U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Capricorn Pharma, Inc. 4/20/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215-3215
Telephone: (410) 779-5454

FEI: 3002908878

WARNING LETTER
CMS#85885

April 20, 2010

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Subraman Rao Cherukuri, President/CEO
Capricorn Pharma, Inc.
6900 English Way, Ste. A
Frederick, Maryland 21703

Dear Mr. Cherukuri:

During our September 15 through October 13, 2009 inspection of your pharmaceutical manufacturing facility, Capricorn Pharma, Inc., located at 6900 English Muffin Way, Ste. A, Frederick, MD, 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 (th 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 October 27, 2009, and note that it lacks sufficient corrective actions.

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

CGMP Violations

1. Your firm has failed to establish an appropriate written testing program, designed to assess the stability characteristic of drug products, to determine appropriate storage conditions and expirations dates [21 C.F.R § 211.166(a)]. For example,

a) Your firm released and distributed four lots of Guaifenesin 50mg Flashbeads - Grape Flavor prior to the **(b)(4)** stability study as described in your "Stability Protocol." In addition, you released and distributed 11 batches of Guaifenesin 100mg Flashbeads - Bubblegum Flavor before generating adequate stability data to support the labeled expiry period.

We reviewed your response of October 27, 2009. Your response states that you have completed the **(b)(4)** of stability for the Guaifenesin; however, your responses do not address the adequacy of the stability of other products manufactured at your site.

b) You released and distributed **(b)(4)** lots of bulk **(b)(4)** 6mg Flashbeads - Grape Flavor 35 days prior to initiating your stability study.

Your response appears adequate. The effectiveness of the implementation of the revised SOP will be verified at the next inspection.

This is a repeat observation from the 2008 inspection of your facility.

2. Your firm has failed to establish written procedures to validate the performance and monitor the output of your manufacturing processes [21 C.F.R. § 211.110(a)], and failed to reject in-process material that did not conform to its specification [21 C.F.R. § 211.110(c)]. For example,

a) During the process validation **(b)(4)** Tablets, your firm failed to reject tablets that were Out-of-Specification (OOS) for hardness.

b) During the routine manufacturing **(b)(4)** Tablets, OOS results were obtained for in-process hardness testing. None of the tablets were rejected due to the OOS hardness results.

Your response states that the specification for hardness is an average of individual results. However, your Process Validation protocol **(b)(4)** does not specify that this specification be applied to an average of all samples.

In addition, CGMP regulation [21 C.F.R. § 211.160(b)] requires that drug manufactures establish "scientifically sound an appropriate specifications, standards, sampling plans, and test procedures designed to assure that. .. .in-process materials ...and drug products conform to appropriate standards of identity, strength, quality, and purity." It is unacceptable to establish process validation acceptance criteria and then dismiss such criteria as insignificant when the results do not conform.

We also note that your Standard Operating Procedure (SOP) **(b)(4)** states that **(b)(4)** Please explain why you did not follow your SOP. In addition, we have noted that your SOP contains a contradictory statement, "NOTE: **(b)(4)**..." Pleas explain this contradictory statement in your SOP.

This is a repeat observation from the 2008 inspection of your facility.

3. Your firm failed to thoroughly investigate the failure of a batch to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example, OOS results were obtained during validation of the manufacturing process for **(b)(4)** Tablets without initiating a subsequent investigation. We note that the Process Validation protocol states, **(b)(4)**."

4. Your firm has failed to establish appropriate written procedures for cleaning the equipment used in the manufacture o processing of a drug product [21 C.F.R. § 211.67(b)]. For example,

a) Using your available method validation data, there is no assurance that the current method for testing **(b)(4)** residue can adequately evaluate equipment cleanliness.

b) Your cleaning validation studies for non-dedicated equipment do not show that product residues are decreased to an acceptable level. Specifically, the percent of recovery at **(b)(4)**% was arbitrarily established without supporting data.

In addition, the recovery swab studies to validate the swab methods did not provide sufficient data to demonstrate manual recovery variability. For example, your "**(b)(4)**" was validated based on swab recovery study that was conducted at a **(b)(4)** concentration and used a **(b)(4)** swab.

We have reviewed your response and cannot determine its adequacy since your swab recovery studies were not complete at the time of your response. The effectiveness of your corrective action will be evaluated during the next

inspection of your facility. In addition, it is our expectation that a thorough and comprehensive review of all cleaning protocols and reports will be performed to ensure that all studies have been adequately conducted.

This is a repeat observation from the 2008 inspection of your facility.

5. Your firm has failed to retain and store, under conditions consistent with product labeling, an appropriately identified reserve sample that is representative of each lot or batch of drug product [21 C.F.R. § 211.170(b)].

For example, retention samples for distributed Guaifenesin drug product were missing and later found in various locations (e.g., room adjacent to packaging, packaging room, etc.). In addition, your firm was unable to locate two reserve samples for Guaifenesin 100 mg Flashbeads - Bubblegum Flavor, lot number **(b)(4)**

Your response appears adequate, but the effectiveness of your revised SOPs will be verified at the next inspection.

6. 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)].

a) Your firm's laboratory analysts have the ability to access and delete raw chromatographic data located on the **(b)(4)** of **(b)(4)** used to conduct HPLC testing. Due to this unrestrictive access, there is no assurance that laboratory records and raw data are accurate and valid.

b) Your firm's laboratory analysts have the ability to access and modify the formulas in the Excel spreadsheets used to calculate assay results for Guaifenesin and **(b)(4)** drug products. Due to this unrestricted access, there is no assurance that the formulas in the Excel spreadsheets are accurate and valid.

Your response appears to be adequate, but the effectiveness of the security features on your laboratory equipment will be verified at the next inspection.

Unapproved Over-the-Counter Drug Product Violations

Your firm manufactures drug products for the over-the-counter use. Specifically, your firm manufacturers, among other products, **(b)(4)**, and **(b)(4)**. The active ingredient in these products (i.e., Guaifenesin) is delivered by a new dosage form described as **(b)(4)**" and **(b)(4)**." In accordance with 21 C.F.R § 310.3(h)(5) the newness of a drug may arise among other reasons by the newness of a dosage or method or duration of administration or application. Your products are not covered by the ongoing OTC Drug Review because this dosage form was not available at the inception of the OT Review, was not evaluated by the Panel evaluating OTC drug products at the time of the review, nor was it contemplated by the agency during the development of the monograph or at the time of the final regulations covering Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC use, 21 C.F.R. Part 341. Therefore, your products listed above are unapproved new drugs.

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 or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for it. These products do not have approved applications and their introduction and delivery into interstate commerce violates these provisions of the Act. We are aware that you also market other OTC drug products such as **(b)(4)**. This and other products that utilize the "**(b)(4)**" or "**(b)(4)**" dosage form would also be unapproved new drugs for the same reasons described above.

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 of distribute any of the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

We acknowledge that you have hired **(b)(4)** to assist with correcting the CGMP deficiencies. It is our expectation that your employees continue to comply with CGMP regulations, and continue identifying and correcting deficiencies once the consultants are no longer employed by your firm.

Your reply should be sent to the following address: U.S. Food and Drug Administration, 6000 Metro Drive, Suite 101, Baltimore, MD 21217, Attn: Randy F. Pack, Compliance Officer.

Sincerely,

/S/
Evelyn Bonnin
District Director
Baltimore District Office

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