magnehelic gauges. However your response did not include any documentation of the recalibration. Please provide documentation that all of your equipment has been appropriately calibrated and will be appropriately maintained in the future.

6. Your firm failed to follow procedures for handling of all written and oral complaints regarding drug products [21 C.F.R. § 211.198(a)].

For example, you stated that you received two (2) complaints from two (2) different sources regarding adverse events (i.e., eye infections) experienced by some patients that received Avastin intraocular injections repacked by your firm. However, as of September 21, 2011, the complaints were not logged and your firm did not have documentation for the complaint investigation as required by your SOPs.

Your response references a revised procedure for complaint handling but this procedure was not included with the response. Please provide an explanation of the measures your firm will take to ensure that your revised procedure will be followed.

7. Your firm does not have an adequate written testing program designed to assess the stability characteristics of drug products in order to determine appropriate storage conditions and expiration dates [21 C.F.R. § 211.166(a)]. For example, your firm lacked reliable stability data to support a beyond-use-date (BUD) of 30 days for Avastin SIPs.

We acknowledge the commitment made in your response to follow the recommendations in the USP for beyond-use dating. Please revise your procedures to ensure that your drug products have the appropriate storage conditions and expiration dates. The implementation of these corrective actions will be verified at the next scheduled inspection.

8. Your firm has failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product [21 C.F.R. § 211.188].

For example:

a) Your firm did not document the number of containers (i.e. syringes and vials) filled per batch on the repackaging records.

b) Batch records for the Avastin product do not accurately record the actual date of manufacture. One of your firm's employees stated to the FDA investigators that the "Date made" sub-heading on the Avastin Logged Formula Worksheets was in some cases representative of the date on which the record was printed and not the date on which the

Avastin was repacked. There were numerous instances where the actual date made was different than the date recorded on the batch record.

c) On July 9, 2011, during a mock demonstration of the repackaging process of Avastin injectable, FDA investigators observed the Pharmacy Technician use a Mini Transfer Device for aliquot purposes. The step involving the Mini Transfer Device was not included in the Avastin repackaging record.

Your firm's failure to provide complete information of the batch manufacturing process for each batch could allow your firm to distribute incorrectly manufactured drug products that pose a risk to patients.

We acknowledge the corrective actions described in your response, including the revisions to SOP 8.008 and retraining of personnel. However, this revised procedure does not address the specific deficiencies, such as requirements to document the actual dates of manufacture and quantities of product produced.

Adulterated Drugs-Product Contamination

FDA has determined that at least one lot of Avastin 2.mg/0.1ml pre-filled syringes (lot 7072011) manufactured at your facility in Hollywood, Florida is adulterated within the meaning of section 501(a)(1) of the Act (21 U.S.C. § 351(a)(1)) in that FDA determined several intact units of the referenced product were contaminated with viable microorganisms.

As stated above, FDA laboratory analysis confirmed the presence of several species of *Streptococcus*, including *Streptococcus Mitus* and *Streptococcus Oralis* in intact, unused, Avastin pre-filled syringes produced by your firm at the Hollywood, Florida facility. In addition, the CDC and Florida Department of Health have independently tested and confirmed that intact units of the Avastin prefilled syringes produced at your Hollywood, Florida facility were contaminated.

Adulterated Drugs-Insanitary Conditions

Your Avastin pre-filled syringes and other sterile drug products are adulterated within the meaning of section 501(a)(2)(A) of the Act (21 U.S.C. § 351(a)(2)(A)) in that they were prepared, packed or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health. The following observations are examples of insanitary conditions observed by FDA investigators during the inspection of your Hollywood, Florida facility.

1. In preparation for and during your firm's aseptic compounding process for Vancomycin on September 19, 2011, you were observed to incorrectly don shoe covers, improperly wash your hands and forearms and dry them with kitchen-grade paper towels, wear a gown which exposed approximately one inch of skin on the wrist area between your gloves and the gown sleeves, and frequently lean your head and torso inside the LAF and over the product.

2. On September 19, 2011, one of your employees was observed inside the clean room performing a demonstration of the bubble point test in the Class 5 LAF. The employee's hairnet was donned improperly, exposing approximately fifteen inches of the employee's hair to the environment throughout the entirety of the demonstration. The supervisor did not instruct the employee to correct the deficiency until the demonstration was completed, after FDA personnel brought it to his attention.

UNAPPROVED NEW DRUG AND MISBRANDING CHARGES

In addition, you manufacture and distribute unapproved new drugs in violation of the Act at your firm. Based on the information collected during the inspection, you manufacture the following drugs, including, but not limited to:

- Avastin (bevacizumab) 1 mL single-use syringes
- HCG (human chorionic gonadotropin) 125 IU injectable syringes

As labeled, the above products are drugs within the meaning of section 201(g)(1) of the Act [21 U.S.C. § 321(g)(1)] because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or because they are intended to affect the structure or function of the body. Further, these drug products, as marketed by your firm, are "new drugs" within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)] because they are not generally recognized as safe and effective for their labeled uses. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced into or

delivered for introduction into interstate commerce unless an application approved by FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the product. Based upon our information, there are no FDA-approved applications on file for the above products. The marketing of these products without an approved application constitutes a violation of these provisions of the Act. Therefore, you should discontinue manufacturing and distributing these unapproved new drugs at all facilities immediately.

In addition, your sterile injectable HCG products are misbranded within the meaning of Section 502(a) of the Act [21 U.S.C. § 352(a)] in that the statements that, with the use of these drug products, one can experience "*rapid weight loss averaging 1 to 3 pounds per day… [and] 20-30 pounds during a 40 day treatment*" as claimed in your product brochure "HCG Diet Patient Packet," are misleading and, in fact, contradict information for patients found in the labeling for approved HCG injection products, which states explicitly:

> "HCG HAS NOT BEEN DEMONSTRATED TO BE EFFECTIVE ADJUNCTIVE THERAPY IN THE TREATMENT OF OBESITY. THERE IS NO SUBSTANTIAL EVIDENCE THAT IT INCREASES WEIGHT LOSS BEYOND THAT RESULTING FROM CALORIC RESTRICTION, THAT IT CAUSES A MORE ATTRACTIVE OR 'NORMAL' DISTRIBUTION OF FAT, OR THAT IT DECREASES THE HUNGER AND DISCOMFORT ASSOCIATED WITH CALORIE RESTRICTED DIETS."

The introduction or delivery for introduction into interstate commerce of this misbranded product is a violation of Section 301(a) of the Act [21 U.S.C. § 331(a)].

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including seizure and/or injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. FDA may reinspect to verify that adequate corrective actions have been completed.

Through our investigators' communications with you and the Florida Department of Health (FDOH) during the course of the outbreak investigation, we understand and appreciate that the affected lots of contaminated Avastin products were voluntarily recalled. We also understand and appreciate that you voluntarily ceased your Avastin repackaging operations. However, you did not include any information regarding the Avastin recall nor the status of your firm's Avastin repackaging operations in your response to the FDA 483. Please include this information in your written response to this Warning Letter.

Your response references information concerning your firm's repackaging and compounding operations which have already been "submitted to State." We assume this information was included in your August 9, 2011, Corrective Action Plan (CAP) and August 15, 2011 Addendum which you submitted to FDOH and which we received via email from FDOH on August 26, 2011. However, since you did not include specific reference to and/or include copies of your CAP and Addendum for FDOH in your response to the FDA 483, we cannot be certain. Please clarify in your written response to this Warning Letter.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen (15) working days, state the reason for the delay and the time within which you will complete the correction. If you no longer manufacture or market any of your drug products, your response should so indicate, including the reasons and the date on which you ceased production.

Please send your response to the U.S. Food and Drug Administration, Attention: Andrea H. Norwood, Compliance Officer, 555 Winderley Place, Suite 200, Maitland, FL 32751. If you have questions regarding any issue in this letter, please contact Ms. Norwood at (407) 475-4724.

Sincerely,

/s/

Emma R. Singleton
Director, Florida District

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