DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

May 8, 2000

WARNING LETTER
SJN-00-09

Mr. John Nine
President, Technical Operations
Schering Laboratories
Schering-Plough Corporation
2015 Galloping Hill Road
Kenilworth, New Jersey 07033-0503

Dear Mr. Nine:

From November 30, 1999 to March 28, 2000, our office conducted an inspection of your human and veterinary pharmaceutical manufacturing facility, Schering-Plough Products, LLC, Road # 686, Km. 0.5, Manati, Puerto Rico. Our evaluation of the information obtained during the inspection determined that the pharmaceutical products manufactured at 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 perform adequate investigation into the cause of out-of-specification results for stability testing of 11 stability stations for 4 different lots of Gentocin® Ophthalmic Solution and 5 stability stations for 3 different batches of Garamycin® Opthalmic Solution, as required by 21 CFR 211.192. Tests for these stations showed out-of-specification results for the presence of benzalkonium chloride. These Out-of-Specification (OOS) results were attributed to problems (probably non-homogeneous packing) with the HPLC column used to test the samples. Based on this conclusion, special composite samples of the lots were prepared from retain samples and tested on a different column. The original OOS results were discarded and the passing results of the composite re-tests were used as the sample results. Our review of the system suitability tests for the column in question determined that the column had

satisfactory system suitability results when it was used to test the samples. During the inspection, the response provided to our investigators for the conclusion that the column was defective despite acceptable system suitability results was that the system suitability results were not necessarily correct. In your written response letter, dated 4/17/00, you stated that the conclusion that the column was defective was partially based on the fact that, "...these batches were manufactured over a 3 year period with no previous BAC stability issues." This statement does not take the following information into consideration:

a. For batch #[redacted]f Gentocin® Ophthalmic Solution, samples for 3, 6, 9, 12, and 18 months at 25°C and 3 and 6 months at 35°C stations were all run on the column in question and all had OOS results when tested using your normal procedures. Your response does not indicate what previous stability history was on record for this batch.

b. For batch #[redacted]of Garamycin® Ophthalmic Solution, the 12, 18 and 24 months at 25°C stations were also run on the column in question. The results of testing at earlier stability stations would not necessarily lead to the conclusion that the product would pass at the next 3 stability test stations.

2. Inadequate laboratory controls as follows:

a. Failure to have documentation of Method Validation for the stability assay method for Trilafon® Injection.

The conclusion of investigations into OOS results for stability testing on two different batches of the product was that the results were caused by high variability of the test method. Your firm was unable to produce any records concerning the validation of this analytical method. 21 CFR 211.194 (b) requires that the suitability of all testing methods shall be verified under actual conditions of use and that the records of determination of the suitability of the method shall be identified in the laboratory records.

b. Failure to document changes to written specifications and to have the changes approved before implementation as required by 21 CFR 211.160 (a). For example:

i) Some analysts were observed preparing a composite sample from units of stability retain sample for the stability assay of benzalkonium chloride in Garamycin® Opthalmic Solution. Other analysts reported using a single unit to prepare the sample. The test records do not indicate whether the sample tested was from a single unit or a composite from several units. Analysts stated that they use either of the methods of sample preparation.

ii) In performance of the Uniformity of Spray Content Assays for Vancenase AQ® and Nasonex® Nasal Suspensions, when out-of-specification results were obtained, analysts were instructed to remove the spray tips of the bottles and wash with methanol before running a re-test. This step is not included in the written procedures. In addition, the results of re-tests are averaged and used to replace individual OOS results in the original report of results. This is contrary to the objective of content uniformity testing, which is to determine the variability of results among a number of sequentially tested, randomly selected samples.

c. Failure to maintain complete data from all laboratory tests as required by 21 CFR 211.94 (a). There is no back-up file for laboratory UV spectrophotometer test results for some tests. The spectrophotometer does not automatically back-up data and the analyst is required to assign an identification number to each individual chromatogram in order for it to be saved. In some cases, original data was lost and the tests had to be performed again to determine final distribution of the lots.

3. Failure to follow written procedures for cleaning of equipment in accordance with 21 CFR 211.67 (b). For example:

a. For lot #[redacted] of Banamine® Solution, a veterinary injectable product, green fibers were found in the finished product. Investigation into the source of the fibers determined that the fibers came from green scouring pads used in the early steps of the cleaning operation. The use of the pads is not part of the validated cleaning procedure for this product. Your firm's corrective action was to reject those vials of product with visible particles and to release the remainer of the lot for distribution. Although the letter in response to the FD-483 states that the sterility of the batch is not considered a concern, it does not address the issue of why employees perform operations which are not a part of the validated process.

4. Failure to test drug product components to assure they meet current specifications in accordance with 21 CFR 211.84 (d)(2). For example:

   a. The hexane extractable specification for [redacted] per pump in the pump assemblies for Vancenase AQ® was changed from [redacted] of pump to [redacted] of pump in July, 1998. Several lots of pump assemblies were tested and released by the contract laboratory using the old specification after the new specification was approved. These pump assemblies were used to manufacture several batches of product which were partially distributed. The investigation into this incident determined the cause of the problem to be inadequate communication of the new specifications to the testing laboratory. Although your response addresses the issue of the quality of the products released under these conditions, it does not address any corrective actions with regard to improving communications within the various departments responsible for testing and release of components.

5. Failure to use reliable, meaningful and specific test methods for stability testing of drug products as required by 21 CFR 211.166 (a)(3). For example:

   a. New stability-indicating test methods have been developed and approved for Diprolene Gel® and Celestone Phosphate Injection®, but lots currently on stability are still tested using the previously approved methods, which are not stability-indicating. In the response to the FD-483, your firm stated that any products which were placed on stability before the approval of the revised methods would continue to be tested with the previous methods, even if the testing occurred after approval of the new methods. This policy is not in accordance with the objective of obtaining the best information available concerning the quality of products currently on the market.

We acknowledge receipt of your firm's letter of response to the FD-483, dated 4/17/00. Our review of this letter finds that the responses to FD-483 observations # 1 c), 2 a & b), 3, 4 b), and 10 are acceptable. Unresolved issues concerning observations # 1 a),b), d) & e), 4 a), 5, 6, and 7 are discussed in the body of the letter above. The responses to observations # 8 & 9 are being reviewed by our Pre-approval Manager.

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 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 Ave., San Juan, Puerto Rico 00901-3223, Attention: Mary L. Mason, Compliance Officer.

Sincerely,

Mildred R. Barber
District Director