DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

WARNING LETTER

FEDEX

WL No. 320-04-01

JAN 15 2004

Martin Borovicka
CEO & Vice-Chairman of the Board
Aliachem A.S.
532 17 Pardubice-Semtin
Czech Republic

Dear Mr. Borovicka:

This letter is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in the Czech Republic, by the United States Food and Drug Administration (FDA) on September 8-10, 2003. The inspection revealed significant deviations from U.S. current good manufacturing practice in the manufacture of APIs. These deficiencies were listed on a Form FDA- 483 issued to[ ] Manager Organic Chemicals Strategic Business Unit, at the completion of the inspection. These deviations cause the APIs manufactured by your firm to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. 21 USC § 351(a)(2)(B). Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice. Failure to comply with current good manufacturing practice constitutes a failure to comply with the requirements of the Act.

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

1. Several batches of finished API are[ ]in a[ ]to produce one larger batch. The individual batches are not tested for residual solvents and found to meet appropriate specifications prior to[ ]This process has not been validated for[ ]of the combined batch. The[ ] batch is tested for residual solvents, but the sampling method, one composite sample, does not provide evidence of[ ]

2. Laboratory records do not include all raw data. For example, weights determined during the preparation of standard solutions were not recorded and

[ ]data was omitted from[ ]calculations during methods validation.

3. Critical production deviations may not have been investigated and documented. Of 235 deviations logged in so far this year, only one was fully investigated and documented. Those not investigated included the failure of one production lot to form product crystals and another production lot that yielded 30% below the expected volume.

4. Production equipment was not designed to minimize contamination and was not maintained in an adequate state of repair. Extensive oxidation was observed on numerous pieces of equipment. Open[ ]used to[ ]did not protect the product from possible external contamination from overhead paint chips and oxidized pipes. In addition, the[ ]were not listed in your Drug Master File which states[ ]are used for this production step.

Similar deficiencies regarding maintenance of equipment, in-process sampling, and incomplete records were observed during the previous inspection of this facility in August 1997. The facility was named Synthesia S.P. at that time.

We have reviewed your September 29, 2003 written response to the Form FDA-483. Although this response indicates you plan to correct these deficiencies, it does not provide sufficient information about how they will be corrected or how similar problems with other equipment, processes, and recordkeeping practices will be detected and corrected, and how your firm will prevent recurrence of these deficiencies. The response does not provide documentation that any of the deficiencies have been corrected. The cGMP deviations identified above or on the Form FDA-483 issued to you are not to be considered an all-inclusive list of deficiencies at this facility. FDA inspections are audits, which are not intended to determine all deviations from cGMP that exist at a firm. It is the responsibility of your firm to assure compliance with all U.S. standards for current good manufacturing practice. If you wish to continue to ship APIs to the United States, you should evaluate all equipment and written procedures, and your employees' adherence to written procedures, for compliance with these standards.

Please respond to this letter within 30 days of receipt regarding the specific steps you have taken to correct the noted violations, including an explanation of each step taken to prevent the recurrence of similar violations. Please submit documentation, with English translation, of these corrective actions. Until FDA has reinspected this facility and confirms compliance with cGMP and correction of these deficiencies, this office will recommend withholding approval of any new drug applications listing this facility as the manufacturer of APIs. Failure to promptly correct these deficiencies may result in the refusal to permit entry of these APIs or finished products made from these APIs into the United States.

Please direct your written response to Compliance Officer John M. Dietrick at the address shown below. Please reference FEI# 3002675552 within your response.

U.S. Food & Drug Administration
CDER HFD-325
11919 Rockville Pike
Rockville, MD 20852
Tel: (301) 827-9021
FAX (301) 827-8909

Please note that a guidance document entitled "Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" (ICH cGMP Guidance), prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), describes current good manufacturing practice (cGMP) for manufacturing of APIs. The guidance is intended to help ensure that all APIs meet the standards for quality and purity they purport or are represented to possess. Although the ICH cGMP Guidance does not impose requirements, FDA considers its recommendations, as well as alternatives intended to accomplish the same goals and provide an equivalent level of quality assurance, in determining whether a firm's APIs have been manufactured, processed, packed, and held according to current good manufacturing practice under Section 501(a)(2)(B) of the Act. We enclose a copy of the ICH cGMP Guidance for your reference.

To schedule a reinspection of this facility after corrections have been completed and it is in compliance with cGMP, contact: Director, International Branch, HFC-130, Division of Field Investigations, 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