



DEPARTMENT OF HEALTH & HUMAN SERVICES

CB/WL

m39031

Food and Drug Administration
466 Fernandez Juncos Avenue
Puerta De Tierra
San Juan, Puerto Rico 00901-3223

June 15, 2000

WARNING LETTER
SJN-00-16

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Kurt M. Lundgraf
Chairman & Chief Executive Officer
DuPont Pharmaceutical Co., Inc.
Route 41
Wilmington, DE 19805

Dear Mr. Lundgraf:

From March 6 to April 10, 2000, our personnel conducted an inspection of your prescription drug manufacturing facility, DuPont Pharma Ltd. Road 686, Km. 2.3, Manati, PR. Our evaluation of the information obtained during the inspection determined that the pharmaceutical products manufactured by the facility are adulterated within the meaning of section 501 (a)(2)(b) of the Federal Food, Drug and Cosmetic Act (the Act) because they were not manufactured in accordance with Good Manufacturing Practice Regulations (GMP) as defined by Title 21, Code of Federal Regulations, Part 211 (21 CFR 211).

The deviations from GMP's found during the inspection, and reported on the List of Inspectional Observations, FD-483, presented at the conclusion of the inspection, include the following:

1. Failure to conduct adequate review prior to approval of production and process controls as required by 21 CFR 211.100 (a) in that validation protocols for several processes were approved when all specified parameters required by the protocols were not met. For example:

- a. During tablet compression validation for Endocet® tablets under protocol # 99-074, one of the three lots had out-of-specification assay results for the last tablets of the compression run. Your firm's investigation into this incident led to the conclusion that the blend was not uniform and a decision was made to discard the last two pails from the compression operation. An additional three lots of tablets were manufactured using the revised procedure, but these batches were not subjected to evaluation of all of the criteria established in the validation protocol. The validation was approved using the limited data collected from the production of the second set of three batches and no discussion or justification was made for the failure to evaluate these batches for all of the pre-determined criteria.
- b. A high degree of variability was reported in blend uniformity results for three lots of Percocet®/Endocet® tablets manufactured under validation protocol # 93-054. Your firm's investigation reached the conclusion that the tool used to collect the blend uniformity samples was not appropriate. The validation was approved based on this conclusion even though no further evaluation of the sampling tool was made to confirm that it was the cause of the problem.
- c. The validation protocol for Sustiva® capsules packaging equipment was approved even though the validation was incomplete because of a label shortage in the last packaging run and only [REDACTED] of the [REDACTED] labels with known defects were recovered.
- d. The media fill validation for lyophilized ampoules was approved after growth was found in some units during all three runs. The investigation into the failures theorized several causes for the failures and changes were made in these areas. No additional media fill runs were made after the changes were implemented to assure that the cause of the problem had been identified and corrected.
- e. The qualification report for the [REDACTED] inspection machine was approved even though no raw data records were produced during the qualification to demonstrate that the machine detected the pre-determined number of defective units.

Mr. Kurt M. Lundgraf
June 15, 2000
Page 3

We acknowledge receipt of your response to the FD-483, dated April 18, 2000. Our evaluation of the response finds that it is adequate except for the items listed above.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice 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.

Please notify the San Juan District office in writing within 15 working days of 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 these or similar violations.

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

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00901-3223, Attention: Mary L. Mason, Compliance Officer.

Sincerely,

Wayne Matthews for

Mildred R. Barber
District Director