



DEPARTMENT OF HEALTH & HUMAN SERVICES

MD 2807
Public Health Service

Central Region

Telephone (973) 526-6008

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

WARNING LETTER

Certified Mail
Return Receipt Requested

File # 99-NWJ-08

December 14, 1998

Carter H. Eckert
President
Knoll Pharmaceutical Co.
3000 Continental Drive North
Mount Olive, NJ 07828

Dear Mr. Eckert:

During the October 5, 1998 through November 4, 1998 inspection of your facility at 30 North Jefferson Road, Whippany, NJ 07981, our investigator documented deviations from Current Good Manufacturing Practices for Finished Pharmaceuticals (Title 21, Code of Federal Regulations). These deviations cause your drug products,

Vicoprofen Tablets
Vicodin Tablets
Vicodin Extra Strength Tablets
Isoptin Sustained Release Tablets
Rythmol Tablets
Mavik Tablets and
Vicodin Tuss Liquid

to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act. The deviations included:

- Your firm released one lot of Vicoprofen Tablets prior to validation of the manufacturing process. That lot was initially a cleaning validation batch, which was disqualified for a reason you were unable to disclose to our investigator. The process validation for Vicoprofen Tablets was conducted on three consecutive lots manufactured following the release of the disqualified lot
- Your firm's process validation for Vicoprofen Tablets is inadequate. Disqualified batches are not identified in the validation report. The validation protocol did not specify lot

numbers and amendments and addenda to the protocol did not allow for the provision of resuming validation via three consecutive lots following a disqualified or failed batch.

- Your firm released one lot of Vicodin Tablets despite out-of specification results for content uniformity (for Acetaminophen) and relative standard deviation. The retest for content uniformity was incorrectly performed, per the USP procedure, resulting in out-of-specification results for both Acetaminophen and Hydrocodone Bitartrate for assay. A second re-test was performed incorrectly in that the previous product sample was used with a new standard. In addition, the product had failed three specifications prior to being re-tested the second time.
- Your firm's quality control/quality assurance unit failed to adequately investigate out-of-specification results for Ibuprofen USP active pharmaceutical ingredient, Vicodin Tuss Liquid finished product, and Vicoprofen in-process tablet cores. Your firm's documentation of the three above examples does not support the investigational conclusions.
- Your firm is not performing periodic monitoring of cleaning validation for Isoptin Sustained Released, Rythmol, Mavik, Vicodin, and Vicoprofen Tablets according to the schedule established and proposed to the Agency .
- Your firm's cleaning validation plan for drug active ingredients used in the Lodige 600L mixer is inadequate in that the mixer's plough blades are not identified as a sampling site. The cleaning validation plan is also inadequate in that one swab per equipment piece is made for residual solvents.
- Your firm's equipment qualifications for the Amsco SG-116 autoclave and the computer control system for the 60" film coating pan were inadequate.

The above deviations are not intended to be an all-inclusive list of violations. As a manufacturer of drug products for human use, you are responsible for assuring that your overall operation and the products you manufacture are in compliance with the law. It is your responsibility to assure adherence with each requirement of the Current Good Manufacturing Practices. Federal agencies are advised of the issuance of all Warning Letters concerning drugs so that they may take this information into account when considering the award of contracts. Additionally, pending Antibiotic Form 6, New Drug Applications, Abbreviated New Drug Applications, or export approval requests may not be approved until the above violations are corrected.

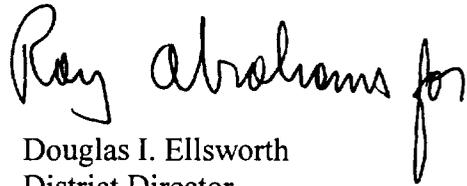
You should take prompt action to correct the above violations and to establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice such as seizure and /or injunction.

You should notify this office in writing, within 15 working days upon receipt of this letter, of the steps you have taken to bring your firm into compliance with the law. Your response should include each step being taken that has been taken or will be taken to correct the violations and prevent their recurrence. If corrective action cannot be completed within 15 working days, state

the reason for the delay and the time frame within the corrections will be completed. Please include copies of any available documentation demonstrating that corrections have been made.

Your reply should be directed to the Food and Drug Administration, Attention: Kirk D. Sooter, Compliance Officer, at the address and telephone number above.

Sincerely yours,

A handwritten signature in black ink that reads "Ray Abrahams for". The signature is written in a cursive style. The word "for" is written in a smaller, simpler font at the end of the signature.

Douglas I. Ellsworth
District Director