

via Federal Express

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

JUL 23 1998

Mr. Michael Berman
President, Scimed Life Sciences, Inc.
Boston Scientific Corp.
One Scimed Place
Maple Grove, Minnesota 55311

Dear Mr. Berman:

During the period May 4 to May 14, 1998, Ms. Jennifer A. L. - Vollom, an investigator with the Food and Drug Administration (FDA), Minneapolis District Office, conducted an inspection at Scimed Life Science, Inc. (Scimed), a wholly owned subsidiary of Boston Scientific Corporation. The purpose of that inspection was to determine whether Scimed's activities as the sponsor/monitor of investigational studies of the Scimed® RADIUS™ Coronary Stent with Delivery System [Premarket approval application (PMA) P970061] complied with applicable FDA regulations. This product is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Our review of information from this inspection, as well as FDA inspectional findings from clinical investigator sites participating in the clinical studies of this device, revealed violations of FDA regulations contained in Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions. The findings, based on FDA's inspection at the sponsor/monitor level, were listed on the form FDA-483, "Inspectional Observations," which was presented to and discussed with Mr. Michael T. Frankenberg, the former Vice President of Regulatory Affairs and Quality Assurance, Ms. Debra A. Lano, the current Vice President of Regulatory Affairs and Quality Assurance, and others at the conclusion that inspection.

The extent of noncompliance observed at several of the participating clinical investigators resulted, in part, from your firm's failure to adequately monitor the clinical investigations at these sites. The following enumeration and discussion of violations and deviations from the regulations is not intended to be an all-inclusive list of problems encountered during our review.

under circumstances that give a subject who is capable of making an informed consent decision sufficient opportunity to consider participation and ask questions. The institutional review board (IRB) for _____ site had not been apprised of the consent methods used; hence it had not reviewed this process. IRB review, and approval, of the consent process is required by regulation.

Furthermore, while monitoring visits made by, or on behalf of Scimed, disclosed that clinical investigators repeatedly failed to comply with the requirements of the investigational plan and/or federal regulations, in some cases no corrective action was taken to prevent recurrence.

For example, a _____ (Philadelphia), six monitoring visits took place during the period of December 16, 1996, to June 17, 1997. Many protocol deviations were evident at this site, including failure to perform required lab tests and diagnostic procedures, failure to perform follow-up evaluations within protocol time-frames, and enrollment of nine subjects not meeting eligibility requirements. Not only did problems persist, but the number of eligibility deviations actually escalated, with eight of nine ineligible enrollments occurring after half of the site's total enrollment had been reached.

2. Failure to ensure proper monitoring of the clinical investigation(s) -- 21 CFR 812.40

The frequency of monitoring visits at study sites deviated considerably from the monitoring plan that your firm established _____ In addition, Scimed's own "Clinical Research Standard Operating Procedures" for this study state that visits will be performed at intervals determined necessary to ensure compliance with the investigational plan. This was not done.

Based on the inspectional observations, FDA feels that your firm's failure to assure that an effective monitoring plan was followed contributed to the recurrent deviations observed at various study sites.

The monitoring plan for the SCORES study anticipated that 32 sites would be monitored by _____ and that Scimed would monitor eight sites (there were eventually 50 sites). It was projected that visits would commence with study initiation (at each site) and a visit would be made two weeks after the first subject was treated. This interim monitoring would also include monthly visits during an enrollment period of six months, and visits every six weeks during the 9-month follow-up period.

Dr. _____ site (_____ treated their first subject on October 15, 1996. Although the monitoring plan required a site visit two weeks after initiation, a monitoring visit was not made at this site until January 13, 1997, approximately three months later.

Furthermore, although enrollment of subjects continued through April 1997, there were no monitoring visits made to this site between April 21, 1997, and February 6, 1998. Scimed failed to monitor this site for the entire nine-month follow up period despite the numerous protocol violations noted at this site prior to April 1997.

There are further examples of inadequate monitoring at a number of sites as evidenced by extended time periods between treatment date and the subsequent monitoring visit. Those sites include _____ (5 months), _____ Hospital (4 months), _____ (3 months), _____ (2 months), _____ (2 months), _____ (3 months), and _____ Hospital (3 months).

We acknowledge Ms. Lano's May 29, 1998, letter to the Director, Minneapolis District Office, which was forwarded to our office. The letter was in response to the observations identified during the May 1998 inspection. Your response reflects an understanding of the observations FDA has made and, in part, addresses some of our concerns about monitoring deficiencies.

The changes in monitoring procedures described, and the training of study personnel proposed, when properly implemented should improve your firm's compliance with bioresearch regulations. Nonetheless, we remain concerned about the extent of your firm's failure to adequately meet its monitoring responsibilities.

FDA recognizes that Scimed took actions in terminating the enrollment at _____, and instituted a corrective action plan (CAP) at _____ Hospital. At other clinical investigator sites with demonstrated compliance problems, including _____, implementing a corrective action plan could have prevented serious and repeated violations.

It is your responsibility to ensure adherence to each requirement of the Act and regulations. Within 15 days of receipt of this letter, please provide this office with written documentation of the specific steps you have taken or will take to prevent the recurrence of similar violations in current or future studies. Should you require additional time to respond please contact Mr. Kalins at the telephone number provided below.

Page 5 - Mr. Michael Berman

Your response should be directed to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 2098 Gaither Road, Rockville, Maryland 20850, Attention: David R. Kalins. A copy of this letter has been sent to the Food and Drug Administration's Minneapolis District Office, 240 Hennepin Avenue, Minneapolis, Minnesota 55401. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Mr. Kalins at (301) 594-4720, ext. 137.

Sincerely yours,



for

Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

cc: Mr. Peter Nicholas
President and Chief Executive Officer
Boston Scientific Corporation
One Boston Scientific Place
Boston, Massachusetts 01760

Ms. Debra A. Lano
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