U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Cephazone Pharma LLC 4/25/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
Pacific Region
19701 Fairchild
Irvine, CA 92612-2506
Telephone: 949-608-2900
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Warning Letter

WL: 34-11

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

April 25, 2011

Avinash G. Ghanekar
Director of Operations
Cephazone Pharma, LLC
250 E Bonita Avenue
Pomona, CA 91767-1924

Dear Mr. Ghanekar:

During our July 12, 2010 to August 26, 2010 inspection of your pharmaceutical manufacturing facility, Cephazone Pharma, LLC, located at 250 E Bonita Avenue, Pomona, CA, 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 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.

We have reviewed your firm's response of September 2, 2010, and note that it lacks sufficient corrective actions. In addition, we acknowledge your written responses dated September 23, 2010, October 11, 2010, October 28, 2010, and December 16, 2010, to the Form FDA 483. However, because these responses were received more than 15 business days after the Form FDA 483 was issued; these responses have not been considered. We plan to evaluate your additional responses to the Form FDA 483, along with any other written material provided, as a direct response to this Warning Letter.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm does not have appropriate laboratory testing to determine if each batch of drug products, purporting to be sterile, conform to such requirements [21 C.F.R. § 211.167(a)].

For example, your firm only uses **(b)(4)** IU of the required **(b)(4)** IU of beta-lactamase neutralizing agent (as per your validation studies) for the purpose of inhibiting the antimicrobial properties of Ceftriaxone during sterility testing. In addition, your firm does not include *Escherichia coli* as part of your test organisms despite your protocol, "Validation of Antibiotic Neutralizer Effectiveness," **(b)(4)**, stating that *Escherichia coli* is the most sensitive challenge organism for evaluating i the antibiotic was effectively neutralized.

In your response, your firm provided protocol **(b)(4)**, "Method Validation Protocol for Recovery studies from PVDF Filter Membrane of Steritest EZ Sterility Testing System Surfaces," that describes the amount of Ceftiofur Sodium recovered from the Steritest EZ Sterility Testing System and correlates it to the amount of neutralizer required by your original neutralizer effectiveness study. Your response, however, is inadequate because your firm has failed to provide any scientific data to justify the correlation between the use of **(b)(4)** IU of beta-lactamase to **(b)(4)** of Ceftiofur Sodium or the use of **(b)(4)** IU of beta-lactamase to **(b)(4)** of Ceftiofur Sodium.

Please provide scientific data to justify the correlation between the amount of beta-lactamase required to neutralize a specific amount of Ceftiofur drug product. Further, please provide information that demonstrates the beta-lactamase effectiveness at this concentration. Future validations should ensure that you include the rationale for your choice of cephalosporin(s) included in the validation. In addition, future validations should include those products that proved to be most difficult to neutralize in your original validation.

2. 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, your firm's written procedures for environmental monitoring, disinfection, and your process simulation media have not been validated. Specifically, your firm has not demonstrated the ability of reconstituted beta-lactamase at a concentration of **(b)(4)** IU (0.1ml/1L Sterile Water for Injection) to neutralize cephalosporins in the Tryptic Soy Broth (TSB) used in aseptic process simulation studies (i.e., media fills) or in your surface swab sampling solution. Furthermore, you have not demonstrated the ability of the neutralizing agents in the surface sampling plates purchased by your firm to neutralize the cephalosporin drug products manufactured at your firm.

In your response, you state that you will determine the residual amount of cephalosporin and then determine the amount of neutralizing agent required. Your respons is inadequate because you have not provided a scientific rationale that demonstrates a correlation between the residual cephalosporin recovered to the necessary amount of beta-lactamase.

In addition, your firm provided procedure **(b)(4)**, "Cephalosporin Residue Determination during Filling Process," to demonstrate the effectiveness of the amount of penase enzyme used to neutralize residual antibiotic during environmental surface sampling. We cannot determine the adequacy and/or effectiveness of your corrective action because you have not provided the data from this study.

3. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that dru products conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. § 211.160(b)].

For example, your firm stores the recovered microbial isolates so that the microbes can be identified at a future date. Your firm stores these isolates for up to three months without any data to demonstrate that the microbial isolates would remain viable during the entire storage period.

In your response, your firm states that you have revised your procedure **(b)(4)**, "Microorganism Identification and Related Tests," to reduce the storage period of the microbial isolates to **(b)(4)** days. Your response, however, does not provide your justification to demonstrate that the microbial isolates are viable at **(b)(4)** days.

4. Your firm has failed to exercise appropriate controls over computer or related systems to assure that changes in master production and control records, or other records, are instituted only by authorized personnel [21 C.F.R § 211.68(b)].

For example, your firm lacks control of the **(b)(4)** computer system which monitors equipment, room differential pressure, room humidity, and stability chambers. Although the system is password protected for temperature and humidity set points, all employees have access to the room where the **(b)(4)** computer system is located and the external hard drive is not password protected. During the inspection we observed that an employee was able to alter or delete data without a password and save the changed file.

In your response, your firm states that additional controls were implemented including validating the remote access to the **(b)(4)** computer, password protecting the room where the computer is stored, and limiting the **(b)(4)** control room to authorized personnel only. Although your corrective actions may adequately address the protection of the **(b)(4)** computer from non-traceable changes, your firm has not taken a global approach to this deficiency. It is our expectation that your other manufacturing and laboratory computerized systems will be reviewed to ensure similar deficiencies do not exist.

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 and the occurrence of other violations. It is your responsibility to assure compliance 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, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute any of the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address: Blake Bevill, Director, Compliance Branch, U.S. Food and Drug Administration, 19701 Fairchild, Irvine, CA 92612-2506.

If you have any questions regarding this letter, please contact Dr. Raymond W. Brullo, Compliance Officer, at (949) 608-2918.

Sincerely,

/s/

Alonza E. Cruse
District Director

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