



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D1148 B

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223

January 31, 1997

WARNING LETTER
SJN-97-03

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Daniel Lebron
President and General Manager
Searle and Company
GPO Box 363826
San Juan, Puerto Rico 00936

Dear Mr. Lebron:

During an inspection of your drug manufacturing facility located at Caguas, Puerto Rico conducted from October 8 to December 12, 1996, our investigators documented deviations from the Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Part 211) in conjunction with your firm's manufacture of tablets and capsules causing these drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, as follows:

1. You have failed to validate the manufacturing process for Norpace (disopyramide phosphate) Controlled Release Capsules {21 CFR 211.110 (a)} for the following reasons:

- The process is not reproducible. There is no fixed method of [REDACTED] the beads. [REDACTED] is critical in giving the drug its sustained release characteristics. Sometimes beads are [REDACTED], sometimes [REDACTED] times and once [REDACTED] times. Sometimes, two or more batches of beads, which by themselves do not meet specifications, are blended together.

- The decision on how to manufacture any individual batch is made on a case by case basis depending on the in process dissolution testing of the beads. For this reason, the uniformity of the dissolution within a batch of beads as well as the representativeness of the in-process sampling and dissolution testing must be validated.

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- Coating with [REDACTED] the final step in the bead manufacturing process, should reduce the dissolution rate. However, your in process testing records say that on the [REDACTED] occasions listed on FD-483 observation 6c, the dissolution rate increased after a [REDACTED] step. This shows there is a problem in that either the [REDACTED] process is ineffective, there is no [REDACTED] of [REDACTED] within a batch of beads or the in process testing of the beads does not give an accurate picture of the [REDACTED] characteristics of the batch.

- Another concern is that the process has changed. Your firm's letter dated March 24, 1987, to FDA, Division of Cardio-Renal Drug Products says "In a small number of cases the desired dissolution profile cannot be achieved. *** In such cases 2 of these lots can be blended together in proportions calculated to yield the correct dissolution profile." Presently, lots must be blended in a large number of cases not in a small number of cases. Documents given to our investigator show [REDACTED] of [REDACTED] batches of beads manufactured between 1994 and 1996 were blended. / The reason for the change must be investigated.

2. Stability samples of Norpace/(disopyramide phosphate) Controlled Release Capsules, lot 5B453, failed dissolution testing at the [REDACTED] week time point. We agree with our investigators that your firm's investigation was inadequate and we do not agree with your conclusion that the failure was due to storage of the stability sample at 30° C rather than at 25 +- 2°C. Our review of the records leads us to conclude the subject lot failed stability testing and this lot does not meet the requirements of 21 CFR 211.137(a) because:

- The records at your plant show the stability storage room was at [REDACTED] for 9 days and at [REDACTED] for 20 days during February and March, 1996. The records say the stability storage room was at 25 + or - 2°C for the remainder of the storage time for this stability sample. We have seen no evidence that a slight (1 or 2°C) increase in temperature for a few [REDACTED] days causes capsules to dry out, become brittle and fail dissolution tests.

- There are no records of where this sample was located in the stability storage room and there was no documentation showing a lack of temperature uniformity in this room.

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- The [REDACTED] study you cited to support your position that storage at [REDACTED] caused the test failure showed little or no change in dissolution for capsules of acetaminophen after six months of storage in HDPE bottles at 40°C. The study showing a decrease in dissolution was for capsules stored in open dishes at 40°C and high humidity. Six months of data at 40°C can not be used to invalidate 29 days of data at 28-29°C.

The retained samples of lot 5B453 were stored below 25°C, not at 25°C.

3. Cytotec (misoprostol) tablets, lot 5S212, were released and distributed during January, 1996, although the finished product testing required by 21 CFR 211.165 (a) was not performed. The quality control unit failed to perform an adequate review of the records as required by 21 CFR 211.22 because this error was not noticed until October, 1996. We acknowledge that the corrective actions described in your December 27, 1996 letter and the actions promised during our meeting of January 29, 1997 appear to be adequate and if implemented will prevent a recurrence of this incident.

We acknowledge receipt of your letter, dated December 27, 1996. Your responses to FD-483 observations 3, 6, and 8 were not adequate for the reasons mentioned under items 1 and 2 above. The responses to the other FD-483 observations appear, if fully implemented, to adequately address the other concerns of the investigators.

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 letter 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.

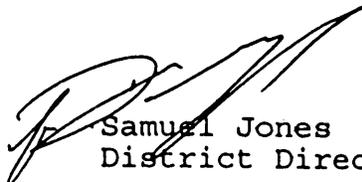
You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

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Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00906-5719, Attention: Philip R. Lindeman, Compliance Officer.

Sincerely,



Samuel Jones
District Director