DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-322
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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL No. 320-01-02

NOV 2 1 2000

P. Anji Reddy
President, Bulk Drugs
SOL Pharmaceuticals Limited
5-9-88/2 "Saphire Building" Fateh Maidan
Hyderabad-500 001 India

Dear Dr. Reddy:

The United States Food & Drug Administration has completed its review of the September 18-21, 2000, inspection of your active pharmaceutical ingredient (API) manufacturing facility in Hyderabad, India, by FDA Investigator Ted L. Anderson and Chemist Michele L. Obert. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of APIs. The deviations were presented to you on an FDA Form 483 Inspectional Observations at the close of the inspection. These deviations cause the API 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.

We have reviewed the October 2 and 31, and November 10, 2000, responses to the FDA 483 Inspectional Observations sent through [ ] Consultant, of [ ] Neither the corrections instituted nor those proposed in the correspondence sufficiently address the deviations observed during the aforementioned inspection.

In FDA 483 observations 1, 3, and 9 the terms "including, but not limited to" and "a general pattern" were used followed by a list of examples. This means that there were additional problems with the subject system which we expect you to evaluate, correct

where necessary, and provide us with your assessment. These systems include the [ ] system, adherence to laboratory standard operating procedures, and equipment maintenance.

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

1. Laboratory records are incomplete and inadequate. The inspection found that the data in numerous records were altered, erased, not recorded, recorded in pencil, or covered with white-out material. Therefore, there is not a complete record of all data secured in the course of each test.

For example, values in at least two [ ] areas were altered. Altered values were written under computer generated values on the [ ] and used in the potency calculations. Review of the electronic data confirmed the incorrect values, which were part of your submission to DMF

In another instance, two pages of a laboratory notebook written in pencil were erased. The letters [ ] your abbreviation for [ ] could be read on one of the erased pages. This data and its impact on the product has not been adequately evaluated and explained. Calculations on at least seven [ ] supporting the [ ] stability indicating method were also written in pencil.

Your company has not provided explanations for many of these record deviations. In four cases, typewritten dates (21/10/1999) were pasted over computer generated dates (04/01/1980) on [ ] You stated that these [ ] were generated on 04/01/2000 (day/month/year) and that the year printed out was a result of a Y2K glitch. But, the date pasted on the [ ] was 21/10/1999. Either this explanation or the date the [ ] was generated is wrong. Further, the [ ] use log has no entries from August 5 to December 17, 1999. This also indicates that the 21/10/1999 date is wrong. In addition, our investigative team found it impossible to trace computer generated [ ] because they were not date stamped.

The inspection team discussed other examples of unreliable data that do not appear in this letter with you during the inspection.

Although your responses promised training, new analytical record books, revalidation of the [ ] methods and repeating [ ] studies, and have provided a standard operating procedure (SOP) for good laboratory record practices, you have failed to address the review of other data generated prior to the institution of these corrective actions. Due to the pervasiveness of the unreliable records found, we believe that a retrospective review of data is necessary to show that your records are true and accurate. You have failed to identify the reasons for the unreliable records. Without an identified cause(s), we conclude that your corrective actions are inadequate.

In addition, please explain the mechanism you are using to control the disposition of your new laboratory worksheets. It is necessary that you demonstrate that pages cannot be duplicated or discarded without documentation of such.

2. Equipment was not properly maintained.

Although your responses describe corrective actions for each of the examples listed on the FDA 483, you failed to state how you will monitor all equipment (e.g., a preventative maintenance plan) in the future, and how you will make sure that maintenance is accomplished in a timely manner.

3. The qualification and maintenance of equipment used in, and the process validation of the [ ] system is inadequate.

Your validation protocol for the [ ] system is inadequate in that it does not address sanitization of the system, or sanitization or change frequency of the [ ]

To assess your control over the system, we need to know the procedure and frequency for sanitizing the [ ] system. Appropriate testing should be done before and after sanitizing and [ ] in order to identify the worst case scenario and effectiveness of sanitization.

Pages 6 and 7 of the protocol state that the [ ] sample for [ ] "is a composite sample of [ ] Compositing samples is not acceptable because it will not allow you to identify the source of contamination when adverse microbial test results are obtained. Please clarify if your sampling results are those of individual sample points or the composite of several sample points.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm. We recommend that you evaluate your facility on an overall basis for CGMP compliance, including the accuracy and reliability of all records. If you wish to ship your APIs to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for APIs.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing the facility as a supplier of active pharmaceutical ingredients. We have recommended that your firm's products be placed on import alert and denied entry into the United States. These articles are subject to refusal of admission

pursuant to Section 801(a)(3) of the FD&C Act in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act.

Please contact Compliance Officer Karen K. Moksnes of this division at the address or telephone number shown below if you have any questions. Please respond in writing to the above CGMP issues within thirty days. Within your response, detail corrective actions you plan to take to bring your operations into compliance. Include a timetable of when each of the corrections will be completed and attach supporting documents, as well as a complete list of FDA-regulated products shipped to the United States. Please reference CFN# 9611135 within your written response.

Food and Drug Administration
Center for Drug Evaluation and Research
Foreign Inspection Team, HFD-322
7520 Standish Place
Rockville, MD 20855

Telephone: 301.594.0095
FAX: 301.594.1033

To schedule a reinspection of your facility, after corrections have been completed and your firm has comprehensively evaluated overall compliance with CGMP requirements, send your request to: Director, International Drug Section, HFC-134, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857. You may also contact that office by telephone at 301.827.5655 or by fax at 301.443.6919.

Sincerely,

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

cc:

[redacted]