



October 23, 2002

WARNING LETTER

SJN-03-03

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Mr. Peter R. Dolan
Bristol-Myers Squibb Manufacturing Company
Worldwide and North American Medicines
Chairman & Chief Executive Officer
345 Park Avenue, 44-61
New York, New York 10154-0037

Dear Mr. Dolan

During an inspection of your manufacturing facility located in Mayaguez, P.R.; conducted on July 03, 2002 to August 01, 2002, our investigator documented deviations from the current Good Manufacturing Practice (cGMP) Regulations (Title 21, Code of Federal Regulations, Parts 210 & 211). These deviations cause your drug products, Cholestyramine Powder for Oral Suspension (Regular) ["Questran Powder"], Cholestyramine Powder for Oral Suspension (Generic Version), and Estrace tablets, to be adulterated within the meaning of Section 501(a) (2) (B) of the Federal Food, Drug, and Cosmetic Act.

The cGMP violations documented during the most recent inspection include:

1. Failure to adequately validate the manufacturing processes for your drug product, Cholestyramine Powder for Oral Suspension (Regular), to assure uniformity and homogeneity in that you did not assess the adequacy of the mixing and filling processes and establish accurate mixing time limits. [21 CFR 211.110(a) (3); 21CFR 211.111]
 - a. No content uniformity samples are collected after the product is mixed and prior to being transferred to the holding tanks used during the filling operation, or throughout the filling operation. Thus, there is no assessment that the mixing process produces a homogeneous product and that the filling operation does not cause segregation of powder product. (483 items #5b, c)
 - b. The manufacturing process validation for Questran Powder does not address the capability of the process to produce a homogeneous drug product in that the mixing time of the powder product is not established. Your manufacturing process controls are inadequate in that if, after the product is mixed and sampled during three different intervals, the results of any of these samples are out of specification for the assay test, your manufacturing instructions allow you to continue mixing (up to seven more minutes) until the results are within specifications. (483 item #5a)

2. Failure to have adequate laboratory controls in that once stability samples are found out of specifications and confirmed by re-test, you continue testing additional samples until passing results are obtained to conclude that the lot is within specification. [21 CFR 211.160; 21 CFR 211.166]
 - a. Cholestyramine Powder for Oral Suspension (Regular), lot [REDACTED] failed to meet the assay specification for Cholestyramine content at the [REDACTED]-month testing point as part of the stability studies of the product. The assay result of samples tested as part of the out-of-specification (OOS) investigation, dated 09/17/01, also showed several OOS results, confirming the initial results. You reported passing results for this [REDACTED]-month interval by averaging the original OOS results obtained with results within specification obtained during your investigation. This acceptance procedure is against your procedures and against the controls expected from a Quality Assurance Unit. (483 item #4)
 - b. Estrace tablets 2-mg, lot [REDACTED], in 500 tablets multi-dose container, were found with out-of-dissolution-specification (OODS) results at the [REDACTED]-month [REDACTED]C stability interval. The OODS results were observed during stages one and two of the dissolution test but not in the re-test results when a new and sealed bottle was used. You failed to investigate and determine why the original 500 tablets bottle failed during two consecutive tests. Instead, you dealt with this [REDACTED]-month-dissolution stability test by invalidating the original results and reporting the average of [REDACTED]-new results, all obtained from a new bottle. This acceptance procedure is against your written procedures and fails to represent actual product shelf life conditions. (483 item #6)

We evaluated your written response, dated August 16, 2002, to the FDA form 483, list of inspectional observations, and the additional information you provided during your meeting with us on October 17, 2002. We conclude that you have not satisfactorily addressed all of the noted deficiencies. Regarding your response to 483 item #4, it is unacceptable to release lots reporting initial out of specification results by testing additional samples, followed by the averaging of all results, i.e., those outside specification and others within specification. It is also unacceptable to apply the acceptance criteria of content uniformity in evaluating assay results to justify your practice of retesting and averaging results. We are requesting that you review all your initial out of specification results that were retested and averaged to obtain a final passing result and provide us, in your response to this warning letter, with a detailed description of the corrective action taken for the batches that were affected by your practice. We also expect to receive your written commitment to stop your retest and averaging practice.

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We are also requesting additional clarification regarding your sampling technique and procedure used to obtain samples for assay of the finished product. Your procedure appears to be inadequate in that it does not address potential differences in assay results that may occur relative to the location of sample collection (i.e., at the beginning, middle, or end of the process). Any difference that appears to be related to sample location may indicate the need to reevaluate your manufacturing process for this product.

Regarding your response to 483 item #5, please provide us, in your response to this warning letter, with the revised acceptance criteria you are using in your revalidation, along with a copy of your validation protocol. In addition, please clearly describe if, according to your response to 483 item #6, the bottle used per each stability interval will be the same bottle or a different bottle. You must have data that represent actual product usage and support the effectiveness of actual product packaging. We are also requesting any additional supporting documentation you have to show that Estrace tablets lot [REDACTED] meets specification and your action plan to assure that the lot remains in compliance.

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. Additionally, pending [REDACTED] NDA, ANDA, or export approval requests may not be approved until the above violations are corrected.

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.

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 recurrence of these or similar violations.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernández Juncos Ave., San Juan, Puerto Rico 00901-3223, Attention: Marisol Faberllé, Acting Compliance Officer, or Carmelo Rosa, Compliance Officer.

Sincerely yours,



Evelyn Bonnin
Acting District Director