



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office

D1102B

HEI-35

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

January 16, 1997

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Miguel I. Arteche
President
Mikart, Inc.
2090 Marietta Blvd.
Atlanta, Georgia 30318

WARNING LETTER

Dear Mr. Arteche:

An inspection of your drug manufacturing facility was conducted on November 18-25, 1996, by Investigator Robert L. Lewis, Investigator Vincent M. Williams, and Chemist Don W. Thompson. This inspection was conducted in follow-up to the previous inspection in April/May 1996, when significant problems had been documented. The current inspection again revealed several significant deviations from the Current Good Manufacturing Practice for Finished Pharmaceuticals (CGMPs), as set forth in Title 21 of the Code of Federal Regulations, Part 211. These deviations cause your generic 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 maintain adequate documentation to substantiate the invalidation of out of specification (OOS) results obtained and that would support the conclusions made during OOS investigations in the stability and quality control laboratories. Between June 1996 and the dates of the inspection, [redacted] OOS investigations were conducted. Approximately [redacted] (70%) of these investigations were directly related to product potency and/or product quality. These investigations involved some type of finished and in-process product assay (blend, composite, content uniformity, and dissolution).

Of the [redacted] investigations which involved finished product samples, only once was the initial OOS analytical result reported as the true value. In all other instances, the initial laboratory OOS result was invalidated predominantly due to analytical error. These investigation results raise concerns about how these conclusions were reached by the laboratory and the ability of your laboratory staff to properly conduct the analytical testing required.

No attempt is made to evaluate the OOS results to detect similarities or trends (from an analyst, methodology, product line, or individual lot perspective) during these investigations. Our analysis of this investigational data revealed repeat failures for the same analytical test on the

same product lot and some test failures on consecutive lots of the same product. Examples of this include [REDACTED] Tablets lot C960728 (low assay), HBA Tablets lots 950172B and 950173B (low assay), HBA Tablets lot K951130E (low assay) and Pyrazinamide Tablets lot 940535E (low assay). We also noted finished product lots which failed multiple tests. Examples of this include Guaifenesin Tablets lot E960482B (low assay and low dissolution), HBA Tablets lot E960480 (high assay, high dissolution, high content uniformity), [REDACTED] lot D960384 (high dissolution, low assay, and low content uniformity), [REDACTED] tablets lot D960390 (low blend assay, low assay, and low content uniformity) and Pyrazinamide Tablets lot 940535E (low assay and high dissolution).

Sixteen of the investigations noted since June 1996 were randomly selected for in-depth review. Five of these investigations revealed limited retesting of the product, invalidation of the original OOS result, and reporting of only the repeat test values obtained. Entries such as "apparent sample prep. error", "it appears that" and "possible incomplete release of analyte" were noted in these investigational records. The assumptions made as to the reason for the OOS results were speculative at best, based on the sparse nature of the supporting documentation available. Many of these investigations were hindered due to the fact that standard solutions were routinely discarded prior to receipt of the analytical results. We are concerned that your OOS investigative methodology and conclusions of analytical error will conceal true product quality problems.

Other problems noted in the laboratories included the failure to document the rationale for not completing analysis, use of a reference standard with no documentation as to its stability, and failure to perform stability testing at two required stations.

We are cognizant of the fact that your firm has implemented a major corrective action plan since the previous inspection. Many of the problems noted during the previous inspection have been aggressively addressed since that time. However, significant CGMP discrepancies continue to exist at Mikart. The above deviations were included on the FDA 483 (Inspectional Observations) issued to and discussed with Ms. Cerie B. McDonald, Executive Vice President, at the conclusion of the inspection. A copy of the FDA 483 is enclosed for your review. 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.

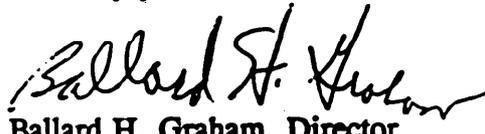
As we have previously brought to your attention, the deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. This is a fact which was evidently misunderstood by some Mikart personnel. It is your responsibility 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 the process of reviewing your firm's FDA 483 response presented at the December 16, 1996 meeting at the Atlanta District Office. A response to your letter will be forthcoming in the immediate future. We are appreciative that you took the initiative to meet with us to discuss these areas of continuing concern. We are also encouraged by the spirit of cooperation exhibited at that meeting by your management staff. As discussed in the meeting, we have decided to issue another Warning Letter at this time in lieu of pursuing other more stringent regulatory actions which could have been pursued. We have taken this approach in the hopes that Mikart will give this problem the full attention it deserves and immediately address these ongoing problems.

You are requested to notify this office within fifteen (15) days of receipt of this letter, of any additional steps you have taken, or intend to take, to correct these violations. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,



Ballard H. Graham, Director
Atlanta District

Enclosure