DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

FEDEX

WL No. 320-01-05

APR 11 2001

Damian Salvador
Director General
Omicron Quimica, S.A.
Carlos Buhigas, 5A, Pol Ind Can Castells
08420 Canovelles, Barcelona
Spain

Dear Mr. Salvador:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Barcelona, Spain by the United States Food and Drug Administration on December 18-20, 2000. The inspection revealed significant deviations from U.S. good manufacturing practices (CGMPs) in the manufacture of active pharmaceutical ingredients (APIs), and resulted in the issuance of a fifteen-item form FDA- 483 to you at the completion of the inspection. These deviations cause these APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

Additionally, a sample of [ ] collected by the U.S. Food and Drug Administration was also found to be adulterated within the meaning of Section 501(b), in that it purports to be and is represented as a drug, the name of which is recognized in an official compendium (United States Pharmacopoeia) and its quality and purity fall below the standard set forth in such compendium because it fails the official [ ] test.

The CGMP deviations, noted during the December 2000 inspection include, but are not limited to:

1. Laboratory tests and procedures were inadequate in that:

   a. Laboratory test methods fail to show that all batches of [ ] conform to appropriate specifications in that the method used is not scientifically appropriate. Specifically, the method used is substantially different than the method described in current compendia. The method used has not been demonstrated to be equivalent to the

current compendial method to determine that the product meets current compendial limits. Furthermore, [ ] equipment needed for the appropriate analytical method was not available.

b. The analytical methods used for stability testing of [ ] have not been demonstrated to be stability indicating methods. Additionally, stability samples were not stored under controlled conditions.

c. Raw data for the preparation of standards and reagents, sample weights, and dilution factors were not always recorded; laboratory worksheets were not always checked by a second individual and crossed-out data on the worksheets was not always observed to have been initialed and dated by the person changing the data. Furthermore, there was no documentation that analysts were trained to perform the laboratory analyses.

2. Various CGMP deviations were noted in the [ ] system that produces [ ] used in the manufacture of APIs. These deviations are as follows:

a. The [ ] system has not been validated.

b. There are no records showing that [ ] manufactured by this facility, or purchased from a supplier, was tested for microbiological specifications. However, the [ ] testing SOP indicates samples are to be collected for microbiological testing, but does not include a procedure for sampling the [ ] Furthermore, neither microbiological test results nor a microbiological test facility was observed on the premises.

c. Dead legs were observed in the [ ] system and there is no temperature control on the storage tank located outside of the building.

3. Batch production records were inadequate in that:

a. Some batch records lacked signatures of the person performing specific steps, the time performed, and verification by a second individual.

b. Batch records lacked actual yields and expected yield at appropriate phases of processing.

4. Documentation of process validation for [ ] was inadequate in that the report indicates that the prospective study was performed in 2000, yet the batch numbers indicate that the validation batches were manufactured in 1997. The validation records lacked operator identification, dates of processing, and signature or date of the person approving the report.

To date we have not received a written response from your firm regarding these CGMP deviations. The CGMP deviations identified above or on the FDA-483 issued to you are not to be considered as an all-inclusive list of deficiencies at this facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish

to continue to ship your APIs to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for current good manufacturing practices.

Please respond to this letter within 30 days and provide documentation regarding correction of the above deviations. Until FDA has reinspected this facility and confirms compliance with CGMPs and correction of these deficiencies, this office will recommend withholding approval of any new drug applications listing this facility as the manufacturer of APIs. If corrections are not initiated promptly any API manufactured by this facility may be denied entry into the United States.

Please direct your written response to Compliance Officer Randall L. Woods at the address shown below. Please reference CFN# 9614126 within your response and provide English translation of the documents submitted.

U.S. Food & Drug Administration
CDER HFD-324
7520 Standish Place
Rockville, MD 20855-2737
Tel: (301) 827-0065
FAX (301) 827-0145

To schedule a reinspection of this facility after corrections have been completed and it is in compliance with CGMPs, contact: Director, International Drug Section, HFC-133, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857, Tel. (301) 827-5655 or FAX (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing & Product Quality
Center for Drug Evaluation & Research