



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region *m3192n*

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 # 00-NWJ-08

November 19, 1999

Peter Tombros  
President and Chief Executive Officer  
Enzon, Inc.  
20 Kingbridge Road  
Piscataway, NJ 08854-3969

Dear Mr. Tombros:

During the July 8-22, 1999 inspection of your facility at 300-C Corporate Court, South Plainfield, NJ 07080, our investigator documented deviations from Current Good Manufacturing Practices for Finished Pharmaceuticals (Title 21, Code of Federal Regulations). These deviations cause your drug product Adagen Injection to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act. The deviations included:

1. Lot B11708 of Adagen Injection failed to meet established specifications for in-process tests for protein concentration and effluent activity, and finished product tests for protein concentration and final yield. This batch was released for distribution. This lot also was found to have unusually high numbers of vials observed with particulates. No documentation was present to indicate the particulate issue was investigated.
2. Seven lots of Adegan Injection failed to meet established specifications for three in-process tests. Five lots failed for protein value, four lots failed for effluent activity (including two lots, which failed that test at both sampling points), and four lots failed for modification assay. Of seven lots, one lot failed all three in-process tests and two lots failed two in-process tests. These lots were released for distribution.
3. Microbiological analyses for environmental samples of your Purified Water System failed action level specifications at two sampling sites on June 3, 1999 and one sampling site on June 7, 1999 and June 10, 1999. No investigation was performed into one of the June 3 incidents. The investigation attributed the failures on June 3, 7 and 10 to a leaking valve; however, no documentation exists to demonstrate the valve was repaired, and no sanitization

or additional cleaning of the water system was performed following encountering the failing results or repair of the valve.

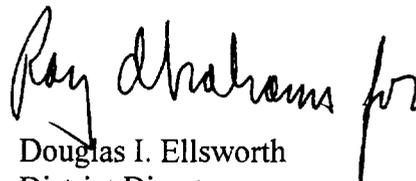
4. Extraneous HPLC peaks appeared in chromatograms for Adagen bulk, finished product, and stability samples; all of which were explained to be due to autoinjector contamination. Despite vendor cleaning of the autoinjector, the peaks continued to occur. No further investigation was initiated to determine the cause of the peaks. Two months later, more extraneous peaks were encountered at similar and different retention times to the previously encountered peaks and again explained by autoinjector contamination with no corresponding investigation. Of further significance is the statement made to our investigator that one of the extraneous peaks was corresponding to a by-product peak encountered on stability testing, enhancing the need for investigation and resolution of the problem.

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.

We have received your August 4, 1999 letter to this office and have evaluated the corrections offered in that letter. The District is satisfied with your corrective actions proposed for each of the above deviations and a response to this Warning Letter is not necessary. However, failure to implement the corrective actions and establish procedures to prevent their reoccurrence may result in regulatory action, such as seizure and /or injunction, without further notice. An inspection will be scheduled in the immediate future where we will determine the adequacy of your corrective actions.

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,



Douglas I. Ellsworth  
District Director