DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

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JUN 12 2002

WARNING LETTER
Via Federal Express

Mitchell D. Creinin, MD
University of Pittsburgh School of Medicine
Department of Obstetrics, Gynecology, and Reproductive Services
Magee-Women's Hospital
300 Halket Street
Pittsburgh, Pennsylvania 15213

Dear Dr. Creinin:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site and to request a prompt reply. Ms. Cynthia L. Rakestraw of the FDA Philadelphia District Office conducted the inspection on January 3-16, 2002.

The purpose of the inspection was to determine if your activities as a clinical investigator in a study entitled "Lea's Shield Colposcopy and Microbiological Testing, Protocol [redacted]" sponsored by Contraceptive Research and Development Program (CONRAD), complied with applicable FDA regulations. The Lea's Shield ® Barrier Contraceptive Shell is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act. [21 U.S.C. 321(h)]

The inspection was conducted under an FDA compliance program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications (510(k) submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations. The clinical investigation was conducted under [redacted] and supported PMA P010043.

Our review of the inspection report prepared by the Philadelphia District Office reveals violations of requirements of Title 21, Code of Federal Regulations (CFR), Part 50 – Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 – Investigational Device Exemptions. At the conclusion of the inspection, Ms. Rakestraw listed her findings on a Form FDA-483 "Inspectional Observations," and discussed these findings with you.

We acknowledge receipt of a copy of your January 25, 2002, response to Ms. Rakestraw's findings. Your response does not adequately address the FDA-483 items, nor does it contain supporting documentation of any corrections.

The following violations were observed:

1. **Failure to ensure that the requirements for obtaining and documenting informed consent were met [21 CFR 812.100, 21 CFR 50.20, 50.25, and 50.27]**

The informed consent document signed by the male subjects in this research study does not identify the foreseeable risks of discomfort and irritation to the [redacted] and does not describe other risks as stated in the sponsor's model consent form, "Addendum Male Partner Agreement" dated September 14, 1999. Also, the signed consent form does not describe the male subject's option to contact the center for treatment of the foreseeable risk and discomfort as stated in the sponsor's model consent.

You also made other important changes to the informed consent document that are inconsistent with the sponsor's model consent form. For example, your consent form states, "***Lea Contraceptive prevents pregnancy when it is used with spermicidal***." The sponsor's consent form does not make this statement. Your consent form states, "The Lea Contraceptive may not protect you against sexual transmitted diseases***." The sponsor model form states, "*** Lea Contraceptive does not protect ***."

Federal regulation 21 CFR 812.100 requires a clinical investigator to ensure that informed consent is obtained in accordance with 21 CFR Part 50. The informed consent document must meet the requirements of 21 CFR 50.20 and 21 CFR 50.27 and contain the information required by 21 CFR 50.25(a) and (b) that are appropriate to the study. The explanation of risks should be reasonable and should not minimize reported adverse effects.

Additionally, you failed to submit the sponsor's model consent form, "Addendum Male Partner Agreement," to the Magee-Womens Hospital Institutional Review Board for their review and approval. The amended consent you did submit was deficient, as described above, in that it did not disclose the foreseeable risks of discomfort and irritation to the male subject and their option to contact the center for treatment.

Your participation in the study is based in part on the IRB's approval. The IRB must receive and review all covered research activities [21 CFR 56.109(a)]. The IRB has the responsibility and authority to determine the adequacy and appropriateness of the entire wording in the informed consent document [21 CFR 56.111(a)(4) and (5)]. The information contained in the informed consent is critical to the IRB's review, and is important to the subject's decision about whether to participate in the investigation.

2. **Failure to conduct the study in accordance with the investigational plan [21 CFR 812.110(b)]**

The study protocol describes study requirements at the 2-week and 8-week visits. These requirements included completing an adverse experience form for each medical problem experienced by the female subject or their male partner. In addition, non-medical experiences were required to be documented on the coital log form.

There were no adverse experience forms completed for the device-related medical problems experienced by the male partners of the following female subjects: [redacted] Coital log forms were not completed for non-medical problems, such as [redacted] experienced by the male partner and reported by [redacted] female subjects on specific dates. Between March 3, 2000, and March 21, 2000, subject [redacted] used the study device nine times and reported that she or her male partner experienced irritation or discomfort on each occasion. This information was not recorded on the appropriate case report forms.

3. Failure to maintain complete, accurate, and current records relating to the investigation [21 CFR 812.140(a)]

You did not maintain complete records of the correspondence with the sponsor. For example, there was no signed investigator agreement at your site. In addition, your records did not include a copy of the informed consent document you revised and reportedly submitted to the sponsor for review as referenced in your June 1999 electronic mails.

You did not maintain complete records related to each subject's case history. There was no documentation of follow-up or medical treatment of male subjects who experienced device-related problems.

The above deviations are not intended to be an all-inclusive list of deficiencies that may exist in the clinical study. We recommend that you review your records for other deficiencies and correct them accordingly. While the deficiencies noted did not affect the eventual approval of the PMA (approved March 15, 2002), it is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and regulations.

Please acknowledge receipt of this letter within 15 working days, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Failure to respond to this letter and take appropriate corrective action could result in regulatory action without further notice.

Please send your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2094 Gaither Road, Rockville, Maryland 20850, Attention: Kevin M. Hopson. If you have any questions or require additional time to respond, please call Mr. Kevin Hopson at (301) 594-4720, extension 128.
A copy of this letter has been sent to FDA's Philadelphia District Office, US Customhouse, 2nd and Chestnut Streets, Philadelphia, Pennsylvania 19106. We request that you send a copy of your response to our Philadelphia District Office.

Sincerely yours,

for Larry D. Spears
Acting Director
Office of Compliance
Center for Devices and Radiological Health

cc: Henry L. Gabelnick, Ph.D.(purged copy)
Director
Contraceptive Research and Development Program
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W. Allen Hogge, MD (purged copy)
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