Inspections, Compliance, Enforcement, and Criminal Investigations

Contract Pharmacal Corporation 10/14/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New York District
158-15 Liberty Avenue
Jamaica, NY 11433

October 14, 2010

WARNING LETTER NYK-2011-03

VIA UPS

Matthew D. Wolf, CEO
Contract Pharmacal Corporation
135 Adams Avenue
Hauppauge, New York 11788

Dear Mr. Wolf:

During our April 8-28, 2010 inspection of your pharmaceutical manufacturing facility Contract Pharmacal Corporation located at 135 Adams Avenue, Hauppauge, New York, investigators 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 products 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, you manufacture a number of prescription drugs without approved applications. As described below, these drugs are unapproved new drugs, and by introducing them into interstate commerce you are in violation of section 505(a) of the Act [21 U.S.C. § 355(a)]. These drugs are also misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)].

We reviewed your firm's responses of April 28, May 7, and May 20, 2010, and note that they lack sufficient corrective actions.

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

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, your firm has not established written procedures for or conducted appropriate process validation studies fo the following drug products: 1) Caffeine 100 mg tablets, 2) **(b)(4)** tablets (Acetaminophen 500 mg/Pamabrom 25 mg), 3) Diphenhydramine HCl 25 mg capsules, and 4) Methenamine Mandelate 500 mg tablets.

Regarding your Diphenhydramine HCl 25 mg capsules, you conducted validation with batches of 1,550,000 tablets. For subsequent lots, you scaled up to 2,400,000 tablets, then 3,500,000 tablets, and most recently to 4,100,000 tablets. The

manufacturing instructions in all Master Batch Records had identical blending times of **(b)(4)** even though the batch size was increased from 1,550,000 tablets to 4,100,000 tablets.

In addition, validation documentation for Methenamine Mandelate 500 mg tablets, revealed that your firm failed to confirm that the process can operate at allowable limits for compression and coating. Specifically, the **(b)(4)** compression machine had allowable speed ranges of **(b)(4)** RPM; however, you ran the validation batches at **(b)(4)** RPM. There were also problems with the film coating set up for validation lots 094324 and 094325. Specifically, you set the flow rate at **(b)(4)** ml/m, but ran validation at **(b)(4)** ml/m; you set pan speed limits at **(b)(4)** RPM, but ran validation at **(b)(4)** RPM; and airflow was **(b)(4)** CFM, but validation airflow amounts were **(b)(4)** CFM.

Your firm failed to provide validation protocols that evaluated the impact of the increasing batch sizes on product quality. You failed to conduct a study to demonstrate at what point each batch size is uniformly blended. You have not conducted any analysis comparing data between your validation batches. Further, your firm uses a general "Master Validation Plan" for process validation on all products. Validation must be demonstrated for each product and process. The critical controls and processing parameters must be known and shown to be in control, and a demonstration of process reproducibility with objective measures must be made.[1]

Finally, we acknowledge your commitment to conduct challenge testing to determine when blend uniformity is achieved for existing products; however, your response lacks specific timeframes for completion. In your response to this letter, please explain when you plan to conduct such testing.

This is a repeat observation from the February 2006 and September 2000 inspections.

> 2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed, or extended investigations to other batches of drug product that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192].

For example, you failed to investigate unexplained discrepancies and conduct or document complete investigations for the following products:

> a) Chlorpheniramine Maleate 4 mg tablets, lot 091556, were compressed on May 4, 2009; however, this lot contained metal slivers compressed into the tablets. The apparent cause was improper set up of the compression machine. Your firm failed to document a root cause and conduct corrective actions for this event.
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> b) Diphenhydramine HCl 25 mg capsules, lot 093383, were encapsulated into gelatin capsules on September 28, 2009; however, the operator used the wrong capsule color and the Quality Assurance inspector failed to notice the mix-up. Your firm failed to document a root cause and implement corrective actions for this lot.

Your response regarding the above examples is inadequate because it fails to include details on how your firm handles investigations, such as which errors or incidents would result in a thorough out-of-specification (OOS) investigation. In addition, your response did not indicate that you conducted an assessment to determine whether other batches may have been impacted and investigated.

> c) Hyoscyamine Sulfate 0.125 mg, lot 101207, had OOS assay results of 90.5%, 91.8%, and 91.7% **(b)(4)** on February 5, 2010, for the initial in-process blend assay testing. In the Quality Control Laboratory Test Report and laboratory notebook Vol. PV-30, dated February 22, 2010, you conducted repeat testing from the same sample in which the assay results of Hyoscyamine Sulfate were all reported to be within specifications.
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> d) Ibuprofen had OOS assay result of 110.3% on **(b)(4)** April 12, 2010, for the initial testing of **(b)(4)** (Ibuprofen), under lot 102005. The analyst performed repeat testing, in duplicate, on the same date, from the same sample. After that, both assay test results were found within specification.

Your response states, "It was determined that each of the OOS results was due to a procedural error on the part of the analyst." However, your response does not include any information regarding which part of the Standard Operating Procedure (SOP) the analyst failed to follow and whether you extended the investigation for the assay testing to associated batches. You should report all test results that have not been invalidated, and these results should be considered in batch release decisions. Finally, we note your commitment to retrain analysts on a routine basis, but your response fails to include timeframes for completing training to address OOS results.

This is a repeat observation from the June 2008 inspection.

3. Your firm has not exercised appropriate controls of mechanical equipment [21 C.F.R. § 211.68]. For example:

a) You have not qualified the **(b)(4)**

b) You have not completely qualified the **(b)(4)** and **(b)(4)**

Your response states: "An IQ/OQ has been written and executed for the **(b)(4)** system and the PQ will be performed by end of June 2010." This response is inadequate because you have not submitted any qualification documentation to support this proposed corrective action. Regarding the observation for the Metal Detectors, your response states: "For the units observed in 3.C -IQ/OQ is complete and the PQs will be executed within 30 days." In your response, please provide your PQ documentation.

4. Your firm's drug product expiration dates are not related to the storage conditions stated on the labeling, as determined by appropriate stability studies [21 C.F.R. §§ 211.137, 211.166].

For example, your firm's practice was to assign product expiration dates using the last day of compression and encapsulation as the start of the product expiry. This practice allows four additional months prior to the start of expiry period rather than at the time of mixing components. Specifically, you failed to have sufficient stability studies for the following drug products: a) Hyoscyamine Sulfate 0.125 mg tablets, b) Pseudoephedrine HCI 30 mg tablets, and c) Meclizine HCI 25 mg tablets.

We acknowledge your commitment to assign expiration dating from the day the Active Pharmaceutical Ingredient is added to the drug product. Your response states: "We will conduct a thorough review of all drug products to gather historical, average processing times in order to identify any products that require production times greater than the established limits." However, your response is inadequate because it did not include timeframes for completion of this review.

This is a repeat observation from the February 2006 inspection.

5. Your firm failed to establish written procedures used in the manufacture of drug products [21 C.F.R. § 211.100(a)].

For example, your firm lacked SOPs for the following: a) appropriate sampling plans for OOS results, b) user access to computer systems with raw data, c) HPLC column inventory control, and d)
coating solution expiration dating.

Your response states: "We have attached a draft of each. These drafts will be finalized and implemented by June 25th, except for C-04 which was finalized May 14th, 2010." We cannot assess the adequacy of this corrective action since the SOPs have not been submitted. Please have these SOPs available for review during the next inspection.

This is a repeat observation from the February 2006 inspection.

Misbranded and Unapproved New Drugs

In addition to violating cGMPs, you manufacture and market unapproved new drugs in violation of the Act at your facility at 135 Adams Avenue Hauppauge, New York 11788. We acknowledge receipt of your letter of April 28, 2010 to the New York District Office. In that letter, you stated that you would be discontinuing the manufacture of many of your unapproved drugs. However, you did not include all of your unapproved drugs. Based on the information your firm submitted to FDA's Drug Registration and Listing System and the information collected during the inspection of your facility, you also manufacture the following prescription drugs, including but not limited to:

- Hyoscyamine Sulfate 125 mcg
- **(b)(4)** (Ferrous Fumarate 324 mg, Folic Acid 1 mg, Sodium Docusate 50 mg)
- **(b)(4)** (Iron 70 mg, Succinic Acid 75 mg, Ascorbic Acid 150 mg, Threonic Acid 2 mg, Folic Acid, USP 1 mg Cyanocobalamin 10 mcg)

These products are drugs within the meaning of Section 201(g) of the Act [21 U.S.C. § 321(g)] because they are intende for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they 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 b FDA under either section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. Based on our information, you do not have any FDA-approved applications on file for these drug products. The marketing of these products, or other applicable products, without an approved application constitutes a violation of these provisions of the Act.

Additionally, because the above products are intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners, adequate directions cannot be written for them so that a layman can use this product safely for its intended uses. Consequently, their labeling fails to bear adequate directions fo their intended uses, causing it to be misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)]. Because your products lack required approved applications, they are not exempt under 21 C.F.R. § 201.115 from the requirements of section 502(f)(1) of the Act. The introduction or delivery for introduction into interstate commerce of these products therefore violates sections 301(a) of the Act [21 U.S.C § 331(a)].

You should discontinue manufacturing and distributing all of your unapproved drugs at all facilities immediately, with the exception of products we may separately discuss. For questions about the regulatory status of your drugs, contact Kathleen Joyce at 301-796-3329. For assistance in communicating with the FDA concerning the application process for your unapproved drugs, contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710.

To ensure that all drugs marketed in the U.S., prescription and over-the-counter, have been shown to be safe and effective, FDA published a Compliance Policy Guide (CPG) Section 440.100, Marketed Unapproved Drugs, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/guidances/UCM070290.pdf[1]. FDA expects manufacturers of products requiring approval to submit applications to the agency showing that their products are safe and effective. The CPG describes the very strict criteria under which the Act permits drugs to be marketed without approval. The CPG also outlines the Agency's enforcement policies aimed at efficiently and rationally bringing all drugs requiring approved applications into the approval process.

Finally, we note that the CGMP violations listed in this letter regarding process validation, stability data, and failure investigations include similar violations to those cited since October 2000. Inspections at your firm continue to reveal violations regarding these above issues, as well as other problems. Despite past commitments that enhancements would achieve CGMP compliance, deviations remain. The repeat citations from prior inspections indicate that your quality control unit is either not exercising its responsibilities or may not have the appropriate authority to carry out its responsibilities. Due to the continuing CGMP issues at your firm, we recommend you engage a third party consultant having appropriate CGMP experience to assess your firm's facility, procedures, and systems on a routine basis to ensure your drug products have their appropriate identity, strength, quality, and purity.

The violations cited in this letter are not intended to be an all inclusive list of violations that may 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 new drug applications listing your facilities, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Include an explanation of each step 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 the drug products manufactured at these facilities, and provide the date(s) and reason(s) you ceased production. For discontinued products, you must update the Drug Listing files in accordance with 2 C.F.R. § 207.30 (a)(2).

Your written response should be sent to Dean R. Rugnetta, Compliance Officer, U.S. Food and Drug Administration, 300 Pearl Street, Suite 100, Buffalo, New York 14202. If you have any questions about this letter, please contact Compliance Officer Dean Rugnetta at (716) 541-0324 or email at dean.rugnetta@fda.hhs.gov.

Sincerely,
/S/
Ronald M. Pace
District Director

New York District

[1] Further information on FDA's current thinking on process validation is available in Food and Drug Administration, Draft Guidance for Industry, Process Validation: General Principles and Practices November 2008, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf[2].

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