

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737TELEPHONE: (301) 594-0093
FAX: (301) 827-0145**WARNING LETTER**CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-01-01

OCT 30 2000Mr. Jaroslav Strop
Chairman of the Board/Managing Director
Spolana a.s.
277 11
Neratovice, Czech Republic

Dear Mr. Strop:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in the Czech Republic by the United States Food and Drug Administration during June 27 - 29, 2000. The inspection revealed significant deviations from U.S. good manufacturing practice in the manufacture of bulk [] that resulted in the issuance of a fourteen-item FDA Form 483 at the completion of the inspection. These deviations cause this 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 (CGMP). 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 July 25, 2000 responses to the FD-483 observations, and conclude that this response lacks sufficient details, explanations, or documentation to adequately address all of the deviations observed during the June 2000 inspection. Our comments regarding the most significant observations are shown below:

1. Written procedures had not been established for the calibration of analytical instruments and equipment in the Quality Control laboratories used for raw material, finished API and stability testing of []. Furthermore, calibration data and results provided by an outside contractor were not checked, reviewed and approved by a responsible Q.C. or Q.A. official.

Our inspection disclosed that analytical instruments and equipment used in testing of the raw materials, intermediates and APIs were not calibrated regularly based on an established written procedure. Most instruments lacked calibration stickers indicating the date of calibration and the due date for the next calibration, and records of calibrations were incomplete in that they lacked raw data, spectra, chromatograms and calculations. Furthermore, our investigators noted that calibration records were not reviewed and approved by responsible members of the Q.C. or Q.A. units to ensure that analytical instruments and equipment were calibrated properly and met the established acceptance criteria.

Your July 25, 2000 response reports that the general procedure for instrument calibrations will be revised by August 31 and that specific instrument procedures and specifications will be established and approved by October 31, 2000. These procedures will specify the calibration frequencies, parameters to be calibrated, operating ranges, procedures for recording, reporting, and maintaining the data, and review of data and test results by Q.C. and Q.A. personnel. Please submit these written procedures to us for review.

2. The [] systems calibrated by an outside contractor did not include verification of the precision (% RSD) of the autoinjector at more than one injection volume, the flow rate below 1 ml/min, or the wavelength accuracy for the wavelength regions used for testing of []. In addition, the [] software programs had not been verified or validated.

Your response reports that the calibration of analytical instruments will be completed by December 31, 2000. In addition, you indicate that you will develop a complex [] software validation schedule in cooperation with the [] software vendor by December 31. However, this validation schedule will not be approved by Spolana until January 31, 2001 and the software validation exercise will not be completed until June 30, 2001.

In essence, it appears that you are proposing to continue to use these [] systems for testing of [] without having completed the calibration of the [] or validation of its software. This is unacceptable. FDA expects companies to complete calibration of instruments and validation of analytical methods before use in order to demonstrate that the analytical instrument and procedures are suitable for their intended use. All analytical procedures are of equal importance from a validation perspective. In general, validated analytical procedures should be used, irrespective of whether they are used for in-process, release, acceptance, or stability testing. Please indicate in your response what actions you plan to take to address this serious CGMP issue.

3. Records and documentation of instrument/equipment calibrations and laboratory testing are incomplete in that they lacked raw data, spectra, chromatograms, and calculations.

During the inspection, our investigators reviewed analysts' notebooks and noticed that the preparation of mobile phases, solvents, sample and standard solutions and their dilutions were not always documented in the notebooks.

Your response indicates that the appropriate written procedure will be revised to require recording of raw data, including preparation of sample solutions, the standard solutions, the mobile phase, etc. This will be effective on August 31, 2000, but a copy of the written procedure was not submitted for our review. Please submit this in your response to this letter.

4. The in-house impurity standard [] was not properly calibrated against its USP reference standard.

Our June 2000 inspection disclosed that the qualification of the in-house impurity standard [] against the USP reference standard was performed using an [] system that was not calibrated for its intended use. The [] method required conducting the qualification using [] However, review of the calibration records showed that the performance calibration of this [] did not cover []

Your response reports that you will requalify the [] in-house working standard against the valid USP reference standard by December 31, 2000 after you complete the calibration of analytical instruments. Thus, it appears that you are proposing to continue to use the unqualified in-house working standard for routine analysis until the end of the year. This is unacceptable. Please indicate in your response what actions you have taken or plan to take to assure that appropriate reference standards are used during laboratory analysis.

5. The [] method for organic volatile impurities (OVIs) used for the release testing of [] Batches [] and [] released for the US market in 1998, was not validated at the time of its use.

Our review of the analytical raw data for the release testing of these three [] batches, disclosed that your firm used a modified [] method for the determination of OVIs in lieu of the USP method. The modified [] method had been used for release testing of [] since at least 1996, but was not validated until January 2000.

Your response states in order to prevent recurrence of using analytical test methods for product release testing which has not been validated, Spolana is revising relevant procedures such as change control of analytical methods, change control of specifications, etc. to provide more efficient Q.A. control and supervision on analytical method validation. While this is an appropriate plan of action, the commitment remains questionable in light of other responses related to the completion of instrument calibration and software validation, and the requalification of in-house working standards, which promise delayed completion dates with no interim action to meet CGMP requirements. Please clarify this issue in your response to this letter and clearly specify what actions you have taken or are planning to take to prevent the testing and release of [] batches using uncalibrated instruments or equipment or unvalidated analytical methods.

6. Written procedures had not been established to describe the receipt, identification, storage, handling, sampling, examination and/or testing, and reconciliation of API container labels. In addition, incoming labels were compared against a previously approved lot of labels in lieu of comparing against a master label.

Your July 25, 2000 response reports that a new procedure addressing these issues and which requires master labels for all APIs manufactured by [] was prepared, approved, and subsequently implemented on August 1, 2000. Please submit a copy of the SOP, a copy of the master label for [] and copies of actual pages from the "Label Reconciliation Logbook" for our review.

7. A written procedure requiring annual product reviews had not been established.

Our inspection revealed that your firm was in the process of writing a product annual review procedure and that there were many separate monthly and quarterly reports that are prepared for the Chairman of the Board covering numerous APIs and addressing most of the basic requirements of product annual reviews. However, no reports were available for []

Your response indicates that the draft procedure for conducting annual reviews has been finalized and was implemented on August 1, 2000. The procedure reportedly includes

provisions for reviewing a representative number of batches (whether approved or rejected) and their associated records for batch failures, process deviations, product quality trending, OOS occurrences, stability data, implemented changes, validation and revalidation activities, consumer complaints and returns. Please submit a copy of the approved procedure for our review.

We recommend that you conduct a complete and extensive evaluation of your facility for CGMP compliance. If you wish to continue shipping APIs to the United States, your firm is responsible for assuring compliance with U.S. standards of good manufacturing practice for active pharmaceutical ingredient manufacturers.

Until the FDA reinspects your facility and confirms that these deficiencies have been corrected, this office will recommend disapproval of all applications listing your firm as a supplier of active pharmaceutical ingredients. Based on your responses, we may also recommend that all active pharmaceutical ingredients you manufacture for U.S. clients be denied entry into the United States. These articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act because 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).

In your response please submit English translations of supporting documents, procedures or other information detailing corrective actions that you plan to take or have taken to bring your API facility into compliance. If you have questions or concerns regarding this letter, please contact Edwin Rivera Martínez, Compliance Officer, at the address and telephone numbers shown below:

Foreign Inspection Team, HFD-322
Food and Drug Administration
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855-2737

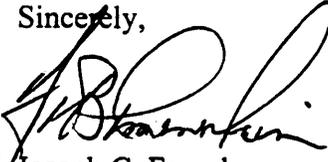
Telephone: (301) 594-0095
FAX: (301) 594-1033

Please reference Central File Number 9610090 in all correspondence.

To schedule a reinspection of your API facility after corrections have been completed, contact the Director of FDA's Division of Emergency and Investigational Operations

(HFC-134), 5600 Fishers Lane, Rockville, Maryland 20857. You can also contact that office by telephone at (301) 827-5653 or by FAX at (301) 443-6919.

Sincerely,



for

Joseph C. Famulare

Director

Division of Manufacturing and Product Quality