DEPARTMENT OF HEALTH & HUMAN SERVICES M842M

Public Health Service
Mid-Atlantic Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (201) 331-2909

April 21, 1997

WARNING LETTER

Mr. Eric P. Milledge
President
Ortho-McNeil Pharmaceuticals
1000 Route 202
Raritan, New Jersey 08869

File No. 97-NWJ-31

Dear Mr. Milledge:

During a comprehensive inspection of your manufacturing facility located at 1000 Route 202, Raritan, New Jersey, conducted January 13 - March 5, 1997, Investigators from this office documented serious deviations from current Good Manufacturing Practice Regulations (cGMPs), Title 21, Code of Federal Regulations (CFR), Parts 210 & 211. These deviations were noted on the Form FDA483, List of Inspectional Observations, issued at the close of the inspection.

The above-stated inspection revealed that drug products manufactured at your facility are considered adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug & Cosmetic Act (ACT), in that the methods used in, or the controls used in manufacturing are not in conformance with cGMPs, as follows:

1) Manufacturing process validation for several product lines were found to be inadequate, for example:

- Grifluvin Tablets - four out of [redacted] batches made in 1995-1996 were rejected for failure to meet dissolution requirements. As a result of your investigation, process changes were made and not validated. The original validation, conducted in 1989, did not consider the critical process parameters to be evaluated. Other process parameters were not evaluated including the effect of additional drying steps and ranges established for mixing times, granulation and temperature.

- Ortho Cyclen Tablets and Micronor Tablets - a matrix approach was used, allowing production batches made at mixed sites and not sequentially manufactured, to be used in support of process validation.

RELEASE

REVIEWED BY [illegible] 4/21/97
C.O. DATE

- There is no validation data to support bulk storage and filling process for Grifulvin Suspension, Retin-A Gel & Liquid and Terazol Cream.

- Deficiencies were noted with validation batches of several low dose products, such as Ortho Novum 1/35 Tablets, Modicon Tablets and Norgestimate Tablets, in that there was no justification for samples sizes taken to evaluate blend uniformity. These samples were not representative of unit dose weights.

- Antimicrobial preservatives were not evaluated in the validation studies for several product lines of creams, such as Retin-A and Terazol. Additionally, analytical methods and/or specifications have not been developed for antimicrobial preservatives.

- Packaging validation studies have yet to be conducted for Grifulvin Tablets, Sultrin Tablets and all oral contraceptive products.

General deficiencies were noted during the review of validation protocols and batches for several previously validated products, in that there was no data to support established process parameters, such as mixing speeds and times, temperature ranges, additional drying steps and demonstrating biobatch equivalency.

2) The practice of accepting supplier tare weights for raw materials allowed for weight variability of materials used in production batches and resulted in process deviations. During a monthly tare weight check, it was determined that the suppliers tare weights for Anhydrous Lactose NF were outside your firm's allowable range. This resulted in an additional 2kg per batch of Anhydrous Lactose NF in the production of multiple batches of oral contraceptives.

The investigation of this process deviation resulted in a decision to increase the allowable range for supplier drum tare weights.

3) Re-test procedures were found to be inadequate, in that out of specification results are included in a grand average used to determine product release, for example:

- Internal action limits were exceeded during the testing of antimicrobial preservatives in several lots of Grifluvin Suspension. Retest procedures allowed for

averaging the out of specification results with four retests results. Products were released based on the average of five test results without determining the assignable cause of the initial out of specification result.

4) Retest investigations were incomplete in the determination of assignable cause and/or lacked documentation to invalidate initial out of range results, for example:

- An initial out of specification assay for Grifulvin 500mg Tablets, Lot 15E238 was invalidated without adequate documentation to support the conclusion that a pipetting error occurred.

- An initial out of specification and four retest assays results for Grifulvin Suspension, Lot 16C745, were invalidated based on an investigation which determined low results were due to improper sample preparation. A new mother sample was prepared for additional retests, which were within specification and the lot was released. There was no data or adequate documentation to support the conclusion that the initial sample was improperly prepared.

- An initial out of specification assay result for Ortho-EST Tablets, Lot 13L115 was invalidated based on the analyst's conclusion that the samples evaporated. The lot was released based on retest results which were within specifications. The retest results were not included in the investigation and there was no documentation to support invalidation of initial results.

5) The decision to release Grifulvin Suspension Lot 16A723 did not follow established Retest procedures, for example:

- One sample injection of Griseofulvin assay for Grifulvin Suspension Lot 16A723 was out of specification when initially tested and upon retesting. The lot was released on an average of five test results. There was no Exception Control report generated to support the decision to release this lot.

- The investigation of this event was incomplete and deviated from the retest procedure, in that it did not include an evaluation of the manufacturing process or raw materials.

As a general comment, it was noted that Annual Product Reviews do not consider product retesting as a factor in evaluating product compliance.

6) The change control system was utilized in lieu of adequate validation data to support the release of some production batches, which were made outside of established processes or procedures, for example:

- Ortho Cyclen Tablets, Lot 16M647 was originally designated as R & D batch PE 1301. Changes were made during manufacturing which deviated from the validated process. After routine QC testing, this lot was converted to a production batch.

- Changes were made in the temperature of the [redacted] preparation used for Grifulvin 250mg Tablets. These changes were implemented as a process improvement after several lots failed to meet dissolution specifications. These changes have not yet been validated.

- Changes were made in the cleaning/sanitization procedures for equipment used to manufacture Terazol Suppositories. Only one lot was used in support of these changes which were implemented when Terazol Lot 14N073, failed microbial specifications.

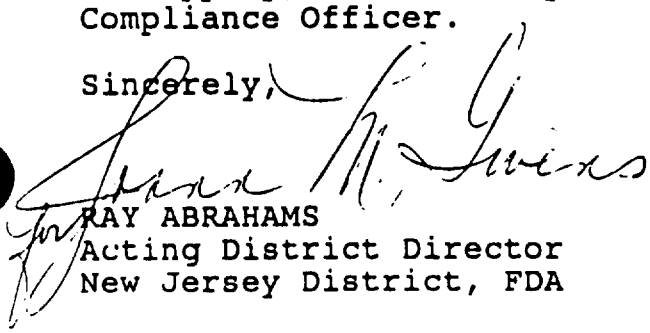
The above list is not intended to be all-inclusive of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued to that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deficiencies. Failure to implement corrective measures may result in regulatory action, including seizure and/or injunction, without further notice.

We are in receipt of your written responses, dated March 18 and April 9, 1997 to the FDA483 list of Inspectional Observations. Generally, your written responses and commitments made during a meeting with New Jersey District on April 16, 1997, find that corrective measures are already being implemented. A reinspection will be needed to verify these corrections.

We recognize that your on-going project to revalidate older product lines, bringing them in-line with current standards, will resolve the majority of noted deficiencies with respect to product validation. A more timely effort in this regard may have averted such deficiencies.

You should notify this office in writing, within 15 working days of receipt of this letter, of the additional steps you have taken to correct the noted deficiencies, including an explanation of each step being taken to prevent the recurrence of similar conditions. If corrective action cannot be completed within 15 working days, state the reason for the delay and timeframe within which corrections will be completed. Your reply should be sent to the New Jersey District Office, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attention: Mercedes B. Mota, Compliance Officer.

Sincerely,



RAY ABRAHAMS
Acting District Director
New Jersey District, FDA

CERTIFIED MAIL -
RETURN RECEIPT REQUESTED

MBM:np