DEPARTMENT OF HEALTH & HUMAN SERVICES

MAY 18 1999

Food and Drug Administration
Rockville MD 20857
Ref. HFD-99-340-0402

WARNING LETTER

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Return Receipt Requested

Irwin Miller
CEO
Harvard Scientific Corp.
1325 Airmotive Way, Suite 125
Reno, Nevada 89502-3239

Dear Mr. Miller:

Between March 10, 1998 and May 13, 1998, the Food and Drug Administration (FDA) inspected Harvard Scientific's conduct as the sponsor of studies of [ ] The inspection was conducted at Harvard Scientific's facilities in Irvine, CA, by Ms. Caryn M. Everly and Ms. Kirsten Tharp and your facilities in Reno, NV, by Mr. Steven R. Gillenwater and Ms. Marie K. Kinkade. At the conclusion of the inspection on May 13, 1998, Mr. Gillenwater and Ms. Kinkade issued to Mr. [ ] a consultant for Harvard Scientific, a Form FDA 483 and discussed with him the inspectional observations.

From our review of your Investigational New Drug Application (IND) file and our evaluation of the inspection reports, the documents collected during the inspection, and Mr. [ ] letter of June 3, 1998, we conclude that you failed to meet the responsibilities of a sponsor as specified in parts 56 and 312 of Title 21 of the Code of Federal Regulations [21 CFR part 56 and part 312].

Your failures are as follows:

1. You submitted to your IND an investigator brochure containing misleading and erroneous information about a clinical study [21 CFR 312.23 (a)(5)(iv)].

   a. Section (iv)(a) of the investigator brochure contains a manuscript attributed to [ ] M.D., F.A.C.C. and [ ] M.D., F.A.C.F.P. The manuscript describes a double blind placebo controlled study of [ ] that allegedly involved 135 subjects, and states that Dr. [ ] treated 72 of these subjects. During the inspection of your Irvine facilities, Dr. [ ] informed FDA Investigators Everly and Tharp that he never treated any of the 135 subjects.

b. At the meeting between Harvard Scientific and FDA on October 22, 1997, Dr. [ ] confirmed that the [ ] study was misrepresented, and that the findings were anecdotal, non-scientific, without raw data or case report forms, and unavailable for inspection.

2. You failed to ensure that studies were conducted in accordance with the protocols in your IND [21 CFR 312.50].

a. During the inspection of Dr. [ ] study, two protocols were identified. One protocol was filed to your IND; the other was not, but identified Drs. [ ] and [ ] as the investigators. You permitted the conduct of a study that was not covered by a protocol contained in the IND [21 CFR 312.30(a)].

b. Both protocols identified during the inspection limited the number of subjects to ten. You authorized Drs. [ ] and [ ] to increase the number of subjects to 32 without amending the IND protocol [21 CFR 312.30(b)(i)].

c. Dr. [ ] stated, during the FDA inspection of his study, that using [ ] of the diluent as specified by the protocol caused burning sensations, and that you agreed to using less diluent. You failed to amend the protocol on file in the IND to reflect the decreased diluent and the reason for decreasing the diluent [21 CFR 312.30(b)(iii)].

3. You failed to obtain signed investigator statements (Form FDA 1572) from investigators before permitting them to participate in a study [21 CFR 312.53(c)].

Dr. [ ] conducted his study between August 9 and November 22, 1996, and Dr. [ ] conducted his study between August 16, and November 8, 1996. Neither Dr. [ ] nor Dr. [ ] signed a "Statement of Investigator" (i.e., Form FDA 1572) until November 26, 1997.

4. You failed to have an IND in effect prior to shipping the investigational new drug to investigators [21 CFR 312.20(b) and 312.40(c)].

Your IND went into effect on June 7, 1996, but you shipped [ ] in 1994 to Dr. [ ] to conduct a 12 subject study.

5. You failed to maintain adequate records showing the receipt, shipment, or other disposition of the study drug [21 CFR 312.57(a)].

   No records were available during the inspection to document receipt, shipment, or distribution of the study drug for any of the clinical studies of [ ].

6. You failed to add new investigators to the IND before shipping the investigational new drug to them [21 CFR 312.40(c)].

   You provided the investigational new drug to Drs. [ ] and [ ] for studies conducted between August 9 and November 22, 1996. You failed to add Drs. [ ] and [ ] as new investigators to your IND until December 5, 1997.

7. You failed to notify FDA of new investigators within 30 days of their being added to a study [21 CFR 312.30(c)].

   Between August 9, 1996, and November 22, 1996, [ ] M.D. and [ ] M.D. conducted clinical studies involving a total of 32 subjects. You failed to amend your IND to identify Drs. [ ] and [ ] as new investigators until December 5, 1997, more than a year after their studies were completed.

8. You failed to ensure proper monitoring of clinical studies [21 CFR 312.50 and 312.56(a)].

   a. Item 14 of the Form FDA 1571 lists Mr. [ ] as the study monitor. Drs. [ ] and [ ] stated to FDA's Investigators that Mr. [ ] failed to explain the protocol and regulatory requirements, and failed to compare the CRFs with the raw data during monitoring visits.

   b. The monitor did not ensure that IRB approval was obtained prior to initiating the study, that a Form FDA 1572 was signed by each investigator before participating in the study, and that adequate drug accountability records were generated and maintained.

9. You failed to select monitors qualified by training and experience to monitor the progress of the studies [21 CFR 312.53(d)].

   Mr. [ ] CV does not report any monitoring experience, monitoring training, or courses in the medical sciences.

10. You failed to ensure (1) that an IRB that conformed to the requirements of part 56 [21 CFR 56] would be responsible for the initial and continuing review and approval of each study, and (2) that the investigators would report to the IRB proposed changes in the research activity [21 CFR 312.23(a)(1)(iv) and 21 CFR 56.103(a)].

    The studies of Drs. [ ] and [ ] were conducted between August 9 and November 22, 1996, but IRB approval was not obtained until November 25, 1996.

11. You failed to give investigators a copy of the investigator brochure before they began their studies [21 CFR 312.55(a)].

    During inspections of the studies conducted by Dr. [ ] and Dr. [ ] no investigator brochures were found at their sites, and both investigators stated that investigator brochures had not been provided to them before they began their studies.

12. You failed to submit annual reports to the IND within 60 days of the anniversary date that the IND went into effect [21 CFR 312.33].

    Your IND became effective on June 7, 1996. You did not submit the annual report that was due on June 7, 1997 (plus or minus 60 days) until July 21, 1998.

As described above, FDA's inspections documented that you failed to meet the responsibilities of a sponsor as specified by Federal regulations. Within 15 calendar days of your receipt of this letter, provide this office with the following written response:

1. your explanation of why the problems identified above occurred

2. your description of the corrective actions you are taking to ensure that these problems will not recur

3. your description of the actions you are taking to ensure the validity, accuracy and reliability of your data

4. your revised standard operating procedures (SOPs), showing all the changes you have made to comply with FDA regulations.

You should send your response to:

Bette L. Barton, Ph.D., M.D.
Division of Scientific Investigations, HFD-344
U.S. Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855
Telephone (301) 594-1032; Fax (301) 827-5290

The above discussion of violations is not intended to be a complete list of the deficiencies at Harvard Scientific. Your failure to promptly correct these deficiencies may result in regulatory action without further notice.

Sincerely,

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research