



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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WARNING LETTER

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

Via Federal Express

Richard D. Anderson
President, Cordis Cardiology
Cordis Corporation
14201 N.W. 60th Avenue
Miami Lakes, FL 33014

Dear Mr. Anderson:

The Food and Drug Administration (FDA) performed post-approval inspections of Cordis Corporation and its facilities involved in the design, manufacture and distribution of the CYPHER™ Sirolimus-Eluting Coronary Stent. The inspections were performed at your facilities located in: Miami Lakes, Florida on September 2 through 12, 2003; San German, Puerto Rico on October 10 through December 1, 2003; Warren, New Jersey on October 29 through December 4, 2003; Roden, Netherlands on October 13 through 16, 2003; Beerse, Belgium on October 20 through 23, 2003; and Latina, Italy on October 27-31, 2003. These drug-eluting stents are regulated as medical devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The purpose of this letter is to apprise top management of the observations made at your facilities and to remind you of your responsibility to assure all facilities are in compliance with the Act and all pertinent regulations. FDA is concerned with the breadth and scope of the specific violations noted in this letter and the inspectional observations noted on the form FDA-483s which we believe are symptomatic of serious underlying problems in your firm's manufacturing and quality systems.

As president of Cordis Cardiology, you have executive responsibility to assure that all devices manufactured or contract manufactured by you or your facilities comply with the Quality System regulation, Title 21, Code of Federal Regulations (CFR), Part 820. The Quality System regulation requires each manufacturer to establish and maintain a quality system that is appropriate for the specific medical device(s) designed and manufactured. Further, management with executive responsibility and the management representative(s) are responsible for ensuring that the quality system requirements are effectively established and effectively maintained. We consider you and the management located at corporate headquarters office listed at the above address to be the highest management individuals in your organization, and therefore, the most responsible and accountable for the actions of all the other corporate manufacturing sites including, but not limited to, those listed above.

These inspections revealed that your CYPHER™ Sirolimus-Eluting Coronary Stents are adulterated under section 501(h) of the Act, in that the methods used in, or the facilities or controls used for, the design, manufacturing, packing, storage, or installation are not

in conformance with the Current Good Manufacturing Practice (CGMP) requirements for medical devices which are set forth in the Quality System (QS) regulation, as specified in 21 CFR § 820. The FDA inspections found systemic violations in the quality management system employed to ensure the safety and effectiveness of your drug-eluting stents that recurred at several of your facilities. Significant deviations from the QS regulation include, but are not limited to, the following:

Corrective and Preventive Action Subsystem

1. Failure to establish and maintain adequate procedures (a) to control product that does not conform to specified requirements including the identification, documentation, evaluation, segregation, and disposition of nonconforming product, as required by 820.90(a); and (b) to review and dispose of nonconforming product, with documented justification for use of nonconforming product, as required by 21 CFR § 820.90(b). For example:

San German, PR:

- There were several instances where laboratory results were invalidated without adequate documentation or scientific justification. Although your firm addressed these subjects in procedures number [REDACTED], Rev 1, "Quality Assurance Lab Deviations" and [REDACTED] Rev. 4, "Management of Suspect OOS Investigations in the Quality Laboratory," those procedures were not followed.
 - Original Out-Of-Specification (OOS) results obtained during the residual solvent analysis of [REDACTED], and [REDACTED] were invalidated without documented assignable causes or adequate scientific rationale. Lots were originally rejected, but later were re-sampled, retested, and released for distribution based on the retest passing results. There were similar deficiencies in handling OOS drug elution results for [REDACTED] and [REDACTED].
 - The retesting of approximately [REDACTED] of [REDACTED] was performed with additional new samples from the lot rather than with the original sample, as required by your procedures. Further, there was no assurance that the new samples were representative of the lots in question.

Warren, NJ:

- Several OOS test results were attributed to analyst or instrument error without documented evidence of the error. OOS laboratory investigations, such as [REDACTED], [REDACTED] and others, failed to document adequately the evaluations of all the possible causes of the OOS results.

Miami Lakes, FL:

- The documentation for the release of lots containing [REDACTED] coated defects did not include adequate data or justification for using nonconforming product. For the [REDACTED] coated defects your firm assigned a Health Hazard score of 1 (scale 1-10, with 10 being the most hazardous) indicating

minimal safety risk to the patient, without developing a justification or data supporting such a conclusion.

2. Failure to establish and maintain adequate procedures for corrective and preventive actions, as required by 21 CFR § 820.100(a). For example:

Miami Lakes, FL:

- There is no documentation that the Quality Board reviewed any additional thrombosis complaints from outside the United States after they reviewed the first nine complaints. Despite the significant issues presented by these complaints, the Quality Board concluded that no action was needed at that time and did not open a CAPA investigation file. Instead, the Quality Board requested Roden QA to monitor this event type closely, but gave no clear documentation or direction to Roden QA on how to monitor the situation. Roden QA reportedly reviews the CYPHER thrombotic complaints during monthly CAPA meetings but since no CAPA was originally initiated there are inadequate procedures to monitor and follow this issue for potential corrective or preventive action.
- The Return Product Analysis and Report Writing SOP [REDACTED], section [REDACTED], states that, if required, the technician shall request the help/assistance of the appropriate engineer and/or supervisor in identifying the cause of a particular product failure. There were instances where there was no assignable cause for CYPHER™ stent related thrombosis and no indication of user failure to follow the CYPHER™ Instructions for Use. For these cases with no assignable cause, there was no documented evidence that an engineer and/or supervisor was requested or that one participated in any deliberations on assigning causes for these product failures. One of your responses proposes a revision to a Corporate Franchise Methods procedure as your correction to this observation. Making revisions to the Corporate Franchise Method procedure does not adequately resolve this issue for technicians using the Report Product Analysis and Report Writing SOP, nor does it address the fundamental problem of technicians not following your own procedures.

San German, PR:

- Confirmed OOS results were not adequately investigated because they were not referred to Manufacturing and/or Operations Quality Assurance to initiate a Material Review Record (MRR). These laboratory investigations were closed before opening an MRR, despite the provisions of your procedure QCOP [REDACTED]. Without proper investigation, your firm cannot identify the action(s) needed to correct and prevent recurrence. A revised SOP ([REDACTED]) submitted in response to this observation is still not adequate because the procedure does not require a production level investigation to rule out manufacturing error in those instances where laboratory error is inconclusive. When there is no clear identification of human error or instrument malfunction during the performance of an analytical procedure, relying on testing alone to invalidate an OOS test result is inadequate.

- Your firm conducted inadequate or incomplete investigations into the cause of nonconformities for MRRs [REDACTED], [REDACTED], and [REDACTED] and [REDACTED].
- Written procedures are inadequate because they do not require that the laboratory data quality source be analyzed and evaluated using appropriate statistical methodology, which is necessary to detect recurring quality problems or potential product problems. Nor is the analysis of laboratory data adequately included as part of management review.
- Your firm failed to conduct adequate investigations or perform adequate corrective and preventive action for [REDACTED] failed lots and an additional [REDACTED] lots for which in-process testing was not conducted. Lots of coated stents were released for distribution based on passing finished device testing. However, your firm used different sampling methods for the in-process testing and the finished device testing. Those divergent sampling methods therefore did not ensure that lots that either failed in-process testing, or were not tested at the in-process stage, were adequately represented in the finished device testing.

Warren, NJ:

- Documentation of several OOS investigations reviewed during the inspection did not contain recommended follow-up and did not address corrective and preventative actions.
 - OOS laboratory investigations, such as [REDACTED], [REDACTED] and others, did not appear to evaluate adequately related lots that may have been associated with the same causes of error.
3. Failure to establish and maintain adequate complaint handling procedures to ensure all complaints are evaluated and investigated, and processed in a uniform and timely manner, as required by 21 CFR § 820.198. For example:

Miami Lakes, FL:

- Failure analysis reports relating to CYPHER™ thrombosis complaints were not completed in a timely manner. For example, reports were signed during the inspection several months after the complaints had been received. The complaint procedure ([REDACTED]) does not adequately address how complaints are to be closed in a timely manner or adequately define how complaints are to be reviewed for assurances of timely handling.
- Complaint [REDACTED] relating to the CYPHER™ stent thrombosis event was received on 6/30/02 but was not closed until 6/20/03. In addition, several hundred complaints received in 2002 and 2003 through [REDACTED] [REDACTED] is an internet-based tracking system developed for physicians in Europe to report CYPHER product related experiences, complaints and adverse events back to the Cordis Roden facility) had not been fully investigated at the time of the inspection.

Warren, NJ:

- The Warren Clinical Research Group occasionally receives complaints of post market events, which are then forwarded to the complaint handling unit located at Cordis Headquarters in Miami Lakes, FL. The Warren, NJ site procedure is inadequate because it does not establish and maintain a method on how to log or record complaints to ensure that all complaints received by the Warren Clinical Research Group are appropriately transferred and captured by the responsible complaint handling unit in Miami Lakes.

Roden, Netherlands:

- All complaints from outside the United States are received first at the Roden facility and then sent to Miami Lakes. Due to the failure of the [REDACTED] Registry, (which was not adequately validated by Cordis for its intended use – see 820.70(i) below), complaints were not being submitted in a timely manner to Roden. As a result, Miami Lakes did not receive complaints from outside the U.S. in a timely manner, which impeded the timely investigation of the complaints arising within the United States, since the Roden complaints were relevant to investigation and follow-up of the domestic complaints.

Production and Process Controls Subsystem

4. Failure to validate with a high degree of assurance, processes, including changed processes, that cannot be fully verified by subsequent investigation and test, as required by 21 CFR § 820.75(a) & (c). For example:

San German, PR:

- The validation of the [REDACTED] Coating Process on the CYPHER™ stents was inadequate.
 - The coated stents cannot be directly tested and stainless steel [REDACTED] are used to represent the adequacy of the [REDACTED] adhesion (peel) test during the validation study. Your firm used only [REDACTED] stainless steel [REDACTED] per batch for each validation run. However, your firm failed to justify how the [REDACTED] stainless steel [REDACTED] could be considered to be representative of the [REDACTED] coating adhesion on every stent in the entire batch inside the [REDACTED] deposition chamber.
 - Additionally, the stainless steel [REDACTED] do not adequately represent the stents because the stents are not subject to the same cleaning procedure as the stainless steel [REDACTED]

Beerse, Belgium:

- Spray coating process validation was inadequate because the firm had not even completed performance qualification at the time of the post approval inspection.

Warren, NJ:

- There was no record of the review or revalidation of a change in tank size for the [REDACTED] Deionization water system.
(3 words)

5. Failure to adequately validate for its intended purpose and according to an established protocol computer software used as part of the production or quality system, and failure to document validation activities and results, as required by 21 CFR § 820.70(i). For example:

Roden, Netherlands:

- The [REDACTED], an internet based reporting system for clinical and post market events for physicians, was not adequately validated. Beginning in April 2002 physicians entered events into the [REDACTED] system, an automatic email was to be generated informing Roden of the event. It was not until August – early September 2003 that employees at the Warren, NJ facility discovered the [REDACTED] system was not performing as intended and was not sending the automatic emails to Roden. As a result there were significant delays in obtaining complaints and event information relevant to post market experience.

Warren, NJ:

- The automated [REDACTED] data acquisition system, used to ensure the integrity of the analytical data generated from laboratory chromatography equipment, was not adequately validated for its intended use. The validation did not include testing and verification of backup and restoration of the electronic data files.

San German, PR:

- Your firm failed to evaluate the need for revalidation of the QC Lab Data Acquisition System (which performs instrumentation control, data acquisition, data processing and report generation for all the activities performed at the San German QC laboratory) after the addition of [REDACTED] new acquisition servers, [REDACTED] new chromatographic systems and changes in the acquisition server configuration. You continued to utilize this revised QC Lab data acquisition system without ensuring that the system would perform as intended.
- In addition, prior to the approval of the Data Acquisition System Formula Validation, protocol [REDACTED] your firm relied on the not yet validated system for automated calculations, obtained by using custom-made formula fields, in making release decisions without manual verification.

Design Control Subsystem

6. Failure to establish and maintain adequate procedures for validating the device design to ensure that the device conforms to defined user needs and intended uses and to ensure that design validation is performed under defined operating conditions on initial production units or their equivalents, as required by 21 CFR § 820.30(g). For example:

San German, PR:

- The documentation supporting the coated stent component shelf life of [REDACTED] weeks, Report No. [REDACTED], "Justification for Component Shelf life Specifications," is inadequate. The coating processes described in it and used on test stents do not represent the current coating procedure conducted at the San German site. Moreover, the three validation lots manufactured at your facility and placed in the stability testing program had a work-in-process time from the [REDACTED] day of coating to sterilization of only [REDACTED] days, yet some lots of components have holding times exceeding [REDACTED] days.
- The coated stent component shelf life study was also inadequate because it failed to include coated stents packaged in [REDACTED] configuration under refrigeration, which are your current in-process storage conditions.

Warren, NJ:

- Entire lots of CYPHER™ stent, consisting of [REDACTED] validation lots from each coating site, were placed in the stability testing program prior to the approval date of April 24, 2003, and complied with conditions of the premarket approval. However, your firm has failed to ensure that this stability data meets the requirements of design validation. Design validation must be performed under defined operating conditions on initial production units, lots or batches or their equivalents to full scale manufacturing. Evidence of full scale manufacturing has shown lots released at the lower assay release limits and atypical lots released after OOS investigations, however, there is no evidence that the stability testing performed prior to approval took these full scale manufacturing issues into appropriate consideration during the initial stability testing. No devices have been placed on stability since the PMA approval and no additional stability validation testing has been performed to show that stability is not affected by lower assay release or lots released after OOS investigations. Therefore, the current design validation data on stability is inadequate.

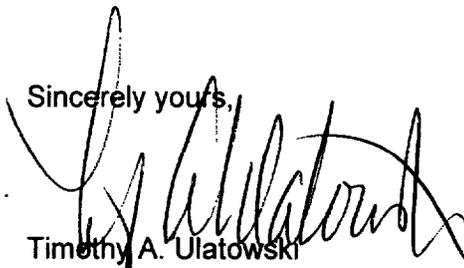
This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the close of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. You also must promptly initiate permanent corrective and preventive action on your Quality System.

You should know that these are serious violations of the law and may result in the FDA initiating regulatory action without further notice. These actions include, but are not limited to, seizing your product inventory, obtaining a court injunction against further marketing of the product, or assessing civil money penalties. Also, other Federal agencies are advised of the issuance of all Warning Letters so that they may take this information into account when considering the award of government contracts.

The agency has received and reviewed several responses that your firm has supplied as a result of FDA 483s issued at the above mentioned facilities. FDA acknowledges the general commitments made and the fact that some of the responses to certain FDA 483 items appear to propose adequate corrective actions. However, in general your responses appear to be specific spot fixes and do not take a systematic approach to comprehensively cover the corrections, the corrective actions and the preventive actions. None of the responses adequately deal with true preventive actions. Further, the responses fail to bring together the corporate corrective and preventive actions necessary to tie the operations of all these facilities together as they all contribute to manufacture this particular product. Therefore, FDA requests that you do not resubmit the individual facility responses as your response to this Warning Letter. FDA is requesting that you respond to this Warning Letter with a Corporate Corrective and Preventive Action plan which ties all facilities involved in the design, manufacture and distribution of the CYPHER™ Sirolimus-Eluting Coronary Stent. After FDA has reviewed any response to this Warning Letter, we would recommend individual meetings with the respective district offices in order to follow-up on the outstanding concerns specifically raised in each of the recent inspections and not specifically addressed in this letter.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the timeframe within which the corrections will be completed. Please direct your response to Gladys Rodriguez, Director, Division of Enforcement B, Office of Compliance, Center for Devices and Radiological Health HFZ-340, 2098 Gaither Road, Rockville, MD 20854. Ms. Rodriguez can also be reached at 301-594-4646.

Sincerely yours,



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