



DEPARTMENT OF HEALTH AND HUMAN SERVICES

D1357B
Food and Drug Administration
Atlanta District Office

HA-35 (BSC)

60 8th Street, N.E.
Atlanta, Georgia 30309

January 8, 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Jeffrey S. Kiel
President
Kiel Laboratories, Inc.
2225 Centennial Drive
Gainesville, Georgia 30504

WARNING LETTER

Dear Dr. Kiel:

An inspection of your drug manufacturing facility was conducted on November 10-26, 1997, by Investigator Robert L. Lewis. Our investigator documented several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

You have failed to adequately validate the manufacturing processes for all of your drug products. You could not provide documented evidence which established a high degree of assurance that the manufacturing processes in use could consistently produce products meeting their predetermined specifications and quality attributes, both initially and throughout their labeled expiration date. The validation lots for BIOHIST-LA tablets (lots GA 099 and GA 101) were noted to have multiple room and accelerated temperature stability failures. These failures were observed in dissolution and assay testing performed at one, two, and three months. Failing dissolution values were also observed in initial analyses of tablets from both lots during the validation study. There were no documented investigations conducted by your firm into any of these failures. You could provide no evidence of any attempt to identify the source of these problems. These two lots were eventually distributed by your firm. The justification for that decision could also not be determined. ~~more~~ more lots of this product were distributed in October 1997, bearing a two year expiration date reportedly based on the deficient stability studies conducted on the two validation lots above.

No prospective validation was conducted for the manufacture of your Guaifenesin 600 mg./Pseudoephedrine HCL 60 mg. tablet or Guaifenesin 600 mg./Phenylpropanolamine 75 mg. tablet products. Several batches of both products have been manufactured and distributed. No formal validation protocol was ever established to include the specifications and acceptance criteria for the current manufacturing processes in use for these drugs.

The dissolution and content uniformity testing procedures in use are inadequate to monitor the output and to validate the performance of the manufacturing processes that may be responsible for causing variability in the characteristics of your drug products. These deficient laboratory methodologies are not sufficient to determine the satisfactory conformance of the drug products to final specifications prior to release for distribution.

Your firm's dissolution methodology fails to include any evaluation of data from individual tablets. This omission has caused the subsequent failure of your firm to recognize, and properly react to, finished product which fails to meet release specifications. Dissolution results are routinely calculated by the averaging of all values. This final average becomes the criteria used for product release of the lot. Numerous instances were noted where failing dissolution values were averaged with passing values to give final results which were then determined to meet specifications. No dissolution specifications have been established for any product which address the conformance of individual tablets.

The practice of averaging dissolution results was noted on production lots, validation lots, and stability samples. This aberrant method of analytical review was extrapolated to the point where your firm was averaging out of specification averages to get an acceptable result. Lot GA 264 (Guaifenesin 600 mg. tablets) was released after it was found to have an out of specification (OOS) dissolution average at the one hour time point. The product was ultimately released because the "cumulative average" of all one hour time points from all samples tested over a six day period was within specification. The justification memo for this release was signed by your Quality Assurance Manager and yourself.

Your firm's methodology for determination of uniformity of dosage units was determined to be inappropriate for four of the five products you manufacture. For the past two years, the uniformity has routinely been evaluated by using the ~~tablet weight variation~~. Four of your products, however, do not meet the United States Pharmacopeia (USP) criteria for the use of this test. These four products contain active ingredients which comprise less than 50% of the total weight of the tablet and/or contain less than 50 mg. of the active ingredient. This has raised the additional question of the quality of the validation data generated for your manufacturing processes, as content uniformity is an important consideration in the evaluation of these processes.

You have failed to appropriately investigate and respond to OOS results. Some of these failures are attributable to your firm's handling and averaging of dissolution results. Other examples include the failure to conduct any investigation into the numerous OOS results noted in the BIOHIST-LA validation lots discussed above. Your laboratory investigation procedures were

deficient in that they lacked the necessary specificity, such as defining what steps analysts should take in the event of an OOS result. The procedures also did not address how to document the investigation or the required steps involved in the investigation itself. There was no established system to notify management, conduct trending of laboratory or product problems, or initiate action in response to laboratory problems.

Your firm was noted to routinely release partial shipments of drug products prior to the completion of required testing of the batch and prior to completion of the review of all pertinent records relating to the batch. Although your firm regards multiple day production as a single batch, product is being released based on partial testing and limited review. Documentation practices and shipping records maintained made it extremely difficult to relate the product shown in shipping records to the date the product was actually produced and what records were reviewed prior to shipment. Some batch records were not documented as being reviewed until up to six months after portions of the lot had been distributed.

The current inspection was also conducted in conjunction with the review of [REDACTED] and [REDACTED]. In addition to the above deviations, additional significant deficiencies were noted specific to each of these [REDACTED]

Your firm has not justified the proposed manufacturing process or demonstrated that the process can yield acceptable tablets for [REDACTED]. Multiple content uniformity and assay failures were noted in biobatch GA 194. The data generated for the biobatch did not support the [REDACTED] manufacturing process. The biobatch was manufactured differently than the proposed commercial process. No hardness data was routinely collected for this or any other of your tablet products.

A review of the laboratory records for [REDACTED] revealed two sets of dissolution data related to the *in-vitro* comparative study of the biobatch with the innovator product. The set of data which failed dissolution specifications was not reported [REDACTED]. No justification or rationale could be provided for this omission. The manufacturing process for exhibit batch GA 198 differed significantly from the proposed commercial process.

Missing raw data was noted for [REDACTED]. This included chromatograms and a back up diskette which contained original laboratory data for the comparative dissolution study, in addition to content uniformity and dissolution data from biobatch GA 185. Although no in-process hardness data was collected, dissolution data was collected from "low compression" tablets. These tablets had reportedly been determined to be soft tablets utilizing a hand test. Your firm had also not physically characterized the active pharmaceutical ingredient used in the biobatch.

[REDACTED]

Many of the above deviations were included on the FDA 483 (Inspectional Observations) which was issued to, and discussed with, you at the conclusion of the inspection. The violations noted in this letter and in the FDA 483 could be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

We are in receipt of your written response, dated December 11, 1997, to a portion of the FDA 483. The response addressed the general GMP portion of the FDA 483 and not the [REDACTED] specific observations. We continue to have concerns about several of the issues discussed in your response. A detailed response to your December 11 letter will be forthcoming.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of any additional steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should include what steps you plan to take, such as retroactive record review to address the observations which directly relate to the performance, uniformity, quality, and stability of products currently in distribution. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely,


Ballard H. Graham, Director
Atlanta District