U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Endotec, Inc. 10/22/09

Department of Health and Human Services

Public Health Service
Food and Drug Administration
555 Winderley Pl., Ste. 200
Maitland, Fl 32751

VIA FEDERAL EXPRESS

WARNING LETTER

FLA-10-02

October 22, 2009

Young Bock Shim
President and Chief Executive Officer
Korea Bone Bank Co., Ltd.
Room 402
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345-30 Gasan-Dong Geumcheon-Gu
Seoul, Korea 153-782

Sok Kyun Hong
Managing Director
Endotec, Inc.
2546 Hansrob Road
Orlando, Florida 32804-3318

Dear Messrs. Shim and Hong:

During an inspection of Endotec, Inc. located in Orlando, Florida, on May 18 through May 29, 2009, an investigator from the United States Food and Drug Administration (FDA) determined that Endotec, Inc. manufactures various orthopedic implants. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that these devices are 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 of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (C.F.R.), Part 820. We received a response from Michael McAvenia, Quality Manager, dated June 14, 2009, concerning our

investigator's observations noted on the Form FDA 483, List of Inspectional Observations, which was issued to Mr. Hong. We address this response below, in relation to the noted violations. These violations include, but are not limited to, the following:

1. Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test, that the process shall be validated with a high degree of assurance and approved according to established procedures, as required by 21 C.F.R. 820.75(a). For example:

a. The procedures titled Sterilization of Orthopedic Products, SLP0022, Rev A, dated 7/7/2008, REFERENCE section 5.3 states, "ANSI/AAMI/ISO Guideline 11135-1994, Validation and Routine Control of Ethylene oxide and section 6.4 states, "EtO validation is performed per ANS/AAMI/ISO 11135 guidelines." However, the ANSI/AAMI/ISO 11135-1994 standard - Medical devices - Validation and routine control of ethylene oxide sterilization, states in the Scope section 1.4 that "[this standard] does not cover sterilization either by the technology of injecting ethylene oxide or its mixtures directly into individual product packages or continuous sterilization processes." Therefore your **(b)(4)** sterilizer **(b)(4)** capacity **(b)(4)** cannot be validated per the ANSI/AAMI/ISO 11135-1994 standards requirements since this sterilizer injects the ethylene oxide gas from an ampoule and the gas spreads through a liner bag and moves from higher concentrations to lower concentrations until equilibrium is reached.

b. You failed to validate the sonication cleaning process to remove a technical grade **(b)(4)** affixed to the porous-coating area to clean implant products such as hip, shoulder, ankle, and knee implant products and included EtO Loads NN317 - NN392. In addition, you currently do not monitor the temperature or time of the cleaning sonication processes
conducted.

c. You failed to validate **(b)(4)** software and thus failed to ensure that the engraving process sequences for orthopedic implants are valid and accurate.

The adequacy of your response cannot be determined at this time because it states only that you have "begun defining the priority and methodology for which processes are to be validated." This response lacks sufficient details regarding the corrective actions that the above processes have been adequately validated.

2. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms t its specifications, as required by 21 C.F.R. 820.70(a).

For example,

a. The routine sterilization loads were not conducted according to the approved validated sterilization parameters. Specifically,

i. The Endotec sterilization validation report, approved on November 25, 2008, reveals the sterilization validation consisted of one type of implant, the Buechel-Pappas Knee
family implant. However, routine sterilization loads contained more than one type of implant. The sterilization validation report contained three half cycle runs consisting of **(b)(4)** units and consisting of one bag. However, sixteen routine production sterilization loads, (NN367 to NN381, and NN391) conducted from November 25, 2008 to February 12, 2009, contained multiple lot sizes ranging from **(b)(4)** units and multiple bags were used in ten routine production sterilization loads (NN382 to NN388 and NN390 to NN392).

ii. The sterilization validation report states the Endotec Implant Family of products can be routinely processed in the **(b)(4)** Sterilization unit utilizing the preset **(b)(4)** default parameters. However twenty six (26) routine sterilization loads NN367 to NN392 were processed in sterilization cycles of **(b)(4)**.

iii. Contract laboratory testing reported that load NN378, processed on January 30, 2009, and load NN392, processed April 17, 2009, failed sterility testing. One orthopedic implant from load NN378 was implanted into a patient on April 15, 2009.

b. The **(b)(4)** engraving procedures lacked adequate instructions on the methods that define and control the manner of production. Specifically, the **(b)(4)** engraving procedures lacked adequate controls and were not monitored. The **(b)(4)** engraving process for orthopedic implants including Conforming Bearings, Catalog #04-33-0ZYX. Work Instructions for Machining Rotation Bearing, WI0433-0000, Revision A (February 23, 2009), outlines the conduct of the **(b)(4)** engraving process of the bearings in Operation #7 and #8, but does not specify an engraving depth. In addition, Drawing #0401-3300-00YX for the bearings specifies the location and font sizes of the engraving, but does not specify an engraving depth. Conversely, Specification S-005, Revision B (February 02, 2006), Section 5.2.1 does specify an engraving depth of "no more than 0.015," however, Inspection Procedure WI04330ZYX does not provide for a measure to ensure the engraving depth specification of **(b)(4)**" is met and the structural integrity of the bearings is not compromised.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks details regarding your corrective actions and their implementation. Your response states only: "Documentation will be reviewed to determine adequacy for process monitoring which will include both production documentation but also inspection methods and testing processes. Engineering specifications will also be reviewed for accuracy and requirements."

3. Failure to establish and maintain procedures for investigating the cause of nonconformities relating to product, processes, and the quality system, as required by 21 C.F.R. 820.100(a)(2). For example:

a. Procedure for Corrective and Preventive Action, Procedure SLP0012, Revision C, dated September 6, 2005 Sections 6.7.2 and 6.7.3, were not implemented in that Endotec did not conduct and document an investigation into the power failures occurring during EtO sterilization of loads NN318, NN331, and NN339. Orthopedic implants processed within these loads were shipped for distribution.

b. Corrective Action Request (CAR) #090208, initiated on September 2, 2008, reports that Conforming Bearings, Lot #04330031C and Lot #04330031D were manufactured with an undersized **(b)(4)** slot depth.

Investigation revealed the bearings were measured incorrectly by the operator after set-up, but does not address the possible root-cause of why the operator measured the bearings incorrectly. Corrective action established a set-up platform with pins to check the bearings. Retraining was implemented before the investigation could determine an appropriate root-cause for the nonconformance.

c. CAR #082508, initiated on August 25, 2008, reports that Conforming Bearings, Lot #04330025H and Lot #04330011C were manufactured with out-of-specification (O/S) cone dimensions. Your investigation revealed nonconforming bearings were placed in the order from the initial set-up, but does not address the possible root-cause of why the nonconforming bearings were not controlled (identified and segregated) by the set-up operator according to established procedures. A corrective action to check eery bearing and notch nonconforming bearings was implemented before investigation could determine an appropriate root-cause fo the nonconformance.

d. CAR #080808, initiated on August 08, 2008, reports that Conforming Bearings, Lot #04330002H and Lot #04330002G were incorrectly set-up for manufacture at **(b)(4)** machine Operation #6, resulting in slots being machined on the wrong side of the bearings. In addition, no set-up bearing was submitted for inspection prior to the run. The investigation revealed the operator had not performed the operation before, but does not address the possible root-cause of why an inexperienced operator was permitted to run the operation. A corrective action to add a stop to the machining fixture, so bearings cannot be machined on the wrong side, was implemented before the investigation could determine an appropriate root-cause for the nonconformance.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks supporting documentation regarding your proposed corrective action. Your response states only that you will 1) review documentation that pertains to the reporting, investigation, and preventive actions related to non-conformances; 2) provide additional training of personnel to adequately understand how to perform a root cause investigation, reporting, documenting, and preventative actions for non-conformances; 3) assure

closure will require definitive root cause analysis; and 4) that your processes will be reviewed and revised to provide a more automated method for reporting and tracking. However, you did include any supporting documentation with your response for our review.

4. Failure to review, evaluate and investigate complaints involving the possible failure of a device, labeling, or packaging to meet any of its specifications unless such investigation has already been performed for a similar complaint and another investigation is not necessary, as required by 21 C.F.R. 820.198(c).

For example, complaints involving the possible failure of Tibial Platforms to meet any of its specifications were not adequately reviewed, evaluated and/or investigated, where necessary.

a. Corrective Action Request (CAR) #061808 was initiated as a result of Device Complaint Record (DCR) #061808, dated June 18, 2008.

The complaint reported a malfunction of Tibial Platform Size 4 Type 1 where the Pin Stop of the Tibial Platform fell out during surgery. Investigation determined the mating holes were oversized causing the Pin Stop to fall out. A root-cause of the oversized mating holes was not determined, in order to implement an appropriate corrective and/or
preventive action. The Pin Stop malfunction occurred previously as reported in DCR #021208.

b. CAR #021208 was initiated as a result of DCR #021208, dated February 12, 2008. The complaint involved a malfunction of the Tibial Platform Size 3 Type 1 where the Pin Stop of the Tibial Platform fell out during surgery. The investigation determined the Tibial Platforms were reworked improperly causing the pin hole to be deformed and resulting in the Pin Stop falling out during surgery. A root-cause of improperly reworked Tibial Platforms was not determined, in order to implement an appropriate corrective and/or preventive action.

c. CAR #041707 was initiated as a result of DCR #041707, dated April 17, 2007. The complaint involved a malfunction of the Conforming Bearing Size 3 x 0mm where during a surgery a surgeon observed a particle of polyethylene to be hanging off the bearing. The investigation did not determine the cause of the hanging polyethylene particle.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details regarding the proposed corrective action and also lacks adequate evidence of implementation. Your response states only that you will: 1) review documentation that pertains to the reporting, investigation and MDR requirements related to complaints; 2) provide additional training of personnel to adequately understand how to perform a root cause investigation, reporting, and documenting complaints; and 3) that closure [of this CAPA] will require definitive root cause analysis. Supporting evidence is not provided.

5. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms t its specifications, as required by 21 C.F.R. 820.70(a). Where deviations from device specifications could occu as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications.

For example, the polishing operators were not qualified using established process control procedures for workmanship expressed in either documented standards or by means of
identified and approved representative samples for polishing operations conducted on manufactured orthopedic implants including hip, shoulder, and knee.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details regarding the corrective action and also lacks adequate evidence of implementation of the corrective action. Your response states only you "will establish documented procedures, workmanship standards, approved samples, and visual aids."

6. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 C.F.R. 820.50. Failure to establish and

maintain the requirements, including the quality requirements, that must be met by suppliers, contractors, and consultants. 21 C.F.R. 820.50(a).

For example, your Procedure for Purchasing (Suppliers), Procedure SLP0007, Revision K, dated April 21, 2009, and Procedure for Vendor Audits, Procedure, SLP0020, Revision D, dated May 16, 2005, are inadequate in that they do not require an evaluation and qualification determinatior of contract service providers for the manufacturing operations including laser etching, porous-coating, solution treatment and fusion welding of orthopedic implants and contract laboratory testing for the analysis of **(b)(4)** and **(b)(4)** in EtO processed orthopedic implants.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details regarding the corrective action and also lacks adequate evidence of implementation of the corrective action. Your response states only that you ''will revise the Purchasing control procedures to address onsite vendor audits, where possible vendor validations of processes. At a minimum, vendors will be required to provide Endoctec Inc. with in process testing, inspection and acceptance documentation, certifications for raw materials, and where appropriate certificates of analysis. Endotec Inc. will perform on-site vendor audits to assess quality systems and controls."

7. Failure to establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met, as required by 21 C.F.R. 820.30(a).

For example, Procedure for Design Control, Procedure SLP0005, Revision F, dated September 9, 2005, was not implemented for the control of the design process for the manufacture of the knee implant, in that:

a. The knee implant design process does not include the results of design validation, including identification of the design, methods, the date, and the individual performing the validation, in accordance with the design control procedure, Section 6.18.

b. The knee implant design process does not include a validation protocol for the assessment of the design input change conducted under Change Request #0833 (May 18, 2008), in accordance with the design contro procedure, Section 6.9. There is no evidence that an assessment was conducted to determine the centerline added to the anterior wall of all tibial platforms will not affect the structural stability of the implants, i.e., depth of laser etching may result in cracks forming in the tibial platforms.

c. The knee implant design process does not include a validation protocol for the assessment of the design input for product stability and packaging integrity of manufactured orthopedic implants, in accordance with the design control procedure, Section 6.9. You have assigned a seven (7) year expiration date to orthopedic implants including hip, shoulder, ankle, and knee implants.

d. The knee implant design process does not address ambiguous design input requirements, in accordance with the design control procedure, Section 6.4.2. Specification #S-O 13, Revision C, dated March 8, 2000, Section 6.2.1 states the implant surface finish for the articulating surface of knee implants is **(b)(4)**; however, routine inspection reports, including that for Drawing #0401-3100-YOOX, state the surface finish specification is **(b)(4)**. The purpose of the surface finish specification for the articulating surface of the knee implants is to facilitate function and inhibit wear.

e. The knee implant design process does not include an established design plan that identifies specific individuals involved in the design process, their assigned activities, and the interfaces with the individuals who provide, or activities that result in, input to the design process, in accordance with the design control procedure, Section 6.4.1.

f. The knee implant design process does not demonstrate that design reviews of design results at appropriat stages of the device's design development were conducted, documented, and maintained in the design history file, in accordance with the design control procedure, Sections 6.4.2, 6.5, and 6.9.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details of the corrective action and also lacks adequate evidence that the corrective action was implemented. Your response states "[a] design control review will be performed to determine the extent tha

a retrospective design review can be performed. A retrospective design review will be based on the initial review, documentation available for review, testing, and validation documentation available." The response lacks any supporting documentation.

8. Failure to establish and maintain design validation procedures to ensure that devices conform to defined user needs and intended uses, and to ensure risk analysis is completed, where appropriate. The results of th design validation, including identification of the design, method(s), the date, and the individual(s) performin the validation shall be documented in the design history file (DHF), as required by 21 C.F.R. 820.30(g).

For example, you did not implement Procedure for Design Control, Procedure SLP0005, Revision F, dated September 9, 2005, Section 6.7 and Procedure for Failure Modes Effects Analysis (FMEA), Procedure SLP0023, Revision B, dated December 6, 2005, for the conduct of risk analysis for the Buechel-Pappas Knee System, RSK04002, Revision B dated December 4, 2007.

Accordingly, the conduct of risk analysis for the Buechel-Pappas Knee System is incomplete in that it does not identify all possible hazards associated with the manufacture of the device; does not assess the risk (severity and probability) in terms of a quantitative score for the manufacturing operations; and does not determine risk control measures for the manufacturing operations including laser etching, **(b)(4)** engraving, cleaning (sonication), polishing, EtO processing and Gamma irradiation.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details regarding the proposed corrective action and also lacks adequate evidence that the corrective action was properly implemented. Your response states only that you "will perform risk analysis fo the products," but fails to include any supporting documentation on how this will be conducted.

9. Failure to establish and maintain procedures for implementing corrective and preventive action, as required by 21 C.F.R. 820.100(a).

For example, the Procedure for Corrective and Preventive Action, Procedure SLP0012, Revision C, dated December 6, 2005, is not complete and does not include requirements for analysis of sources of quality data by means of appropriate statistical methodology to identify existing and potential causes of nonconforming product or other quality problems. The procedure fails to include requirements for verifying or validating corrective and preventive actions and ensuring that the actions do not adversely affect the finished device. The procedure fails to include requirements for submitting relevant information on identified quality problems, as well as corrective and preventative actions, for management review.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details regarding the corrective action and lacks adequate evidence to ensure the corrective action was implemented. Your response states only that you "will revise the corrective preventive action procedure to include nonconforming issues, data analysis, verification, and management review at a minimum." However no supporting documentation is provided.

10. Failure to establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. These quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited, as required by 21 C.F.R. 820.22.

For example, your Procedure for Internal Quality Audit, Procedure SLP0018, Revision H, dated March 8, 2007, Audit Check Lists, Form F-018, Revision A, dated October 30, 2000, Internal Audit Planning Matrix, and the 2009 Master Schedule Memo, do not include defined provisions for conducting quality audits of all major quality criteria including corrections and removals (recall). Also your procedure for Internal Quality Audit, Procedure SLP0018, Revision H, dated March 8, 2007, does not include defined provisions to ensure individuals who conduct quality audits do not have direct responsibility for the matters being audited.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details of the corrective action and also lacks adequate evidence that the corrective action was

implemented. Your response states only that you "will revise the internal audit procedure to include criteria to define all aspects of major audit criteria." However, no supporting documentation is provided.

11. Failure to designate an individual(s) to review for adequacy and approve prior to issuance all documents established to meet the requirements of this part. The approval, including the date and signature of the individual(s) approving the document, shall be documented. Documents established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use, as required by 21 C.F.R. 820.40(a).

For example, documents that were obsolete were observed at a location where they could be used. Specifically, Procedure for Packaging & Labeling, Procedure SLP0015, Revision D, dated September 17, 2005 was available for use by employees, was not identified as obsolete, and was not otherwise prevented from unintended use. This procedure describes the conduct of sterilization by a contract service provider. The procedure has since been revised under Revision E, dated August 22, 2008, employees were trained on the revised procedure on January 8,2009, and the revised procedure has been implemented.

The adequacy of your response dated June 14, 2009, cannot be determined at this time because it lacks sufficient details regarding the corrective action and lacks adequate evidence that the corrective action was implemented. Your response states only that you "will revise the document control system to define adequate controls for the revision, implementation, and distribution controls for all documents." However the response lacks any supporting documentation.

Our inspection also revealed that the BP-Hip implants are misbranded under section 502(t)(2) of the Act, 21 U.S.C. 352(t)(2), in that your firm failed or refused to furnish material or information respecting the device that is required by or under section 519 of the Act, 21 U.S.C. 360i, and 21 C.F.R. Part 806- Reports of Corrections and Removals regulation. Significant deviations include, but are not limited to, the following:

1. Failure to submit a written report to FDA of any correction or removal of a device initiated by a manufacturer to reduce a risk to heath posed by a device, within 10 working days of initiating such correctio or removal, as required by 21 C.F.R. 806.10(b).

For example, you confirmed through contract laboratory testing results that EtO Loads NN378 and NN392, processed on January 30 and April 17, 2009, respectively, failed sterility testing. Two Acetabular Bearings, 3 I.D. x 58 O.D., Catalog No. 01-02-3258, Lot No. 01023258BNN378, underwent processing in these two Eta Loads that failed sterility testing. On April 9 and May 7, 2009, via e-mail, you initiated a removal of these tw non-sterile Acetabular Bearings, 32 I.D. x 58 O.D., Catalog No. 01-02-3258, Lot No. 01023258BNN378, from the market, which were shipped to and in the possession of one of your distributors.

On or before April 15, 2009, you had become aware that one of the Acetabular Bearings, 32 I.D. x 58 O.D., Catalog No. 01-02-3258, Lot No. 01023258BNN378, was implanted into a patient on April 15, 2009. You obtained the other Acetabular Bearings, 32 I.D. x 58 O.D., Catalog No. 01-02-3258, Lot No. 01023258BNN378, from your distributor on May 27, 2009, via overnight delivery. You did not submit a report of the correction or removal to FDA until June 4, 2009.

2. Failure to include in the report of corrections and removals to FDA, information of the model, catalog, or code number of the device and the manufacturing lot or serial number of the device or other identification number, as required by 21 CFR 806.10(c)(5).

For example, the report of the correction or removal submitted to FDA on June 4, 2009, regarding the two non-sterile Acetabular Bearings, 32 I.D. x 58 O.D., Catalog No. 01-023258, Lot No. 01023258BNN378, is incomplete in that you did not specify what components are in the sterilization load in order to identify what components or devices are subject to the correction or removal.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, 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 contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected.

Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

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. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to: Jimmy E. Walthall, Director, Compliance Branch, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, Florida 32751. If you have any questions about the content of this letter please contact: Mr. Walthall at 407-475-4734.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems.

You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely

/S/
Emma R Singleton

Director, Florida District

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