



WARNING LETTER

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

SEP 20 2000

Robert W. Christensen, D.D.S.
President
TMJ Implants, Inc.
17301 W. Colfax Avenue, #135
Golden, Colorado 80401

Dear Dr. Christensen:

During the period of May 10 through June 5, 2000, TMJ Implants, Inc. was visited by Ms. Martina LaGrange, an investigator from the Food and Drug Administration's (FDA) Denver District Office. The purpose of this visit was to determine, by inspection, whether your activities and procedures as a Sponsor/Monitor of the investigational study of the [REDACTED] ([REDACTED]) 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).

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] 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 the scientific investigation.

Our review of the inspection report submitted by the Denver District Office, as well as reports of FDA-conducted data audits at three of your clinical investigator (CI) sites, revealed significant deviations from the requirements under Title 21 Code of Federal Regulations (21 CFR), Part 812—Investigational Device Exemptions and Part 50—Protection of Human Subjects. The deviations below were listed on a form FDA-483 "Inspectional Observations," which was presented to and discussed with [REDACTED]

We acknowledge receipt of a copy of your letter dated June 28, 2000, in response to the items listed on the Form FDA-483. The deviations noted on the Form FDA-483, our

subsequent review of the inspection report, and your response to the FDA-483 items are discussed below. Deviations noted include:

Failure to ensure proper monitoring of the clinical investigation and secure investigator compliance (21 CFR Parts 812.40, 812.43(c)(iii), and 812.46(a); and 21 CFR Part 50).

The conditions of approval for this investigational study require that the participating physician seek and obtain IRB approval for each study subject prior to implanting the investigational device into the subject .

You failed to properly monitor the clinical investigation, to ensure that IRB approval and informed consent were obtained prior to allowing study subjects to participate in a clinical investigation, and to ensure that the study was conducted in accordance with the investigational plan and conditions of approval imposed by the FDA and the IRB.

██████████ and ██████████ failed to obtain IRB approval before allowing study subjects to participate in an investigational study. For example, study subjects ██████████ and ██████████ received implant surgery on 10/13/99 and 9/18/99, respectively, before notification of the IRB on 10/19/99 and 9/18/99, respectively. On 11/5/99, the IRB sent ██████████ a letter informing him that he violated IRB policies and procedures by using the study device without IRB approval. The IRB further stated that the use of the device for study subjects ██████████ and ██████████ did not meet the criteria for emergency use.

While the IRB was notified on 10/18/99 of the 10/22/99 implant surgery planned for study subject ██████████, the IRB's response letter, dated 11/18/99, informed ██████████ that the use of the device on study subject ██████████ was not approved. The implant surgery was conducted without IRB approval.

Further, clinical investigators ██████████ and ██████████ failed to submit notification to the IRB of implant surgery for ██████████ and ██████████ performed implant surgery on subject ██████████ on 8/25/99. ██████████ performed implant surgery on ██████████ on 9/3/99.

In addition to the above, there are other examples of your clinical investigators' failing to obtain informed consent from some subjects prior to surgery.

As a condition of approval of your study, FDA required that an independent assessment by an uninvolved physician be obtained before surgery in order to assure the rights, safety, and welfare of the compassionate use subjects. Some of the participating investigators failed to follow the conditions of approval in that no independent

assessment by an uninvolved physician was obtained for Compassionate Use [REDACTED], [REDACTED]. Independent assessment was received after surgery for the following Compassionate Use Subjects:

- [REDACTED] – Independent assessment 10/8/99 – surgery date 9/3/99;
- [REDACTED] – Independent assessment 9/16/99 – surgery date 9/8/99;
- [REDACTED] – independent assessment 10/18/99 – surgery date 10/13/99;
- [REDACTED] – independent assessment 2/3/00 – Surgery date 10/8/99;
- [REDACTED] – independent assessment 10/18/99 – surgery date 9/18/99;
- [REDACTED] – independent assessment 10/27/99 – surgery date 10/22/99;
- [REDACTED] – independent assessment 1/11/00 – surgery date 12/13/99;
- [REDACTED] – independent assessment 12/27/99 – surgery date 12/8/99;
- [REDACTED] – independent assessment 4/7/00 – surgery date 3/22/00;
- [REDACTED] – independent assessment 1/24/00 – surgery date 1/12/00;
- [REDACTED] – independent assessment 3/3/00 – surgery date 3/1/00; and
- [REDACTED] – independent assessment 4/27/00 – surgery date 4/5/00.

The above deviations are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is the sponsor's responsibility to ensure adherence to each requirement of the Act and regulations. Recently, the Division of Bioresearch Monitoring issued a Warning Letter to [REDACTED] for violations during his participation in this study. Some of the violations noted for [REDACTED] include failure to obtain IRB approval and informed consent before allowing study subjects to participate in the investigation; failure to submit adverse event reports in a timely manner; and failure to conduct the investigation in accordance with the investigational plan. [REDACTED] participation in the study was suspended by the IRB. The IRB has since reinstated [REDACTED].

As a sponsor, when you discover that an investigator is not complying with the signed investigator agreement, the investigational plan, the requirements of FDA regulations or any conditions of approval imposed by the reviewing IRB and FDA, you are required to promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation.

Your response states that the "Company" will take corrective action by not distributing any devices "until all required documents are in hand, i.e., a copy of the signed informed consent, IRB approval, and where possible, an independent assessment from an uninvolved physician." Please be aware that, as outlined in the firm's conditions of approval, physicians **must** obtain an independent assessment from an uninvolved physician before implanting the device under "compassionate use." Your corrective action may be assessed and verified during a future inspection.

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Within 15 working days of receipt of this letter, please provide this office with written documentation of any other specific steps you have taken or will be taking to correct these violations and to prevent the recurrence of similar violations in current and future studies. Failure to respond can result in further regulatory action without additional notice. Please address your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring HFZ-312, 2094 Gaither Road, Rockville, Maryland 20850. Attn: Pamela Reynolds.

A copy of this letter has been sent to the FDA's Denver District Office, Denver Federal Center, Building 20, 6th Avenue and Kipling Street, Denver, Colorado 80225. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Pamela Reynolds at (301) 594-4720, ext. 155.

Sincerely yours,



for

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