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September 11, 2000

WARNING LETTER

CEER-00-018 -B

CERTIFIED MAIL - RETURN RECEIPT REQUESTED

Mr. H. Joseph Larsen
President and Chief Executive Officer
SP Pharmaceuticals LLC
4272 Balloon Park Road N.E.
Albuquerque, NM 87109

Dear Mr. Larsen:

An inspection of SP Pharmaceuticals, LLC, located at 4272 Balloon Park Road N.E., Albuquerque, NM, was conducted from June 27- July 3, 2000. The inspection covered the product, CEA-Scan® (Arcitumomab), manufactured under contract for [REDACTED]. During the inspection, violations of Section 502(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), and Title 21, Code of Federal Regulations, Subchapter F, Parts 600-680 and Subchapter C, Parts 210-211, were documented as follows:

1. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that:
 - a. The [REDACTED] filters used to render CEA-Scan® sterile have not been validated for bacterial retention using in-process product or an appropriate surrogate.
 - b. The lyophilization cycle for CEA-Scan® (Arcitumomab) has not been validated.
2. Failure to follow the written specifications, standards, sampling plans, and test procedures designed to assure that in-process materials conform to appropriate standards of identity, strength, quality, and purity, in that, the in-process [REDACTED] testing was not performed for the CEA Scan® bulk solution for lots IMR-017 and IMR-018 [21 CFR 211.160(b)].

3. Failure to assure an adequate system for monitoring environmental conditions in that smoke studies to demonstrate laminar air flow have not been conducted under dynamic conditions and static smoke studies lack evaluation of the upward and swirling movements in the aseptic filling room [21 CFR 211.42(c)(10)(iv) and 211.67].
4. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment in that there have been no efficacy studies performed on the [REDACTED], and [REDACTED] sanitizing agents used in the aseptic filling areas [21 CFR 211.42 (c)(10)(v)].
5. Failure to assure that drug product containers and closures are not additive, or absorptive so as to alter the safety identity, strength, quality, or purity of the drug beyond established requirements [21 CFR 211.94 and 600.11(h)], in that, integrity testing of the drug product containers and closures for CEA-Scan® has not been performed.
6. Failure to routinely calibrate, inspect, or check equipment used in the manufacture, processing, packing, and holding of a drug product according to a written program designed to assure proper performance in that, the [REDACTED] transfer cart has not been qualified to assure adequate delivery of [REDACTED] throughout the transfer cart [21 CFR 211.68].
7. Failure to adhere to written specifications, standards, sampling plans, test procedures or other laboratory control mechanisms in that the [REDACTED] and [REDACTED] tests required by SOP 05-203 [REDACTED], [REDACTED] were not performed for the in-process CEA-Scan® product [21 CFR 211.160(a)].

We acknowledge receipt of your written responses dated July 18, 2000, and July 28, 2000, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letters may be referenced in your response to this letter as appropriate. We have reviewed your responses, however, and we have concluded that they do not provide sufficient detail to fully assess the adequacy of some of the corrective actions. Our comments and requests for further information regarding corrective actions are detailed below.

FDA 483 Observation 1

Your response is incomplete. Please provide the results of the product analysis and the particulate identification performed by [REDACTED] the vial manufacturer, and a contract laboratory, as referenced in your response. Also, please explain the conclusion documented in the "Particle Investigation Report" that "the vials with particulate may be

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just a small quantity from an isolated incident during the vial manufacture," when the investigation of lot IMR018 revealed that [REDACTED] of [REDACTED] finished vials had black specs on the inside neck of the vial, six of six vials investigated by SP Pharmaceuticals contained a black particle on the inner side of the vial, the black particles were not washed out of the vials using the standard procedure, and an initially unaffected vial showed traces of very small similar black particles following a [REDACTED] rinse. Further, please describe the corrective action taken by SP Pharmaceuticals to prevent recurrence of this event and advise FDA of the final disposition of CEA-Scan®, lot number IMR018.

FDA 483 Observation 5

Your response is inadequate. While we agree that some level of retrospective review of data (e.g. defining critical process and product parameters and then retrospectively reviewing available data) may be appropriate to provide an initial assessment of the process, it is our view that prospective or concurrent validation of the lyophilization cycle is necessary. The documentation submitted, which consists of a retrospective compilation of data for certain parameters, is insufficient and fails to demonstrate that the lyophilization cycle for CEA-Scan® has been validated.

FDA 483 Observation 6

Your response is incomplete. [REDACTED] validation studies of all [REDACTED] filters using in-process CEA-Scan® and appropriate operating parameters should be performed in a timely manner. The [REDACTED] should be small enough to challenge the retentivity of the filter and simulate the smallest microorganism that may occur in production. Please explain why the validation study cannot be initiated prior to the next production run of CEA-Scan® and provide the estimated time frame for completion.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with all requirements of the federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of any steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include injunction and seizure. Your reply should be sent to the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, 1401

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Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,



Deborah D. Ralston
Director
Office of Regional Operations

cc:

