U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

PrimaPharm Inc. 31-Oct-08

Department of Health and Human Services

Public Health Service
Food and Drug Administration

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WARNING LETTER

CERTITIED MAIL
RETURN RECEIPT REQUESTED

October 31, 2008

WL 03-09

Lewis J. Shuster, President and CEO
PrimaPharm Inc.
3443 Tripp Court
San Diego, CA 92121

Dear Mr. Shuster:

An inspection of your drug manufacturing facility located at 3443 Tripp Court, San Diego, California, conducted by our Food and Drug Administration (FDA) investigators on May 1-14, 2008, determined that you are a **[(b)(4)]** manufacturer of **[(b)(4)]** drug products such as **[(b)(4)]** and **[(b)(4)]**. The inspection found significant violations of the FDA's current good manufacturing practice (CGMP) regulations in 21 Code of Federal Regulations (CFR) Part 211. These CGMP violations cause products. manufactured by your facility to be adulterated within the meaning of 21 U.S.C. § 351(a)(2)(B) (Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act)).

In addition, this inspection also revealed that your firm is manufacturing and/or marketing unapproved drugs in violation of 21 U.S.C. § 355(a) (Section 505(a) of the Act) and the drugs are also misbranded in violation of 21 U.S.C. § 352(f)(1) (Section 502(f)(1) of the Act).

CGMP Deviations

We acknowledge receipt of your letter dated **[(b)(4)]** responding to the deficiencies listed on an Inspection Observations (Form FDA-483). Examples of the violations observed, along with comments regarding your responses to the Form FDA 483, are as follows:

1. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed and to extend the investigation to other batches that may have been associated with the specific failure or discrepancies [21 CFR § 211.192].

a. The investigation into the **[(b)(4)]** was not completed until the initiation of the current inspection. In addition, prior to completing your investigation of the **[(b)(4)]** firm completed **[(b)(4)]** production batches. Your firm's **[(b)(4)]** investigation recovered the organisms **[(b)(4)]** and **[(b)(4)]** from **[(b)(4)]** locations on the **[(b)(4)]** machine **[(b)(4)]**. In addition, **[(b)(4)]** (including the **[(b)(4)]** organism) were also isolated from the media vials. Your failure investigation did not assess the impact of the contamination on lots subsequent to the last successful media fill and after the media fill failure.

Your response to the Form FDA 483 states, "In the future, there will be a more formal close out of the investigation surrounding any media failure before QA will authorize further activity in a room where a media failure occurred." However, you provide no additional information to support the conclusion that the media fill contamination was related to only the **[(b)(4)]** batches. In light of the significant problems you encountered with the control of the **[(b)(4)]** facility in **[(b)(4)]** including **[(b)(4)]**, as well as the significant CGMP observations documented during the current inspection, we are concerned about your incomplete investigations and your conclusions regarding the media fill failure noted above. These deviations raise significant concerns with sterility assurance of products that were produced under these conditions. While we acknowledge that you are taking steps to address many of these deficiencies, please provide your rationale for the distribution of products potentially implicated by the media fill contamination and the significant CGMP violations described below.

b. The investigation for **[(b)(4)]** lots **[(b)(4)]** and **[(b)(4)]** regarding **[(b)(4)]** that exceeded the alert limit of **[(b)(4)]** is inadequate. The investigation documents the root cause as: "**[(b)(4)]**." The investigation lacks a description of any steps taken to identify the source of the **[(b)(4)]** found in the **[(b)(4)]** vials.

Your response to the Form FDA 483 acknowledges the investigation cited above was incomplete in that the source was not identified. Further, your response stated that another incident of **[(b)(4)]** was recently found in **[(b)(4)]** vials and an investigation has been initiated regarding the **[(b)(4)]**. Please provide the results of your completed investigation report for this incident, specifically the actions you have taken to ensure adequate **[(b)(4)]**

2. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR § 211.113(b)]. For example:

a. **[(b)(4)]** are not continuously monitored nor frequently recorded during **[(b)(4)]** operations. There is no system in place to adequately monitor or record **[(b)(4)]** to assure that the **[(b)(4)]** are maintained at the **[(b)(4)]** at all times.

Your response for this observation on the Form FDA 483 states that your firm will continue to visually observe **[(b)(4)]** to monitor **[(b)(4)]** until your firm **[(b)(4)]** the corrective action, **[(b)(4)]** states that **[(b)(4)]**. Please justify how monitoring at **[(b)(4)]** intervals is considered continuous monitoring in order to provide assurance that your facility is acceptable for **[(b)(4)]** manufacturing. Please provide further interim measures to ensure appropriate **[(b)(4)]** are constantly maintained (i.e., use of alarm system).

b. Entry into **[(b)(4)]** are directly through a **[(b)(4)]**. For example, the **[(b)(4)]** Rooms are **[(b)(4)]** and are adjacent to **[(b)(4)]**. Additional controls are not provided to minimize potential ingress of contamination to these **[(b)(4)]**.

Your response states you plan to evaluate engineering changes for the **[(b)(4)]** . Rooms adjacent to the **[(b)(4)]** to determine how to reclassify the rooms to at least **[(b)(4)]**. Also, you state that your firm plans to complete these engineering changes by the end of **[(b)(4)]**. Please provide your firm's explanation of how your operational design and control approach would assure **[(b)(4)]** assurance for products manufactured prior to that date.

c. Media fills used to validate the **[(b)(4)]** processes are deficient. For example, your firm's Standard Operating Procedure (SOP) **[(b)(4)]** is inadequate in that it lacks a rationale for the selection of **[(b)(4)]** used to qualify the **[(b)(4)]**. Therefore, there is no assurance that the **[(b)(4)]**

used include worst-case **[(b)(4)]** to ensure **[(b)(4)]** adequately represent the **[(b)(4)]**

Your response states the **[(b)(4)]** was revised to rotate **[(b)(4)]** but we are unclear from the update **[(b)(4)]** provided in your response on how you plan to conduct your **[(b)(4)]**

3. Failure to have an adequate system for monitoring environmental conditions in an **[(b)(4)]** For example:

a. Your monitoring program does not include sampling of critical surfaces. There is no documented explanation or justification for the selection of surfaces defined in **[(b)(4)]**. The sampling sites stipulated by the **[(b)(4)]** do not include any surfaces that come into direct contact with the [redacted] product or **[(b)(4)]** components (i.e. stopper bowl or stopper chute).

Your response states that you will now sample critical equipment such as the **[(b)(4)]** and **[(b)(4)]** However, according to your response you will not be testing all critical equipment. For example, you state that the dimensions of the **[(b)(4)]** does not facilitate **[(b)(4)]**. Please describe additional or alternate surface monitoring you will conduct to ensure all critical equipment is adequately monitored.

b. **[(b)(4)]** performed at the start of a process, rather than at the conclusion of a product fill. Specifically **[(b)(4)]** requires **[(b)(4)]** only at the beginning of a clean room process in **[(b)(4)]** . Your firm's practice of taking all **[(b)(4)]** prior to actual processing operations provides for an inadequate means to detect **[(b)(4)]** contamination that may be present during the conduct of your **[(b)(4)]**

Your response states that you will conduct sampling at appropriate locations during the manufacturing process. However, your response does not state how these locations were identified or what is considered a critical operation.

c. Your monitoring program for **[(b)(4)]** personnel fails to establish appropriate action limits for environmental excursions. **[(b)(4)]** inadequate. Specifically, the action limit for personnel monitoring in the **[(b)(4)]** areas is when the alert limit is exceeded on **[(b)(4)]**. However, the action limit does not account for the significance of the individual results exceeding the alert limit. There is no difference between action and alert limits except number of incidents of excursions (i.e. a single very high excursion (over, the alert limit) would trigger an investigation, but would not prompt corrective action).

Regarding example (c) and lack of action limits for environmental monitoring, you submitted a revised **[(b)(4)]** that does not include an action limit for **[(b)(4)]** excursion of the room specification.

4. Failure to establish and document the accuracy, sensitivity, specificity, and reproducibility of test methods [21 CFR § 211.165(e)). For example, **[(b)(4)]** states that a **[(b)(4)]** is required for operators inspecting finished product **[(b)(4)]** however, the method of determining, **[(b)(4)]** is not defined in the procedure. Also, the frequency of retraining or requalification for operators is not documented in the procedure. Finally, there is no maximum allowable time limit to perform **[(b)(4)]**

Your response to this observation states **[(b)(4)]** was revised to address the above item. However,the revised SOP in your response does not have an effective date. Please provide a timeframe when this revised SOP will be considered effective.

5. Failure to have an adequate system for cleaning and disinfecting the rooms and equipment used to produce **[(b)(4)]** [21 CFR § 211.42(c)(10)(v)). For example, your firm utilizes **[(b)(4)]** with **[(b)(4)]**. Your firm does not assure that a **[(b)(4)]** system is employed, or that the disinfectant is otherwise rendered sterile prior to use.

Your response for this observation on the FDA-483 notes that your firm will **[(b)(4)]** before use. However, the response is inadequate because the following were not addressed: 1) effectiveness of **[(b)(4)]** solution at the dilution used, and 2) effectiveness of **[(b)(4)]** throughout shelf life (up to expiry date).

6. Failure to adequately maintain system equipment used to control **[(b)(4)]** conditions in the **[(b)(4)]** [21 CFR §211.42(c)(10)(vi)). Specifically, the **[(b)(4)]** is inadequate. For example:

a. There is no written procedure for **[(b)(4)]** detailing the testing requirements and the establishment of acceptance criteria.

b. **[(b)(4)]** performed by a vendor does not include documentation of the average **[(b)(4)]** located in the following rooms: **[(b)(4)]** Furthermore, while **[(b)(4)]** were documented by a vendor for **[(b)(4)]** no acceptance criteria existed to determine the acceptability of the data.

Your response for this observation on the FDA-483 citing **[(b)(4)]** is inadequate in that your current SOP lacks an appropriate range for **[(b)(4)]** test criteria for areas other than **[(b)(4)]** and a description of how the **[(b)(4)]** is to be performed. We acknowledge your commitment to increase **[(b)(4)]**

7. Failure to establish written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess (21 CPR §211.100(a)]. Specifically, process validation studies were not performed to support the scale up of **[(b)(4)]**. Process validation of **[(b)(4)]** was for approximately **[(b)(4)]**. However, for **[(b)(4)]** manufacturing of **[(b)(4)]** the target batch size was increased to approximately [redacted] In addition, prospective validation studies were not conducted on these lots to validate the extended hold times used during the manufacture of these lots. A validation protocol for manufacture of the larger batch size was not developed until initiation of the current inspection. Despite these deficiencies, these lots were released by Quality Assurance.

Your response for this observation on the FDA-483 is inadequate. Your response included your most current corrective action at the time, the **[(b)(4)]**. Our review of Section **[(b)(4)]** of this report noted fox the related scaled-up lots that while filling lot **[(b)(4)]** your firm stopped filling of this **[(b)(4)]**, then held it for **[(b)(4)]** before filling final product. In addition, for process validation of lots **[(b)(4)]** reject rates were exceeded for **[(b)(4)]**

We also note that your **[(b)(4)]** lacks information on any additional testing conducted for these lots to demonstrate that the process is under control and reproducible. In addition, during the process validation (manufacture of lot **[(b)(4)]** you reported that the **[(b)(4)]** malfunctioned. We acknowledge your statement that you will not release lot **[(b)(4)]** until a separate protocol is written to address this deviation. Please include this protocol and details regarding, your subsequent actions in handling this lot. Finally, your response states **[(b)(4)]** was opened to determine the root cause for the **[(b)(4)]** found in the other lots **[(b)(4)]** that formed part of the process validation study. Please provide details regarding corrective actions taken **[(b)(4)]**

8. Failure to follow written procedures for evaluating at least annually, the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures [21 CFR §211.180(e)]. For example:

a. The **[(b)(4)]** annual product review has not been completed for the following commercial drug products: **[(b)(4)]**

b. The **[(b)(4)]** annual product review is inadequate in that there is no documented evaluation to determine the need for changes in drug product specifications or manufacturing or control procedures. An assessment was not made to determine whether changes are required to improve production of **[(b)(4)]**

Your response for this observation on the FDA-483 notes that your firm revised the SOP and this revised SOP "will be the driver to bring the Annual Product Review up to current FDA expectations." You also stated that starting in **[(b)(4)]**, you will review a product each month until the full line of products have been reviewed. However, you did not state when the **[(b)(4)]** annual product reviews would be completed.

Unapproved New Drugs

In addition to the CGMP violations, you manufacture and market unapproved new drugs in violation of the Act at your facility at 3443 Tripp Court, San Diego, California. Based on the information your firm submitted to FDA's Drug Registration and Listing System and information collected during the inspection of your facility, you manufacture the following prescription drugs:

[(b)(4)]
[(b)(4)]

The above products are drugs within the meaning of Section 201(g) of the Act, [21 U.S.C. § 321(g)] because they are intended 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(a), (d) and 355(a)] a new drug may not be introduced into or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for the drug. Based on our information, you do not have any FDA-approved applications on file for these drug

products.

Additionally, the above products are misbranded because, as prescription drugs, adequate directions cannot be written for them so that a layman can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for use as required under Sections 502 (f)(1) of the Act [21 U.S.C. § 352(f)(1)) and because they lack required approved applications, they are not exempt from this requirement under 21 CFR § 201.115. As noted above, the introduction or delivery for introduction into interstate commerce of these products without approved hew drug applications violates Section 301(a) and (d) of the Act [21 U.S.C. §§ 331(a) and(d)].

Over the Counter (OTC) Drugs

Moreover, we also note that your firm manufactures and markets over-the-counter (OTC) drugs that may require approved applications. An OTC drug product is generally recognized as safe and effective and not misbranded if it meets the applicable conditions in 21 CFR § 330 and all conditions in an applicable OTC monograph in 21 CFR §§ 331-358. However, any OTC product failing to conform to these conditions would require an approved application prior to marketing. OTC drugs are also required to comply with other statutory and regulatory requirements including those applicable misbranding provisions under sections 502 and 503 of the Act.

The issues and violations cited in this letter are not intended to be an all-inclusive list 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 conduct a comprehensive audit of your facility and operations and assure compliance with all requirements of the Act and FDA regulations.

We also request that you outline the action you are taking to discontinue the marketing of the unapproved drug products at your facility, or any other applicable drug which you may market. Also please note that if you are no longer marketing this (these) product(s), you must update the Drug Listing files in accordance with 21 CFR 207.30 (a)(2).

Within 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 recurrence of similar violations as well as copies of related documentation. If you cannot complete corrective action within fifteen 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 products, your response should so indicate, include the reasons for, and the date on which you ceased production.

If you have questions regarding this letter, please contact Ms. Mariza Jafary at (949) 608 **[(b)(6)]**. You can find guidance and information regarding regulations through links at FDA's Internet website at http://www.fda.qov/oc/industry[1].

Your written response should be sent to:

J. Lawrence Stevens
Acting Director, Compliance Branch
Los Angeles District
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

Sincerely,

/S/

Alonza E. Cruse
District Director
Los Angeles District

Cc:
Jeff Farrar, DVM, PhD, MPH
Branch Chief
Food and Drug Branch
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Links on this page:

1. http://www.fda.qov/oc/industry