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May 4, 2001

Food and Drug Administration

466 Fernandez Juncos Avenue
Puerta De Tierra
San Juan, Puerto Rico 00901-3223

WARNING LETTER
SJN-01-12

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Alan G. Lafley
President & Chief Executive Officer
Procter & Gamble
P.O. Box 599
Cincinnati, OH 45202

Dear Mr. Lafley:

From January 25, 2001 to March 2, 2001, our office conducted an inspection of your human drug manufacturing facility, Procter & Gamble Pharmaceuticals Puerto Rico, Inc., Highway 2 Km 45.7 Manati, Puerto Rico 00674, and found significant violations of the regulations covering the Current Good Manufacturing Practices for finished pharmaceuticals as defined by Title 21, Code of Federal Regulations, Part 210 & 211 (21 CFR 211). These violations cause the drug products manufactured by your firm, to be adulterated within the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). The violations include:

Facilities and Equipment System

1. Failure to have equipment of appropriate design and construction to facilitate operations for its intended use in the manufacture of drug products, in accordance with 21 CFR 211.63. For example:
 - a) The centralized system to deliver compressed air was not adequate to simultaneously supply all areas in the plant where it was needed. In order to have sufficient compressed air pressure for the micronization step for Dantrolene Sodium Active Pharmaceutical Ingredient (API), it was necessary to assure that the compressed air system was not being used in other areas of the plant at the same time that the micronization process was in progress. There were no controls to assure that other areas of the plant did not use the compressed air

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system during the micronization process and no checks on air pressure being delivered to the micronization system were recorded during the process.

Your response to the FDA-483 observation related to the compressed air system does not seem adequate. Your response does not explain how the manufacturing and other plant operations will be staggered to prevent that these are adversely affected due to the unavailability of compressed air. In addition, our review of records collected by our Investigator during the inspection and of your response show that the current system is not capable of producing the compressed air pressure needed for a reproducible micronization process. The proposed completion date for purchase, installation and qualification of an additional compressor of December 30, 2001 is not acceptable.

Production System

2. Failure to establish production and process control procedures designed to assure your drug products have the required identity, strength, quality and purity as required by 21CFR 211.100 (a). For example:
 - a) Since the process validation of Dantrolene Sodium was completed in 1997, there has been an increase in lots that needed to be reprocessed (re-micronized) in order to meet particle size specifications. This reprocess often causes a decrease in moisture content that results in a rework (re-hydration) to comply with the moisture specifications for the Dantrolene Sodium. The re-hydration sometimes causes an increase in particle size, which then requires another re-micronization and possible re-hydration. No limits have been set for the number of times the API can be re-micronized and re-hydrated. There has been no evaluation of the effect of the repetition of these processes on the stability of the drug product. No stability samples were collected during the re-hydration validation exercise and the assay of the product was not evaluated during the validation of either step in the re-processing.
 - b) During the process validation of Dantrolene Sodium approved on 2/25/97, the final product contained in individual drums was not sampled and tested in a way that could detect variability in particle size results. Although the samples were taken from different levels across the drum, they were tested as a composite sample and not as individual sample.

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- c) The operating range currently established for the micronization grinding pressure for Dantrolene Sodium is not validated. Micronization grinding pressure is listed in the product's validation protocol as a critical process parameter. The micronization grinding pressure currently used is [REDACTED] psig; however, three of the four lots used to validate the process used a micronization grinding pressure of [REDACTED] psig. The grinding pressure used for the fourth lot was not documented. The technical report for the micronization process optimization studies recommended that the air pressure in the micronizer be increased to [REDACTED] psig to "increase the probability of meeting the current particle size specification".
- d) The validation of the re-hydration process conducted in 1992 is not adequate.
- i) The validation consisted of a retrospective evaluation of only three lots that were re-hydrated.
 - ii) According to the validation protocol, the product was hydrated as per SOP 010-020, however, this SOP does not give any instructions on how to hydrate the product.
 - iii) The study did not establish for how long the product has to be re-hydrated, depending on its moisture content before the rework, in order to comply with the specification for moisture. Your response does not explain how limits on re-hydration time will be established.
 - iv) There is no documentation to show that in-process samples were taken and tested for moisture as instructed in the re-hydration procedure.
3. Failure to have written procedures that include steps to be taken to insure that reprocessed batches will conform with all established standards, specifications and characteristics, as required by 21 CFR 211.115. For example:
- a) The validation of the re-micronization process conducted in 1992 is not adequate.
 - i) The validation of the re-micronization process conducted in 1992 was approved even when one re-micronized lot (62239) failed to meet the

validation acceptance criteria for moisture. The validation report did not discuss the possible reason for this failure. The lot was re-hydrated, but it was not tested after re-hydration to determine compliance with all the required specifications, including particle size.

- ii) The protocol used for the validation of the re-micronization process conducted in 1992 did not specify the location and size of the analytical samples taken and tested to determine conformance to established specifications. The same protocol requested additional samples from top, middle and bottom of container for particle size analysis only. Only one of the validation lots was analyzed for this purpose and there is no evidence to show that the top portion of the container was analyzed.

Quality System

4. Failure of the quality control unit to conduct an adequate and timely review and approval of production and process control procedures designed to assure your drug products have the required identity, strength, quality and purity as required by 21CFR 211.100 (a). For example:
 - a) The quality control unit did not ensure that production and process controls designed to assure that Dantrolene Sodium consistently meets particle size and moisture specifications were established and validated in a timely manner.
 - b) The quality control unit failed to evaluate, in a timely manner, the need for revalidation of production and process controls that were retrospectively validated in 1984 for the following products: Furadantin Oral Suspension, Dantrium Capsules 25, 50 and 100 mg, and Macroductin Capsules 25, 50 and 100 mg. The date proposed in your response for completion of the revalidation for these products (by the end of June 2002) is not acceptable.

We acknowledge receipt of your response to the FD-483, dated March 16, 2001. Our evaluation of the response finds that, except for the items listed above, the proposed corrections will satisfactorily address the observations if adequately implemented.

Neither this letter nor the list of inspectional observations is meant to be an all-inclusive list of deviations at your facility. It is your responsibility to ensure that

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your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations and standards. 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 your responses to the violations identified in this letter. Corrective actions addressed in your letter may be referenced in your response to this letter as appropriate. Failure to promptly correct these deviations 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 Avenue, San Juan, Puerto Rico 00901-3223, Attention: Mary L. Mason or Rebeca Rodríguez, Compliance Officers.

Sincerely,



Mildred R. Barber
District Director

Cc:

Ramón Sepulveda

Vice-president/ General Manager

Procter & Gamble Pharmaceuticals Puerto Rico, Inc.

Highway 2 Km 45.7

Manatí, P.R. 00674