Inspections, Compliance, Enforcement, and Criminal Investigations

Catalent Pharma Solutions 28-Mar-08

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville MD 20857

MAR 28 2008

WARNING LETTER

OEWL-08-01

EXPRESS MAIL

Mr. Kent Payne
Vice President and General Manager
Catalent Pharma Solutions
8900 Capital Boulevard
Raleigh, North Carolina 27616

Dear Mr. Payne:

The Food and Drug Administration (FDA) conducted an inspection of Catalent Pharma Solutions, 8900 Capital Boulevard, Raleigh, North Carolina, between November 6 and November 15, 2007. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP), including the applicable standards and requirements in Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21, Code of Federal Regulations (21 CFR) Parts 210 and 211, in the manufacture of [redacted].

At the close of the inspection, our investigators issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your facility's compliance with CGMP. Significant deviations observed during the inspection include, but are not limited to, the following:

1. Failure of your quality con trol unit to investigate thoroughly any unexplained discrepancy or the failure of a batch or any ofits components to meet any of its specifications, and failure to ensure that written records of investigations are madeand include conclusions and follow-up (21 CFR 211.192]. For example:

a) Your quality unit failed to adequately identify trends for numerous environmental excursions found between July 2007 and November 2007.

b) Regarding investigations initiated by your quality control unit:

i. Investigation Report PR108688 was initiated on April 13, 2007, for total aerobic count excursions in the purified water loop between February and March 2007. The report was closed on September

21,
2007, and identified the corrective action as the addition of a [redacted] to the purified water loop.

At the time of the FDA inspection, the heat exchanger had not been ordered.

ii. Investigation report PR112361 was initiated on May 14, 2007, for total aerobic count excursions in the purified watcr loop sampled on May 1, 2007. The report remained open at the time of the FDA inspection.

iii. Investigation report PR87671 was initiated on November 6, 2006, for non-viable particulate excursions in several grade [redacted], grade [redacted] or Grade [redacted] areas. Corrective actions were not completed until February 20, 2007.

iv. A sample collected from Room 1627 (1627.5) on May 12, 2007, and documented in investigation report PR117911 was not sent for microbial identification until June 26, 2007.

v. A sample collected from Room 1624 (R1624.14) on August 30, 2007, and documented in investigation report PR128513 was not submitted for microbial identification until October 5, 2007.

vi. A sample collected from Room 1627 (R1627.18) on August 31, 2007, and documented in investigation report PR131057 was not sent for microbial identification until October 31, 2007.

2. Failure to maintain separate or defined areas or other such control systems for your operations as necessary to prevent contamination during the course of aseptic processing, including a system for cleaning and disinfecting rooms and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v)]. For example:

a) Systematic facility cleaning for mold was not initiated in a timely manner. Systematic cleaning was initiated after several months of environmental excursions for mold throughout the manufacturing areas, including aseptic areas.

b) Disinfectant effectiveness studies against representative microorganisms and/or specific in-house isolates were not conducted for cleaning agents used in your facility to disinfect production areas, including aseptic areas.

3. Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. Some examples include:

a) Not all Water for Injection use points was monitored; examples include use points WI-FV-027 and WI-FV-034.

b) Your quality unit failed to review all environmental monitoring data as required by your standard operating procedure (SOP) STR-MIC-0021 entitled "Facility Routine Environmental Monitoring Program." Some examples include:

I. Environmental Monitoring form #STR-MIC-0021-F37 for Room 1618, [redacted] Monitoring results recorded on the following dates were not reviewed by the quality unit, as required: February 26,2007; March 22, 2007; April 6, 20, and 30, 2007.

ii. Environmental Monitoring form STR MIC-0021-F21 for Room 1627, [redacted] Monitoring results recorded on the following dates were not reviewed by the quality unit, as required: February 26, 2007;
March 2, 4, 12, and 19, 2007; April 3, 6, and 10, 2007.

iii. Environmental Monitoring form STR-MIC-0021-F38 for Room 1624, [redacted] Monitoring results recorded on the following dates were not-reviewed by the quality unit as required: February 12 and 25,2007; March 19 and 31, 2007; April 6, 2007.

iv. Environmental Monitoring form STR-MIC-0021-F33 for Room 1643, [redacted]. Monitoring results recorded on the following dates were not reviewed by the quality unit, as required: February 25, 2007; March 19 and 28, 2007; April 3, 2007.

c) Personnel who exceeded environmental monitoring limits during manufacturing were not always notified of the excursions, as required by your SOP STR-MIC-0020 entitled "Routine Personnel Monitoring." For example:

i. There is no documentation indicating that manufacturing technician [redacted] was notified of the excursion for personnel monitoring performed on May 31, 2006.

ii. There is no documentation indicating that EM technician [redacted] was notified of the excursion for personnel monitoring performed on May 3, 2007.

iii. There is no documentation indicating that EM technician [redacted] and manufacturing technician [redacted] were notified of excursions for personnel monitoring performed on August 30, 2007.

4. Failure to establish the accuracy, sensitivity, specificity, and reproducibility of test methods, in that analytical methods have not been validated [21 CFR 211.165(e)].
For example:

a) Sterility test method STR-MTM-0006 has not been validated for sterility testing of [redacted] liquid bulk.

b) bioburden test method STR-MTM-0004 has not been validated for bioburden testing of [redacted] pre-filtration bulk.

5. Failure to establish and follow scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity, and failure to ensure that such specifications, standards, plans, and procedures, including any changes, are reviewed and approved by the quality control unit [21 CFR 211.160(a) and (b)]. For example:

a) Deviation Report PR 90028, initiated. November 21, 2006, documented that finished product samples for [redacted] lot [redacted] submitted per requirements in the master batch record (MBR), did not conform to the sample quantities specified in SOP STR-CTM-0008 entitled "Acceptance Testing of [redacted]

b) Deviation Report PR 111797, initiated on May 9, 2007, documented that samples for [redacted] lot obtained for release chemistry testing per requirements in the MBR, did not conform to the sample quantities specified in the [redacted] specification STR-F-PAN313.0.

c) Testing performed by your testing facility did not meet the requirements for growth promotion testing outlined in your SOP STR-MIC-0025 entitled "Receipt and Growth Promotion Testing of Microbiological Medium." Test organisms and incubation parameters did not conform to your specified
requirements.

d) Testing performed by your testing facility did not meet the requirements for growth promotion testing outlined in it SOP PDR-MIC-0001 entitled "Receipt and Growth Promotion of [redacted] Media/Diluents." A review of testing logs revealed that on numerous occasions samples were not incubated according to the parameters specified in the SOP.

e) There were no data available to demonstrate that the incubation parameters for test samples specified in your SOP STR-MIC-0021 entitled "Facility Routine Environmental Monitoring Program" promote the growth/identification of all organisms, including yeasts and/or molds. Further, these incubation parameters do not conform to the parameters specified in your SOP for growth promotion testing of microbiological medium.

The deficiencies described in the Form FDA,483 and this letter are indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your manufactured drug products. Please describe in detail how Catalent Pharma Solutions will attain CGMP compliance with regard to investigations. Please include in that description how you will use all relevant information to conduct root cause analysis, to ensure that adequate steps are taken to evaluate whether deviations impact product, and to implement effective corrective and preventive actions.

We acknowledge receipt of your written responses dated December 14, 2007, and January 31, 2008, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letters may be referenced in your response to this

letter; however, we believe that your responses did not provide sufficient detail to fully assess the adequacy of the corrective actions.

We have the following specific comments regarding your responses. The items are numbered to correspond to the observations listed on the Form FDA 483.

FDA 483 item 4.B
Please clarify whether revisions have been implemented to require that documentation of sterility test results address whether results relate to samples from the beginning, middle, orend of the fill cycle.

FDA 483 item 5.C
Please describe the criteria that you will use to determine which environmental isolates will be included in the environmental isolates library. Also, please explain how these criteria will be incorporated into your written procedures.

FDA 483 item 12.A
Please provide your rationale for deferring the installation of the [redacted] on the purified water loop until the June 2008 semi-annual plant maintenance shutdown.

FDA 483 item 18.B
Your response did not address plans for a routine inspection/maintenance program to assure the integrity of the light fixtures used throughout the manufacturing areas. Please clarify whether you plan to institute such a program and, if so, provide details.

Neither this list nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FD&C Act and applicable FDA regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action may include seizure and/or injunction.

Please notify us in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the Food and Drug Administration, ORA/OE/Division of Compliance Management and Operations, HFC-210, 5600 Fishers Lane, Rockville, MD, 20857. If you have any questions regarding this letter, please contact Mr. Fabio Mattiasich, Compliance Officer, Division of Compliance Management and Operations, at (718) 662-5580.

In addition, you have requested a meeting with FDA to further discuss your corrective actions addressing the deviations identified during the inspection. Please telephone Fabio Mattiasich at (718) 662-5580 to discuss an appropriate time for the meeting or if you have any questions regarding this matter.

Sincerely,

/S/

David K. Elder
Director
Office of Enforcement

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