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Food and Drug Administration
Rockville MD 20857

Via Federal Express

CORRECTED WARNING LETTER

Frederic B. Kremer, M.D.
Kremer Laser Eye Center
200 Mall Boulevard
King of Prussia, Pennsylvania 19406

[REDACTED]

Dear Dr. Kremer:

The purpose of this letter is to warn you that [REDACTED] located at the Kremer Laser Eye Center in King of Prussia, Pennsylvania, may not be used in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). In particular, your [REDACTED] is the subject of an [REDACTED] approved by the United States Food and Drug Administration (FDA or agency), and it may not be used to treat patients beyond the conditions of approval of your [REDACTED] or in violation of FDA's [REDACTED]. As discussed further below, inspection of your facility by FDA reveals that you have used your [REDACTED] in a manner that does not comply with Federal law.

Background

On May 8, 1996, you submitted an [REDACTED] for studies of [REDACTED] using an [REDACTED] (hereafter "[REDACTED]"). By letter dated June 7, 1996, (the [REDACTED] letter), FDA approved your [REDACTED]. Under the [REDACTED] you may perform [REDACTED] to treat [REDACTED] for 300 patients at one institution. FDA also requested in the [REDACTED] approval letter that, within 45 days, you respond to a list of deficiencies regarding your [REDACTED], including a request that you submit information regarding "aspects of your device hardware, firmware, and software which mitigate against device failure and ensure adequate calibration of its output."

By letter dated July 22, 1996, you responded to the deficiencies cited in the [REDACTED] approval letter. However, FDA informed you, by letter dated August 29, 1996, that the agency considered your response to be inadequate. In your response dated November 27, 1996, you adequately addressed the primary concerns FDA had regarding your [REDACTED] application.

In September 1996, you submitted supplements to your [REDACTED], in which you requested permission to expand your [REDACTED] to include treatment of [REDACTED] and [REDACTED] and for the [REDACTED]. In a letter dated October 8, 1996, (the October 8, 1996, letter), FDA disapproved [REDACTED] because you failed to submit technical information necessary to evaluate the safety and effectiveness of the requested expansion. In the October 8, 1996, letter, FDA also informed you

that, because [REDACTED] had been disapproved, you could not expand your [REDACTED] to include these treatments.

In a letter to FDA dated November 19, 1996, you requested withdrawal of [REDACTED]. On November 22, 1996, in a telephone conversation with Dr. Morris Waxler and Ms. Jan Callaway, from the Office of Device Evaluation (ODE), you were told that if you withdrew these supplements, you could not treat [REDACTED] and [REDACTED] and you could not [REDACTED]. Subsequently, in a November 26, 1996, letter, you rescinded your request for withdrawal of these supplements. However, because you did not submit the necessary technical information, you never received the required approval to begin such treatments.

By letter dated September 26, 1996, you requested a supplement to your [REDACTED] to demonstrate the comparability of the [REDACTED] ([REDACTED]) (which is the [REDACTED] listed in your [REDACTED] application and initially used in your [REDACTED] and the [REDACTED]. On October 25, 1996, FDA disapproved [REDACTED] and informed you that you could not "implement the change in your investigation."

During a May 9, 1997, telephone conversation with Dr. Waxler and Ms. Callaway, you stated that there was a leak in the [REDACTED] of the [REDACTED] in your [REDACTED], and you requested that you be allowed to use the [REDACTED] as a substitute in your [REDACTED] while the [REDACTED] was being repaired. You were told during that conversation that there would not be enough time to establish comparability with a new [REDACTED] before your [REDACTED] could be repaired. At that point you were warned that you could not treat patients using your [REDACTED] with the substitute [REDACTED]. Despite this warning, FDA has evidence that you used the [REDACTED] in your [REDACTED] during the month of May 1997.

On January 31, 1997, FDA received the [REDACTED] for your [REDACTED]. You [REDACTED] was given [REDACTED] of January 31, 1997. In a letter received by FDA on March 11, 1997, you requested that your [REDACTED] be granted [REDACTED]. FDA denied this request in a letter dated March 28, 1997. By letter dated July 7, 1997, (the July 7, 1997, FDA letter), FDA notified you that your [REDACTED] lacks information needed to complete the review. The July 7, 1997, FDA letter listed significant deficiencies in your [REDACTED] that required a response from you. On August 7, 1997, FDA received your response to these deficiencies and is currently reviewing this response.

In March 1997, you requested an expansion of your investigation under your [REDACTED] to allow you to enroll additional subjects beyond the number initially approved under your [REDACTED] while your [REDACTED] was under review. On March 24, 1997, FDA sent you a letter granting you approval for an additional 300 subjects to be treated at one institution during a 6-month period ending September 24, 1997.

On June 27, 1997, you submitted a supplement to your [REDACTED] in which you requested further expansion of your study to 900 subjects. In a letter dated July 14, 1997, (the July 14, 1997, FDA letter), FDA denied this expansion because of deficiencies in [REDACTED]. These deficiencies included the lack of a detailed description of the [REDACTED] and [REDACTED] for your [REDACTED] and your failure to submit a progress report to FDA for your [REDACTED] as required by [REDACTED]. The July 14, 1997, FDA letter warned you that "treatment of subjects outside of the limits and conditions of approval of this [REDACTED] is a violation of the [FD&C Act] and FDA regulations."

FDA's Inspection of the Kremer Laser Eye Center

During the period of May 22 through July 9, 1997, FDA inspected the Kremer Laser Eye Center in King of Prussia, Pennsylvania and reviewed records of some of the patients treated with the [REDACTED]. That inspection revealed the following:

1. You have used your [REDACTED] to perform [REDACTED] for indications not approved under your [REDACTED]. For example, you used your [REDACTED] to treat at least three patients for [REDACTED] at least one patient, and to treat at least two patients for [REDACTED]. None of these indications are approved under your [REDACTED].
2. During the month of May 1997, you treated patients with your [REDACTED] using a substitute component [REDACTED] that was not part of your approved [REDACTED], and for which you did not get an approved [REDACTED] supplement. In fact, your request to use this substitute component was specifically rejected by FDA because you did not supply technical information necessary to determine the comparability of the [REDACTED] to the [REDACTED].
3. Your [REDACTED] did not bear the required statement "Caution - Investigational Device Limited by Federal (or United States) law to investigational use." See 21 CFR 812.5.
4. You are violating the [REDACTED] regulations by representing that your [REDACTED] device is safe and effective for the purposes for which it is being investigated. See 21 CFR 812.7(d). In particular, the FDA inspection revealed that you are making such representations about your [REDACTED] by giving patients a brochure entitled "See Without Glasses or Contacts" (hereafter referred to as "the Kremer patient brochure"), which states that "[t]hrough extensive monitoring of the [REDACTED] procedure, we have demonstrated that it is relatively safe and effective for most applications."
5. The composition of your Institutional Review Board (IRB) does not comply with the requirements of 21 CFR 56.107. For example, some members of your IRB have conflicting interests in that they are also members of your staff. In addition, you and your wife, as members of the IRB, would also have conflicting interests. See 21 CFR 56.107(a).

The violations listed above are not all-inclusive. Moreover, the concerns raised by these violations are separate from, and in addition to, the deficiencies noted in FDA's July 7, 1997, letter to you concerning your [REDACTED]

At the conclusion of the May-July FDA inspection of Kremer Laser Eye Center, FDA issued to you a list of inspectional observations (form FDA-483), which included some of the violations discussed above. On July 29, 1997, you sent FDA a letter in which you responded to the items on the form FDA-483.

Violations of FDA's Regulations and the FD&C Act

1. Treatment of patients beyond the conditions of your [REDACTED]

Any treatment of patients with your [REDACTED] that does not conform with the conditions of approval of your [REDACTED] FDA's regulations, or the FD&C Act causes that laser to be adulterated under Federal law. As discussed above, you have used your [REDACTED] to perform [REDACTED] for indications not approved under your [REDACTED]

In communications you have had with the agency, you have stated your belief that your [REDACTED] is a custom device that is exempt from FDA regulation and from the IDE regulations. See, e.g. your letter to FDA dated November 8, 1996. Similarly, the Kremer patient brochure states that, "[a]s a custom device used only for our patients, our instrumentation fits the FDA category of physician exception for custom device."

FDA does not consider your [REDACTED] to be a custom device. In order for a device to fall within the definition of a custom device, the FD&C Act, 21 USC 360j(b), requires, in part, that the device be made to meet either the specific anatomical requirements of an individual patient or the special needs of an individual practitioner; a practitioner's special needs may be either an individual anatomical need or a special practice need that is not shared by other physicians.

We do not believe your device is designed to meet any special anatomical needs that you or an individual patient of yours may have. In addition, we do not believe the requirements of your medical practice are unique because they are shared by numerous other health professionals. Accordingly, your [REDACTED] is not a custom device, and it is not exempt from the conditions of your [REDACTED] the requirements of the [REDACTED] or any other applicable requirements under the FD&C Act.

In response to FDA's observation in the form FDA-483 that you have used your [REDACTED] to perform [REDACTED] for indications not approved under your IDE, you stated that "[o]ne of the understandings [you] reached with the agency prior to submission of the [REDACTED] was that [you] would be allowed to treat patients who did not fall within the [REDACTED] but had types of conditions that [you] had been treating prior to submission of the [REDACTED]"

The agency has never agreed to allow you to treat patients outside of the terms of your [REDACTED]. In fact, FDA disapproved your request in [REDACTED] to expand your investigational studies to include specific treatments that had not been approved under your [REDACTED]. In addition, FDA has warned you on several occasions that you may not treat patients outside of the terms of your [REDACTED]. For example, in a letter dated June 7, 1996, to you from FDA, FDA stated that:

Although an approved [REDACTED] would exempt your [REDACTED] from misbranding and adulteration provisions and GMP requirements during the [REDACTED] phase, that exemption does not apply under the following conditions; (1) if the [REDACTED] is used on patients outside the study; [and] (2) if the laser is used for refractive procedures not covered by the [REDACTED]....

Moreover, the July 14, 1997, FDA letter warned you that "treatment of subjects outside of the limits and conditions of approval of this [REDACTED] is a violation of the [FD&C Act] and FDA regulations."

Your response to FDA's observation in the form FDA-483 is inadequate and fails to commit to ceasing the illegal use of your [REDACTED] beyond the conditions of your [REDACTED]. Indeed, you indicate that you intend to continue such use because you "believed this practice is acceptable." Your past, as well as any future, use of your [REDACTED] outside of the conditions of your [REDACTED] causes your [REDACTED] to be adulterated within the meaning of 21 USC 351(i) of the FD&C Act.

2. Treatment of patients in excess of the limit approved under your [REDACTED]

As you are aware, your [REDACTED] limits the number of subjects to a total of 600. All treatments of all patients that have been performed with your [REDACTED] device after the date of approval of your [REDACTED] are included in the total patient count. This is true regardless of whether you believe the patients were treated under your [REDACTED] outside of your [REDACTED] or under a "custom device exemption."

FDA believes that you have already treated the entire allotment of 600 subjects. If, in fact, you already have treated 600 subjects, you must immediately cease all further use of the [REDACTED] to treat patients unless and until you receive an FDA-approved expansion of your study through an [REDACTED] supplement. In the absence of such an approved supplement, treatment of any additional patients is a violation of the FD&C Act, and causes your [REDACTED] to be adulterated within the meaning of 21 USC 351(i).

3. Substitution of the [REDACTED] in your [REDACTED]

Under the IDE regulations, you are required to "[s]ubmit to FDA [for approval] a supplemental application if [you] propose[] a change in the investigational plan that may affect its scientific soundness or the rights, safety, or welfare of subjects." 21 CFR 812.35. Your substitution of the [REDACTED]

for the [REDACTED] constitutes a "change in the investigational plan that may affect its scientific soundness [as well as] the rights, safety, or welfare of subjects," because the substitution of this major component could affect the performance characteristics of your [REDACTED]. Although you submitted [REDACTED] seeking to use the substitute [REDACTED], FDA disapproved this supplement because you did not supply technical information necessary to determine the comparability of the [REDACTED] to the [REDACTED].

You have attempted to justify this unapproved change stating that you did it "to minimize disruption of the [REDACTED] study;" you have asserted that "patients were not jeopardized in any fashion by use of this component." You also stated that you are "working expeditiously to try to return to the original configuration and to submit a supplemental [REDACTED]."

Your past, as well as any future, use of your [REDACTED] with the substituted [REDACTED] is illegal, and it causes your [REDACTED] to be adulterated within the meaning of 21 USC 351(i) of the FD&C Act. In addition, you should also be aware that your substitution of a major component in your [REDACTED] may have caused that [REDACTED] to be a new device that is not covered by your IDE. In that event, your device is an unapproved Class III device that is adulterated within the meaning of 21 USC 351(f)(1)(B), and its use is illegal.

4. Lack of required statement on your [REDACTED]

At the time of FDA's inspection of your facility, your [REDACTED] did not bear the required statement "Caution - Investigational Device Limited by Federal (or United States) law to investigational use." You have represented that this labeling has been replaced. Please be advised that, should you again fail to include this labeling on your [REDACTED], that device will be adulterated within the meaning of 21 USC 351(i) of the FD&C Act.

5. Representations that your [REDACTED] is safe and effective

As discussed above, the Kremer patient brochure, which is used to promote your [REDACTED], states that "[t]hrough extensive monitoring of the [REDACTED] procedure, we have demonstrated that it is relatively safe and effective for most applications." FDA regulations prohibit representations that an investigational device is safe and effective for the purposes for which it is being investigated. 21 CFR 812.7(d).

In a June 7, 1996, letter from FDA, you were warned that such representations constitute a violation of FDA's [REDACTED] regulations. You have stated that you are "currently working on an updated patient brochure. The language will be changed to address this observation in the new patient brochure." Despite FDA's warning, you have continued to represent that your [REDACTED] device is safe and effective for the purposes for which it is being investigated. Your past, as well as any future, representations that your [REDACTED]

██████████ is safe and effective cause the device to be adulterated within the meaning of 21 USC 351(i) of the FD&C Act.

6. Promotion of your ██████████

Although an investigator or a sponsor may make known the availability of an investigational device for the purpose of obtaining clinical investigators and study subjects, FDA regulations prohibit the promotion of an investigational device prior to FDA approval of the device for commercial distribution. 21 CFR 812.7(a). FDA has become aware of your extensive promotion of your ██████████ through a number of media, including:

- Promotion of the device through the Kremer patient brochure.
- Promotion of the device through a radio commercial featuring an endorsement by two former patients.
- Promotion of the device through advertisements in the Inquirer Magazine.
- Promotion of the device through a billboard on Interstate 95, in Philadelphia, Pennsylvania.
- Promotion of the device on your internet web site.

These promotional materials go beyond mere solicitation of clinical investigators and study subjects; they actively promote treatment with your ██████████, including treatment for indications for which you have not received approval under your ██████████ (e.g. treatment of ██████████). For example, the Kremer patient brochure states:

The ██████████ procedure was developed by Dr. Kremer and is available exclusively at Kremer Laser Eye Center. This procedure utilizes an ██████████ developed by Dr. Kremer. The ██████████ procedure is the most advanced procedure available to correct ██████████ (██████████, ██████████, ██████████) and ██████████.

Similar representations have been made in your advertisements in the Inquirer Magazine and on your internet web site. In addition, your promotional materials fail to mention that your ██████████ is an investigational device which can be used only as part of an investigational study. See 21 CFR 812.7(a). Indeed, you convey the impression that you are exempt from the requirements of FDA's ██████████ regulations and the FD&C Act because you claim in the Kremer patient brochures that your ██████████ device "fits into the FDA category of physician exception for custom device."

On May 8, 1996, you requested that, pursuant to 21 CFR 812.10, FDA waive among other things, the prohibition under 21 CFR 812.7(a) against

promotion of an investigational device prior to FDA approval of the device for commercial distribution. Your request was denied in a June 7, 1996, letter (waiver denial letter) from FDA, and you were warned that:

As a sponsor-investigator, you are subject to limitations associated with promotion and advertising of the investigational device. 21 CFR 812.7(a). Once you have received clearance for your [REDACTED], you may only solicit for patients who meet the [REDACTED] criteria for patient inclusion.... Therefore, all advertising and promotional materials must be limited in content and scope to those patients and procedures covered by the approved [REDACTED] and supplements.

Similarly, in an October 3, 1996, letter, FDA informed you that the agency objects to your promotional activities and that any commercialization of your [REDACTED] would adulterate your device. Despite FDA's denial of your waiver request and warnings from the agency that you must not promote your [REDACTED], you have continued such promotion. This promotion causes your [REDACTED] to be adulterated within the meaning of 21 USC 351(i) of the FD&C Act.

7. Conflicting interests of IRB members

As discussed above, the composition of your IRB does not comply with the requirements of 21 CFR 56.107. For example, some members of your IRB have conflicting interests in that they are also members of your staff. See 21 CFR 56.107(e). Your past, as well as any future, failure to have a properly constituted IRB in place for your investigations for your IDE causes your IDE laser to be adulterated within the meaning of 21 USC 351(i) of the FD&C Act.

Summary

Because your [REDACTED] is not a custom device and does not have an approved [REDACTED], it may be used to treat patients only in strict compliance with the conditions of an [REDACTED] and the [REDACTED]. As discussed above, you have been treating patients outside of the conditions of your [REDACTED] and in violation of the [REDACTED] regulations. Such use causes your [REDACTED] to be adulterated within the meaning of 21 USC 351(i) of the FD&C Act. You must immediately cease all treatment of patients beyond the parameters of your [REDACTED] approval and all applicable regulations.

Within 15 working days of your receipt of this letter, please notify this office of what actions you are taking to bring your device into compliance with the requirements of the FD&C Act. In addition, your response should include a list of all treatments with your [REDACTED] since the [REDACTED] was approved on June 7, 1996, regardless of whether you consider the treatment to be under your [REDACTED] outside of your [REDACTED] or under a "custom device exemption." This list should specify a patient identification number with each corresponding treatment date, the indication for which the treatment was made, and the eye treated. Your response should be sent

Page 9 - Frederic B. Kremer, M.D.

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: Jean Toth-Allen, Ph.D.

In addition, within 3 working days of your receipt of this letter, you should submit a written statement that, as of the close of business on the date of your receipt of this letter, you, as well as all employees of, and all persons associated with, the Kremer Laser Eye Center will use your [REDACTED] only in a manner that complies with the conditions of approval of your [REDACTED], the regulations, and the FD&C Act, including, but not limited to, using the device only for [REDACTED] for treatment of [REDACTED]

[REDACTED] Please send the statement requested above by facsimile to Jean Toth-Allen at (301) 594 - 4731. In addition, please send the original statement to the address listed in the paragraph above.

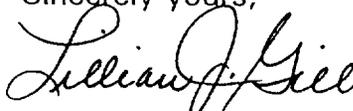
Please be advised that a person who knowingly and willfully falsifies or conceals a material fact in any matter within the jurisdiction of the United States may be subject to criminal prosecution under Federal law.

A copy of this letter has been forwarded to our Philadelphia District Office, 900 U.S. Customhouse, 2nd and Chestnut Streets, Philadelphia, Pennsylvania 19106. We request that a copy of your response be sent to that office.

We want you to be aware that failure to comply with the law may result in further regulatory action against you or the device by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties.

If you have any questions, you may contact Jean Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,



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