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Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850
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Michael J. Pappas, Ph.D., P.E.
President
Endotec, Inc.
20 Valley Street
Suite 210
South Orange, New Jersey 07079

Re: Reclassification of Non-Constrained, Mobile-Bearing Ankle Prosthesis
Docket Number 2004P-0457/CCP 1
Dated: September 4, 2001
Amended: October 22, 2004

Dear Dr. Pappas:

The Food and Drug Administration has reviewed the above referenced petition for reclassification pursuant to section 513(e) of the Food Drug and Cosmetic Act (Act). Mobile-bearing ankles are currently Class III (PMA) devices. This petition seeks reclassification of Non-Constrained, Mobile-Bearing Ankle Prostheses from Class III (PMA) status to Class II (510(k)) status. Currently, only mobile-bearing ankles to be implanted with cement are classified. Mobile-bearing ankles to be implanted without cement are not classified.

Although this petition requests reclassification of only uncemented ankle prostheses, it is reasonable to consider cemented ankle prostheses as well. Therefore, there are two product codes which may be affected by this petition:

- **KXC:** Prosthesis, Ankle, Cemented, Non-constrained (21 CFR 888.3120, Ankle joint metal/polymer non-constrained cemented prosthesis).
- **NTG:** Prosthesis, Ankle, Uncemented, Non-constrained (unclassified)

As you are aware, when non-constrained, cemented ankle joints (21 CFR 888.3120) were originally classified, the classification panel identified risks to health which became the basis for classifying this device as class III. The basis for the classification was that the Panel believed these risks could not be controlled by either general controls (e.g., Registration and Listing, adherence to Good Manufacturing Practices (GMPs)) or special controls (e.g., performance standards, development and dissemination of industry standards, professional guidelines, specific labeling, FDA Guidance Documents, postmarket surveillance, patient registries).

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The purpose of a reclassification petition is to demonstrate that the risks previously identified for a preamendments Class III device, in light of new information, can be adequately addressed/minimized by either general or special controls, and, therefore, should be reclassified as Class II devices.

Based on review of the data submitted in your petition, we are unable to further consider reclassification of these devices until the following concerns have been adequately addressed.

1. For a device to be reclassified, you must identify the risks associated with the generic device, in this case, mobile-bearing ankles, both cemented and uncemented. Under most circumstances, these risks are identified in preclinical, animal, and clinical data. In addition, you must also identify the special controls to mitigate the risks. We have several concerns about the adequacy of the identified risks and special controls in your reclassification petition. Please address the following items:
 - a. FDA reclassifies generic types of devices which share common characteristics. Your petition appears to be limited in scope to one mobile-bearing ankle design. A reclassification of mobile-bearing ankles, however, would not be limited to the Buechel-Pappas Ankle design. Therefore, this petition should address the entire class of mobile-bearing ankle designs. Furthermore, although we believe you may have provided a thorough list of risks associated with your mobile-bearing ankle design, in order to reclassify mobile-bearing ankles, the risks for the entire class of mobile bearing ankle designs need to be identified, along with the special controls to mitigate those risks. Please identify other potential risks that encompass all mobile-bearing ankles, both cemented and uncemented, and special controls for the different designs (see 1.b.).
 - b. In the section entitled “Risks to Health,” you identify potential risks and list four potential means to control them, however the details associated with these are not provided in full (e.g., labeling, warnings, precautions, testing standards, etc.), nor are there provisions which relate the results of testing or any other controls to the identification and/or mitigation of risks.

In addition, your special controls section references many standards generic to orthopaedic implants, but not specific to mobile-bearing ankle devices. Although you describe testing performed on the Buechel-Pappas Ankle and refer to hip and knee testing, none of these test methods are recognized as standard testing for ankle joint devices. Further, hip and knee testing may not be applicable to the ankle joint due to differences in anatomy and biomechanics.

Moreover, the petition does not contain information to address how well preclinical test results from the proposed special controls will correlate to clinical results, and whether the proposed controls can adequately control the risks to health associated with the use of mobile-bearing ankles. Therefore, please develop special controls that

are able to mitigate the risks associated with mobile-bearing ankles, and allow for the prediction of the safety or effectiveness of this ankle design or future ankle replacement devices. Our concerns regarding the lack of special controls pertain to the following: device stability and constraint; polyethylene bearing; labeling; surgical technique; metal sensitivity; patient selection; and device dislocation and fracture. We have listed specific special controls concerns below.

2. In support of your petition, you reference data collected under your IDE, a clinical trial of the Buechel-Pappas Ankle. Endotec was placed under Application Integrity Policy (AIP) restrictions on February 14, 2002. At this time, we are unable to consider the complete IDE data set to be “valid scientific evidence.” Preliminary audit results indicate that data from a number of the IDE study subjects need to be removed leaving an insufficient number of subjects with reliable data to evaluate the safety and effectiveness of the device. Furthermore, since these clinical studies are under AIP, such data may not be submitted to FDA for consideration until removal of the AIP restrictions. For these reasons, FDA believes that no conclusions from the IDE data can be made at this time regarding the safety and effectiveness of the Buechel-Pappas Ankle. In addition, your clinical data were collected on one type of ankle design.

We believe that in order to reclassify mobile-bearing ankles, adequate clinical data are needed on your design as well as other mobile-bearing ankle designs in order to adequately identify the potential risks. Please provide valid clinical data that clearly demonstrate the safety and effectiveness of these devices and allow you to identify all potential risks.

3. On page 7, you state you do not believe that financial disclosure is applicable to this reclassification petition. According to 21 CFR 54, however, financial disclosure by clinical investigators is required of all investigators participating in a “covered clinical trial.” According to 21 CFR 54.2(e), a *covered clinical trial* means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. Because the clinical data used to support this reclassification petition are “covered clinical trials,” please provide the financial certification or disclosure statement or both as required by 21 CFR 54, as specified in 21 CFR 860.123(a)(10).
4. Several administrative elements described in 21 CFR 860.123, which specify the content and form of a reclassification petition were not addressed in this reclassification petition. Please amend the content of your reclassification petition to address the following concerns:
 - a. You did not include a completed supplemental data sheet for the mobile-bearing ankle. Although some of the information was provided in the petition, not all elements described in 860.3(g) were addressed. Please amend your petition to

include the information described on the supplemental data sheet. According to 21 CFR 860.3(g), a *Supplemental data sheet* means information compiled by a classification panel or submitted in a petition for reclassification, including:

- i. A summary of the reasons for the recommendation (or petition);
 - ii. A summary of the data upon which the recommendation (or petition) is based;
 - iii. An identification of the risks to health (if any) presented by the device;
 - iv. To the extent practicable in the case of a class II or class III device, a recommendation for the assignment of a priority for the application of the requirements of performance standards or premarket approval;
 - v. In the case of a class I device, a recommendation whether the device should be exempted from any of the requirements of registration, record-keeping and reporting, or good manufacturing practice regulations;
 - vi. In the case of an implant or a life-supporting or life-sustaining device for which classification in class III is not recommended, a statement of the reasons for not recommending that the device be classified in class III;
 - vii. Identification of any needed restrictions on the use of the device, e.g., whether the device requires special labeling, should be banned, or should be used only upon authorization of a practitioner licensed by law to administer or use such device; and
 - viii. Any known existing standards applicable to the device, device components, or device materials.
- b. Please be advised that, according to 21 CFR 860.123(a)(7), representative data and information known by the petitioner that are unfavorable to the petitioner's position, should also be included in a reclassification petition.
5. You state that the stability and constraint against motion of the ankle device are dependent on the "the malleolar articulations and ankle ligaments that must be present and viable to provide needed normal stability" (Section V. 2., p. 9/82) and not by the prosthetic elements. In some of the proposed diagnoses for which this device is indicated, patients have attenuated ligaments and tendons (e.g., osteoarthritis cases) or deformity due to autoimmune destruction of bone and surrounding soft tissue (e.g., rheumatoid arthritis cases) or deformity of the bony structures leading to altered strength of ligamentous or tendinous structures (e.g., post trauma or avascular necrosis related arthritis). This is a safety concern that needs to be addressed by describing the stability of the device as it stands alone, which could be described as the worst case scenario. A special control to

evaluate mobile-bearing ankle stability and constraint needs to be developed. The validity of any proposed stability and constraint testing should be supported by providing evidence of its ability to identify clinically successful mobile-bearing ankle designs. In addition to these concerns, be sure that any special controls developed address the following concerns:

- a. You state that the bearing component, when properly installed, resists medial to lateral dislocation by engaging the deep sulcus of the talar component, however you have not demonstrated this with testing. Further you have not described how dislocation in the anterior/posterior direction is controlled. The petition further states that the only torsional loads transmitted to the prosthesis are through friction that is minimal, but does not reference how this was determined (Section VI. 3., p. 12/82). Please identify the special controls you will employ to address these concerns.
 - b. In this reclassification petition, you state that “no reports of meniscal bearing dislocation independent of tibial or talar component malpositioning due to subsidence or improper placement have been received” (p.35/82). In addition, this petition cites an unpublished study in which the BP design did show subsidence due to talar necrosis (p. 43) and subluxation. A special control needs to be developed to address these potential failure modes (i.e., component malpositioning due to subsidence or improper placement). Please identify such a control.
 - c. You state the talar component affords “normal inversion-eversion stability and prevents the bearing from moving medially and laterally or to axially rotate relative to the talar component.” Please describe how this was determined for the Buechel-Pappas Ankle, the normal ankle, and how it could be determined for future mobile-bearing ankle device designs.
6. Please develop and provide special controls relating to the polyethylene bearing. The validity of any proposed special controls relating to the bearing should demonstrate how all potential risks are mitigated concerning the polyethylene bearing. Be sure that any special controls developed address the following concerns:
 - a. A special control is needed to evaluate the occurrence of “backside wear” because the polyethylene bearing articulates on both its superior and inferior surfaces.
 - b. A special control is needed to establish an appropriate minimum thickness of the polyethylene bearing.
 7. The petition states that labeling including precautions and warnings is a special control but does not provide any labeling requirements to demonstrate what these specific labeling components would be.

- a. Please identify the labeling requirements you intend to include as special controls (e.g., identify the specific precautions and warnings which will be included in the package insert).
 - b. The surgical technique manual which comprises part of the device labeling also may serve as a special control. A surgical technique should be written to highlight which steps or instruments are meant to control potential risks of device failure and updated to address the following concerns:
 - i. The surgical technique manual should highlight the importance of tibial and talar component sizing and should include a description of how the correct size is determined. Be sure to include a sizing table which correlates a patient's anatomical dimensions with implant size.
 - ii. The surgical technique manual should identify the proper placement of instrument guides, (e.g., when performing distal tibial resection, the guide should be placed at the center of the tibia and at the lowest level of pathology). Please amend the surgical technique to include these cautions.
 - iii. The surgical technique manual should describe preoperative or intraoperative planning methods to help avoid the risk of component malalignment which may lead to device failure. Ideally, the manual also should describe troubleshooting techniques for when component malalignment occurs, or when impingement of the trial bearings against the malleoli occurs. Please amend the surgical technique to include a description of methods for achieving proper implant alignment, including the proper placement of implant trials.
 - iv. The surgical technique manual should describe any limitations on the amount of bone resection. Although you state that the Buechel-Pappas Ankle requires less than 1 cm of bone resection, you do not specify whether future devices must limit the amount of bone resection to 1 cm. Please amend your petition to include a discussion regarding bone resection.
8. The petition states that only a qualified physician can purchase these devices and that all personnel entitled to purchase these items are trained experts in the field of orthopedic or podiatric surgery. You also state that during the IDE for the Buechel-Pappas Ankle clinical trial, although adequate guidance had been provided to the surgeons with regard to surgical technique, due to the steep learning curve associated with the surgery, additional procedures needed to be implemented. Please describe any required surgical training which may serve as a special control.
 9. The petition recommends that the patients who expect to have a metal implant have their physician check for sensitivity to CoCr or stainless steel. However the petition does not state how this would be accomplished. FDA believes such testing should be described in

labeling, and not left up to the patient. The next paragraph then states that this situation should be avoided by using only titanium alloys to construct these prostheses (p. 32), but not all future prosthetics will have the same design or materials of construction. Please describe the specific special controls you will employ to minimize the risk of metal sensitivity.

10. The petition cites only one reason for revision (i.e., wear or component loosening) and states this risk is mitigated by the mobile-bearing design which causes less contact stress and wear. Dislocation and fracture of components are not included as potential reasons for revision surgery. Special controls to evaluate device dislocation and fracture of components should be developed because these are potential risks for patients implanted with a mobile-bearing ankle. Please describe the specific special controls you will employ to minimize the risks of device dislocation and fracture.
11. Several statements in the reclassification petition appear inconsistent with FDA's experience with your IDE for the Buechel-Pappas Ankle. For example, on page 27, you state that "three prostheses were removed as a result of infection and two were removed as a result of persistent pain. None were removed due to design." These statements imply that only 5 ankle implants of the 123 implanted as part of the Buechel-Pappas Ankle were removed. However, there have been more than 5 "compassionate use" requests for revision cases. Please amend your petition as needed to accurately reflect your IDE experience.
12. On page 34, you state, "Clinical studies have proven that uncemented implants have better overall results than those implanted with cement." However, of the two articles referenced in this statement, one evaluated only uncemented ankles and a copy of the other article was not included in the reclassification petition. Please amend your statement as necessary and provide a copy of the missing article.
13. Many articles and unpublished papers were referenced, but not provided in your petition other than being listed in the bibliography. Therefore, a complete clinical review of the cited references is not possible. Please provide copies of all referenced articles, including unpublished papers and references provided to Endotec by a private source.
14. This petition does not include longer-term mobile-bearing ankle data gathered by investigators, other than those involved with Buechel-Pappas Ankle. This includes clinical data gathered by physicians other than the surgeon inventor which shows safe and effective use of mobile-bearing ankles in the general orthopaedic community. Please provide all available longer-term mobile-bearing ankle data gathered by investigators, other than those involved with Buechel-Pappas Ankle design.
15. You state that "FDA dictates that porous coating must fall within the following ranges for acceptable ingrowth per 21 CFR 888.3358:..." In actuality, the specifications quoted pertain to porous coating specifications for hips and knees. Please provide evidence that

these ranges for porous coating parameters are appropriate for achieving biological fixation in the ankle.

16. You reference “deep sulcus” and “shallow sulcus” designs of the Buechel-Pappas Ankle, but do not appear to have provided a complete description of the differences between these designs. Please provide a detailed explanation, including engineering drawings, showing the differences between these two designs.
17. Regarding the design of the talar component, the petition states that the fixation augments should be configured so as to produce minimal disruption of the inferior blood supply to the distal talus, as compared to a single central fin. (Section VI 5. p.13) However, the petition does not describe how this was determined and no reference was provided. Please describe how you determined that fixation augments of the talar component should be configured so as to produce minimal disruption of the inferior blood supply to the distal talus, as well as any applicable references.

FDA wishes to advise you of the following:

18. It does not appear that you specifically addressed the first three concerns noted in our filing letter, dated September 27, 2004. Please identify where in the current petition you address these filing concerns or amend your petition to address them.
19. Your petition includes comparisons of the Buechel-Pappas Ankle and Class II ankle designs. Although there are clinical references showing good clinical outcomes with Class II ankle designs, this reclassification petition does not include data showing such results. For example, although the outcomes of the Agility Ankle studies are exemplified as failures, the long-term (i.e., 9 year) outcome in at least one study is similar to those defined by the inventor surgeon for the Buechel-Pappas Ankle (88% vs. 92%). In addition, while it is known that age and diagnosis affect the outcomes, patient demographics in these studies are not clearly compared in your discussion. Furthermore, in some studies, reoperation, not revision or device failure was used in Kaplan Meier determinations for failure. Therefore FDA believes the petition presents a potentially skewed view of prior experience. Please amend your petition to more accurately reflect the clinical outcomes observed for Class II ankle designs in your comparisons with the Buechel-Pappas Ankle.
20. Please consecutively paginate all future submissions.
21. Appendix B appears to be out of order. Please check this section and resubmit if necessary.
22. FDA noted several inadvertent references to knees in your discussion of ankles. Please remove or correct these references if they are a part of your response.

Page 9 – Michael J. Pappas, Ph.D., P.E.

If you submit information correcting these deficiencies, we will reevaluate your reclassification petition. Please provide five (5) copies of your response to this letter. The information should reference the above docket number (2004P-0457/CCP 1) and be submitted to:

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

If you have any questions related to reclassification, please contact Ms. Marjorie Shulman at (301) 594-1190, extension 144. For scientific and technical assistance, please contact Ms. Hollace Saas Rhodes by email (hollace.rhodes@fda.hhs.gov) or by phone at (301) 594-2036, extension 165.

Sincerely yours,

A handwritten signature in black ink, appearing to read "D. Tillman", written over a horizontal line.

Donna-Bea Tillman, Ph.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health