



Via Federal Express

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

**WARNING LETTER**

JUN -- 4 2004

Joachim Langer, President  
Biotronik, Inc.  
6024 Jean Road  
Lake Oswego, OR 97035

Dear Mr. Langer:

This Warning Letter informs you of objectionable conditions revealed during Food and Drug Administration (FDA) inspections recently conducted at your facility and at two of your clinical study sites. This letter also requests that prompt corrective actions are implemented in response to the violations cited. Ms. Lori J. Silverstein and Ms. Deborah A. Nebenzahl, Investigators from FDA's Seattle District Office conducted the inspection at your facility during the period of December 16, 2003 through January 22, 2004. The purpose of the inspection was to determine if your activities as a Sponsor of the studies for the [REDACTED] PMA [REDACTED] and IDE [REDACTED] complied with applicable FDA regulations, published in Title 21, Code of Federal Regulations, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions [21 CFR Parts 50 and 812]. FDA inspected the clinical study site of Dr. [REDACTED] on December 9, 2003-January 7, 2004, and inspected the clinical study site of Dr. [REDACTED] on January 13-29, 2004. The products used in the study are devices as that term is defined in Section 201(h) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 321(h)].

These inspections were conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemption (IDE), Pre-Market Approval (PMA), and Pre-Market Notification [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 investigation.

Our review of the inspection reports and related documents revealed that you violated regulations governing the responsibilities of Sponsors, as published under 21 CFR Part 812 - Investigational Device Exemptions (available at <http://www.gpoaccess.gov/cfr/index.html>). [REDACTED]

**You failed to allow FDA Investigators to inspect and copy all records relating to an inspection [21 CFR 812.145 (b)].**

An example of this failure includes but is not limited to the following:

You refused to allow the FDA investigators direct access to the monitoring reports for the [REDACTED] during the inspection, but only allowed examination of correspondence files related to the monitoring visits. Quality audits or "internal audits" as required by the Quality System Regulations (21 CFR Part 820) refer to manufacturing processes and are generally exempt from FDA review, however, monitoring reports for clinical trials are not considered by FDA to be internal audits, and therefore are not exempt from review during FDA inspections.

Responsibilities of sponsors include ensuring proper monitoring of the investigation [21 CFR 812.40] in order to secure compliance with the investigational plan [21 CFR 812.46 (a)]. By not allowing FDA to inspect and copy all records related to the inspection, including the monitoring reports, the FDA investigators were unable to determine whether the monitoring for this study was adequate to ensure investigator compliance.

**You failed to secure the investigator's compliance with the investigational plan and applicable FDA regulations [21 CFR 812.46(a)].**

A sponsor who discovers that an investigator is not complying with the signed investigator agreement, the investigational plan, the requirements of applicable FDA regulations, or any conditions of approval imposed by FDA or the reviewing Institutional Review Board (IRB) must promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation [21 CFR 812.46(a)].

Examples of this failure include but are not limited to the following:

Our review of the inspection reports for the inspections of Drs. [REDACTED] and [REDACTED] clinical study sites disclosed that, despite periodic clinical monitoring visits from your firm's designated monitors, violations were repeatedly committed at the sites during the clinical investigation.

- Dr. [REDACTED] reported several Serious Adverse Events (SAEs) months after their occurrence to the IRB. During the inspection, the FDA investigator also discovered one SAE that had not been reported at all. There were numerous protocol deviations for missed visits, missed procedures, and visits outside the protocol-defined visit windows that were not included in your August 2003 update report to the FDA.

- Dr. [REDACTED] failed to follow the investigational plan by [REDACTED] [REDACTED] not maintaining the minimum Activated Clotting Time as required by the protocol in 27 of 28 enrolled subjects, and failing to perform required blood tests for 25 of 28 enrolled subjects.

There were no records to demonstrate that your firm obtained prompt correction and subsequent compliance by the clinical investigators in question, or that your firm terminated these clinical investigators' participation in the study to prevent the recurrence of serious protocol deviations or regulatory violations.

In addition, you failed to notify the FDA within 10 working days that records custody and responsibility were transferred from the sponsor to another party [21 CFR 812.140(e)].

You stated during the inspection that Biotronik, Inc. did not maintain the clinical data, as that responsibility had been transferred to a clinical research organization, [REDACTED]. However, federal regulations require sponsors to maintain all records related to research, unless custody of specific records has been transferred to another person or party who will accept responsibility for them. If this situation occurs, sponsors are required to notify FDA not later than 10 working days after the transfer occurs. The PMA Clinical Report sent by you to the FDA in August 2003 states "Biotronik is under contract with [REDACTED] for the collection, management and analysis of the [REDACTED] patient data." However, this does not constitute notification of transfer of custody. You provided the FDA Investigators with a copy of correspondence from Biotronik, Inc., dated December 19, 2003, to FDA's Center for Devices and Radiological Health regarding an Amendment to PMA [REDACTED] for transfer of clinical data records to [REDACTED]. As part of the Amendment, you must also provide a letter from [REDACTED] indicating their receipt of the clinical data records, and their agreement to accept responsibility for the records under the applicable requirements of 21 CFR Part 812. If you have questions regarding the responsibility transfer process, please contact Ms. Lisa C. Fisher of the CDRH, Office of Device Evaluation, Program Operations Staff, at (301) 594-2186.

Because notification of records custody was not performed as required, the FDA investigators were unable to perform the required PMA Data Audit in order to verify the accuracy of the clinical data being reported to the FDA by the sponsor.

The deviations presented in this letter are not intended to be an all-inclusive list of objectionable practices that may exist at Biotronik, Inc. It is your responsibility to ensure adherence to each requirement of the Act and all pertinent federal 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

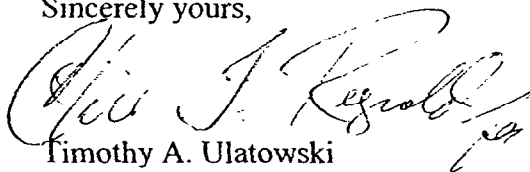
Page 4 - Joachim Langer

respond to this letter and take appropriate corrective action could result in regulatory action without further notice. Please respond in writing to:

Food and Drug Administration  
Center for Devices and Radiological Health, Office of Compliance  
Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312)  
2094 Gaither Road, Rockville, Maryland 20850  
Attn: Mr. Kevin Hopson, Consumer Safety Officer.

A copy of this letter has been sent to FDA's Seattle District Office, Food and Drug Administration, 22201 23<sup>rd</sup> Drive SE, Bothell, WA 98021. We request that you copy the district on your response.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is written in a cursive style and is positioned above the printed name.

Timothy A. Ulatowski  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health