



DEPARTMENT OF HEALTH & HUMAN SERVICES

94683d
Public Health Service

Central Region

Telephone (973) 526-6010

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

May 5, 2004

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Michael A. Zeher
President
Pharmaceutical Formulations, Inc.
460 Plainfield Avenue
Edison, New Jersey 08817-2415

04-NWJ-12

Dear Mr. Zeher:

An inspection of your manufacturing facility located at 460 Plainfield Avenue, Edison, NJ, was conducted from January 12 through February 9, 2004. During the inspection our investigator documented deviations from the Current Good Manufacturing Practice Regulations, Title 21, Code of Federal Regulations, Parts 210 and 211 (21 CFR 210/211) for drug products manufactured and tested at this site. These deviations 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).

1. An adequate quality control unit having the responsibility and authority to approve or reject in-process materials and drug products, and the authority to assure that errors in production have been fully investigated has not been established (21 CFR 211.22 (a)). For example, production and process errors resulting in substantial losses of product have not been investigated to determine the root causes. Reworking of these products was allowed take place without approval of the quality control unit. In addition, change control procedures established by the quality control unit are inadequate in that they do not document that all changes to master formula batch records have been reviewed by the designated personnel (21 CFR 211.22(c) and (d)).
2. Each component is not adequately verified by a second person prior to addition to the batch. Specifically, there was a lack of assurance that verification was actually occurring since incorrect blends were approved for use in critical manufacturing steps (21 CFR 211.101(c) and (d)). For example, although verification of the introduction of the correct powder blend for Aspirin 500 mg tablets was documented on the batch record, a blend for Aspirin 81 Mg tablets was added instead.
3. Employees engaged in the manufacturing, processing or holding of drugs, or in the supervision thereof, lack the education, training or experience to enable them to perform their assigned functions (21 CFR 211.25(a) and (b)). For example, on four occasions within the past year, employees have introduced powder blends of incorrect products into tableting operations, even after documenting the

addition of correct ingredients on the batch records, In addition, employees have continued to operate a roller compaction machine in an incorrect manner even after being instructed in its proper use by a representative of the equipment manufacturer. Also, specific training in current good manufacturing practices (CGMPs) is not provided to the firm's employees.

4. Process failures resulting in the rejection of substantial quantities of drug products were not investigated and there is no documentation to show any corrective actions (21 CFR 211.192). For example, [REDACTED] tablets from a lot of Pseudoephedrine HCl 39mg were rejected with no documentation of a reason for rejection or corrective action. In addition, a total of [REDACTED] tablets from a lot of Cimetidine 200 mg and [REDACTED] tablets from a lot of [REDACTED] tablets from a lot of Ibuprofen 200mg were rejected for rough surfaces. In each case there was no documentation to show any investigation into the root cause of the problem or any corrective action.
5. Rejected in-process materials were not identified and controlled in a quarantine system to prevent their use. Specifically, rejected in-process material is not identified in a manner sufficient to prevent its accidental use (21 CFR 211.110(d)).
6. Batch production records do not contain complete information related to the production and control of each batch of drug product (21 CFR 211.188). For example, a spill of powder blend during production of a lot of [REDACTED] tablets was not recorded at the time of occurrence. Impact upon the product could not be properly assessed because your firm did not know where the spill occurred in the manufacturing process. In addition, an investigation resulting from an incorrect mule of powder blend being used was initiated when the tablet press operator observed out-of-specification (OOS) tablet weights. These in-process test results were not recorded in the batch record (21 CFR 211.188(b)(5)).
7. Equipment is not maintained appropriately to prevent malfunctions that might alter the safety, identity, strength, quality or purity of drug products (21 CFR 211.67(a)). Specifically, in September 2003, recommendations were made by the [REDACTED] service representative regarding pressure problems with the chilsonator. At the time of the inspection, approximately four months later, the recommendations for repair had not been implemented.
8. Adequate written procedures for the cleaning and maintenance of equipment used in drug manufacture have not been established and followed (21 CFR 211.67(b)). For example, the cleaning validation study for the [REDACTED] Fluid Bed Dryer does not address the effectiveness of the cleaning process on all parts of the equipment. In addition, procedures for disassembly and cleaning of other major drug processing units have not been established.
9. Master production and control records did not specify minimum and maximum percentages of theoretical yields beyond which an investigation is required (21 CFR 211.186(b)(7)). For example, the master production and control records for Cimetidine 200mg and Ibuprofen 200mg do not specify acceptance levels for percent of theoretical yield in the last production step.

10. Master production and control records did not include complete manufacturing instructions and procedures (21 CFR 211.186(b)(9)). For example, the master production and control record for Acetaminophen PM does not include or reference specific instructions for operation of the fluid bed dryer.
11. Laboratory controls are inadequate in that determination of conformance to written sampling procedures cannot be made and samples are not fully identified (21 CFR 211.160(b)(3)). For example, complete information on the origin, size, and method of sampling used for samples taken from suspect drums of Acetaminophen 500mg tablets as part of mix-up investigation is not found in the analysis reports, sample logs or investigation report.
12. Written procedures containing provisions for remedial action in the event of laboratory instrumentation failing to meeting accuracy and precision limits are not followed (21 CFR 211.160(b)(4)). For example, on three occasions, corrective actions following HPLC system suitability failures were not recorded in the instrument maintenance logs as required by your SOP.
13. Inspection of packaging facilities immediately before use was not conducted in a manner sufficient to assure all drug products from previous packaging operations had been removed (21 CFR 211.130(e)). For example, foreign tablets from a previous packaging operation were found in the packaging area during the packaging of a lot of [REDACTED] tablets.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that drug products your firm manufactures are in compliance with the Act and the regulations promulgated under it. Federal Agencies are advised of the issuance of all warning letters about drug products so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct deficiencies at your facility. Failure to do so may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

We have received your March 8, 2004 written response to the FDA-483. We will assess the adequacy and completeness of the corrective actions you have outlined during a future inspection. However, at this time we would like to address the lack of global assessments in your written response. Please note that the investigator used the systems-based approach for the inspection of your firm and evaluated the state of control of your firm by examining the six major manufacturing systems, specifically the quality system, production system, laboratory system, facilities and equipment system, materials system, and packaging and labeling system. Several observations about a single system are indicative of problems with the overall system. Our investigator observed several deficiencies with each system, thereby indicating widespread inadequacies and weaknesses with your manufacturing practices. Instead of addressing the possible system failures, your response merely addressed the individual items cited on the FDA-483 even though the investigator informed you that the individual citations were only examples of problems, not the only problems with each individual system. With your current approach to corrective actions, it is likely that the overall systems will remain deficient.

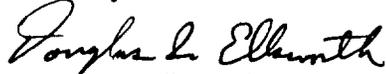
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Pharmaceutical formulations, Inc.
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You should notify this office in writing, within 15 working days of the receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations, as well as how you plan to assure that each of the systems at your firm are in an overall state of control. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the time frame within which corrective actions will be completed.

Your response should be addressed to: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely,



Douglas I. Ellsworth
District Director
New Jersey District