



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

**WARNING LETTER**

VIA FEDERAL EXPRESS

JUL 16 2004

Mr. Uwe Ahrens  
CEO  
Aap Implantate AG  
Lorenzweg 5  
12099 Berlin, Germany

Dear Mr. Ahrens:

During the inspection of your firm located in Berlin, Germany on January 26-29, 2004, United States Food and Drug Administration (FDA) investigator, James P. McCreavey, determined that your firm manufactures labeled non-sterile Class I and labeled non-sterile Class II orthopedic implants. Additionally, your firm has a current 510(k) under review for a labeled sterile Class II orthopedic implant. These products are devices within the meaning of Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(h)].

The investigator documented significant violations from the Quality System (QS) regulation Title 21, Code of Federal Regulations (CFR), Part 820. These violations cause the devices listed above to be adulterated within the meaning of section 501(h) of the Act [21 U.S.C. § 351(h)], in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements established by the QS regulation.

Your firm's significant violations include, but are not limited to, the following:

**1. Failure to establish and maintain adequate design input procedures, as required by 21 CFR 820.30(c), Design Input.**

The QS regulation under 21 CFR 820.30(c) requires the Design Input procedures to include a mechanism for addressing incomplete, ambiguous, or conflicting requirements.

Your firm failed to comply with the requirements of 21 CFR 820.30(c). For example, your design control procedures for the knee endoprosthesis device lack a mechanism for addressing incomplete, ambiguous or conflicting design input requirements. FDA acknowledges receipt of your firm's March 05, 2004 response to

the FDA Form 483 observations. In the response, your firm promised to provide a revised procedure by March 2004. To date, we have not received any correspondence from your firm with the promised correction. Please supply the revised procedure.

**2. Failure to adequately maintain device master records, as required by 21 CFR 820.181, Device Master Record (DMR).**

The regulation under 21 CFR 820.181 requires that the DMR for each type of device shall include, or refer to the location of, the following information: device specifications, production process specifications, quality assurance procedures and specifications, packaging and labeling specifications and installation, maintenance and serving procedures and methods.

Your firm failed to comply with the requirements of 21 CFR 820.181. For example, the knee endoprosthesis DMR did not contain or reference (1) device drawings, (2) equipment specifications for the Roders machine used to manufacture the device, and (3) packaging and labeling specifications.

FDA acknowledges that these deficiencies were corrected by your firm and verified at the close-out of the inspection by the investigator. You appear to have adequately corrected this quality problem. Please explain how your firm intends to ensure that this kind of quality problem is not repeated.

**3. Failure to validate, according to an established protocol, computer software for its intended use, when that software is used as part of the Quality System or part of production as required by 21 CFR 820.70(i), Automated Processes.**

The regulation under 21 CFR 820.70(i) requires that when computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.

Your firm failed to comply with the requirements of 21 CFR 820.70(i). For example:

- (1) The [ ] software used in the design and development process is not validated.
- (2) The [ ] program used by the [ ] machine has not been validated for its intended use.
- (3) The [ ] software used for inventory and process control has not been validated for its intended use.

The March 05, 2004 response indicates that your firm would provide the missing validation information for the [ ] software programs by

July 2004. The response is not adequate. Please provide the software validation protocols for these three software programs and explain how your firm plans to prevent this error from recurring in the future.

**4. Failure to establish and maintain a Design History File for each type of device as required by 21 CFR 820.30(j), Design History File (DHF).**

The regulation under 21 CFR 820.30(j) requires that each manufacturer shall establish and maintain a DHF for each type of device.

You failed to comply with the requirements of 21 CFR 820.30(j). For example, there is no DHF for the knee endoprosthesis device. Your firm's response dated March 05, 2004 promises correction by July 2004 and states your R&D manager has begun to provide the DHF and it should be completed and sent before the promised date. This is not an adequate response. Please provide a copy of the DHF for the knee endoprosthesis device, a copy of the procedure(s) your firm utilizes for assembling the DHF to fulfill the requirements of 820.30(j), and explain how your company plans to ensure this error is not repeated.

FDA also wishes to address a potential design verification violation. Although FDA acknowledges that your firm's knee endoprosthesis has not yet been marketed in the USA and that all design control activities related to this device may not have been completed, at the time of the inspection your firm lacked documentation establishing that [redacted] sterilization of the [redacted] packaging did not impact on the performance of the [redacted] packaging. This observation was noted on the List of Inspectional Observations (Form FDA 483) issued at the closeout of the inspection.

FDA acknowledges that the investigator annotated this Form FDA 483 observation as Corrected and Verified. Additionally, your response, dated March 05, 2004, states that the certification from the supplier which assures that materials could be used for [redacted] sterilization has been integrated into the Device Master Record (DMR). The verification by the investigator and the response from your firm appear to be adequate. However, please take note that if your firm had not corrected this problem before marketing the device in the United States, it would have resulted in a failure to adequately document all design verification activities establishing that Design Outputs meet the Design Input requirements as required by 21 CFR 820.30(f), Design Verification.

This letter is not intended to be an all-inclusive list of violations at your facility. It is your responsibility to ensure adherence to each requirement of the Act and applicable regulations. The specific violations noted in this letter and Form FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

U.S. federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of government contracts.

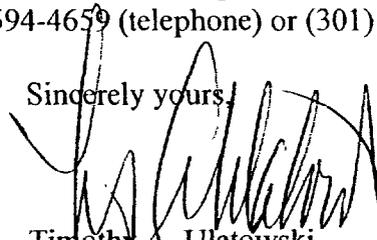
Given the serious nature of these violations of the Act, the various orthopedic implants manufactured by your firm imported or offered for import are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA may take steps to refuse these products, known as "detained without physical examination," until these violations are corrected. In order to prevent your devices from being detained without physical examination, you should provide a written response to this Warning Letter as described below and correct the violations described in this letter. We will notify you if your response is adequate, and we may need to re-inspect your facility to verify that the appropriate corrections have been made.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter, of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. You should include all documentation of the corrective action you have already taken. If you plan to make any corrections in the future, include those plans with your response to this letter as well. If the documentation is not in English, please provide a translation to facilitate our review.

Your response should be sent to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Enforcement B, Orthopedic, Physical Medicine and Anesthesiology Devices Branch, 2094 Gaither Road, Rockville, Maryland 20850 USA, to the attention of Ms. Christy Foreman.

If you need help in understanding the contents of this letter, please contact Ms. Christy Foreman at the above address, or at (301) 594-4659 (telephone) or (301) 594-4672 (telefax).

Sincerely yours,



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