DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

FEDEX

WL No. 320-01-10

JUN 28 2001

Dr. Cynthia Sicchieri
Director of Technical Development
FIDIA s.p.a.
Via Ponte della Fabbrica, 3/A
35031 Abano Terme – Padova
Italy

Dear Dr. Sicchieri:

This is regarding an inspection of your pharmaceutical manufacturing operations in Padova, Italy, by Investigator Jorge Guadalupe and Microbiologist Chryste' Best, on March 12-19, 2001. The inspection revealed significant deficiencies which cause your pharmaceutical products to be adulterated within the meaning of Section 501(a)(2)(A)) of the Federal Food, Drug, and Cosmetic Act in that these products have been prepared under unsanitary conditions whereby they may have been rendered injurious to health, and within the meaning of 501(a)(2)(B) of the Act in that they were not manufactured in conformity with current good manufacturing practices as defined in 21 CFR 210 and 211. These deficiencies were listed on a form FDA- 483 issued to you at the completion of the inspection.

Specific areas of concern include, but are not limited to:

1. Trace back of the supply chain was inadequate in that you have not verified the integrity of the brains used as a raw material in the manufacture of [redacted] in regard to the species (bovine), country of origin, feeding and disease control practices of the originating dairy farm(s), and the possibility of contamination with BSE causative agent. Bovine brain material was accepted based only on review of import documents such as the shipper's declaration and certificates of origin of the materials. No audit of the supply chain was conducted to verify the certificates.

   CGMPs require assurance that the brain material used in the manufacture of the drug product is of appropriate quality. In the absence of a confirmatory test to establish that the brain material was of bovine origin, and that it was free from Bovine Spongiform

Encephalopathy (BSE) causative agent as a contaminant, we would expect you to audit your supply chain as part of the qualification of your supplier.

Your March 29, 2001 response provides a commitment to audit the supply chain for new material by the end of 2001, but does not address the material already manufactured. Please provide this office with an an inventory of all batches of _____ made using the old material and shipped to, or intended for shipment to the U.S. Also, advise us of any action your firm plans regarding the disposition of any of this material which may still be available for clinical use.

2. No positive control was used in the [_____] for active ingredient lots [____] and [____]

Our inspection revealed that your firm did not use a positive control in the [_____] for active ingredient lots [____] and [____] either at the early analyzable stage of the manufacturing process corresponding to [_____] or at the end of the manufacturing of the bulk product. This is an important test intended to detect the possible introduction of BSE causative agent into the drug product. You were advised of this deficiency in an IND deficiency letter on 6/8/1993, and a reminder letter on 12/14/1998.

Your response provides a commitment for execution of the test by April 30, 2001. However, your proposed corrective action does not provide adequate assurance regarding the safety of the bulk batches [____] and [____] and the finished product produced from these bulk batches and still available for clinical use.

3. Validation of the batch release and stability test methods for assay and impurities was inadequate in that your study did not include demonstration of accuracy, specificity, range, ruggedness, robustness and system suitability.

Your response commits to complete a revalidation study by 6/15/2001. Please provide English translation of the method validation protocol and report, including results of forced degradation and any other studies conducted in determining impurities in the bulk drug product.

4. Cleaning validation studies for the multi-use process equipment were inadequate in that
   - The cleaning procedure did not specify the quantity and time for rinsing the [____] machine components therefore any organic residue found can not be quantified
   - Swab sampling was not representative of the total surface area of the [_____] as three swab samples from three different washings were collected from the same location (middle of the [____]
   - No recovery data for swab samples was available.

Your response, commits to revalidate cleaning procedure for the [____] machine and [_____] by 6/30/2001. Please keep this office advised of the status of these corrective actions and submit copies of the final study protocols and reports when they are completed.

The CGMP deviations identified above or 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 bulk or finished drug products 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 and provide a status report on the ongoing corrective actions within 30 days. 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. Failure to promptly correct these deficiencies may result in the refusal to permit entry of these products into the United States.

Please direct your written response to Compliance Officer Muralidhara Gavini at the address shown below. Please reference CFN# 9610200 within your response.

U.S. Food & Drug Administration
CDER HFD-322
7520 Standish Place
Rockville, MD 20855-2737
Tel: (301) 594-0095
FAX (301) 594-1033

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

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