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**Re: FDA Docket 2004P-0457/CCP 1;
Comments in Opposition to Reclassification Petition.**

Dear Sir or Madam:

The undersigned submits the following comments under 21 C.F.R. 860.134(b) in opposition to the petition for reclassification of the Buechel-Pappas Non-Constrained, Mobile-Bearing Ankle Prosthesis submitted by Michael J. Pappas, Ph.D., of Endotec, Inc. (2004P-0457/CCP 1).

I. Introduction

Endotec's petition requests that the Commissioner of the Food and Drug Administration ("FDA") reclassify the Buechel-Pappas Total Ankle replacement device ("B-P Ankle"). The B-P Ankle is currently classified as a new class III device in accordance with Section 513(f) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). The B-P Ankle is a non-constrained device designed for cementless use in ankle arthroplasty. Because the B-P Ankle uses cementless fixation, it does not meet the definition described in 21 C.F.R. § 888.3120 (a regulation covering metal/polymer ankle joint prostheses that are non-constrained and cemented). It also fails to meet the definitions of either 21 C.F.R. § 888.3100 or § 888.3110, which cover semi-constrained cemented prostheses. Endotec, therefore, requests that the B-P Ankle be reclassified to class II as a new generic type for ankle joint replacements.

We oppose Endotec's petition to downclassify the B-P Ankle from a class III to a class II device as the special controls required for class II designation are insufficient to provide a reasonable assurance of the safety and effectiveness of the device. There is ample evidence in the literature that the use of total ankle

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replacement prostheses raises safety concerns that can only be addressed adequately through the premarket approval (“PMA”) process. This is the reason that FDA has determined that PMA approval is necessary for non-constrained ankle prostheses. As discussed further below, clinical data on the use of prostheses such as the B-P Ankle have only recently begun to emerge. Moreover, little mechanical testing of the device has been performed to supplement the preliminary clinical data published. While the emerging data support ankle replacement as a potential viable alternative to traditional arthrodesis (fusion) treatments, recent literature shows the need for continued, comprehensive clinical trials and biomechanical studies to fully identify the types of safety risks posed by ankle prostheses and the frequency of those risks. Particularly in comparison to joint implants such as hip and knee replacements that have class II designation, ankle replacements do not yet have a public clinical track record of sufficient length to determine whether special controls alone are adequate to reasonably assure their safety and effectiveness in clinical use and mitigate the risk of device failure.

II. **Reclassification Standard**

Under Section 513(e)(A), 21 U.S.C. § 360c(e)(2), of the FDCA, the FDA may change the classification of a device from class III to class II “if [FDA] determines that special controls would provide a reasonable assurance of the safety and effectiveness of the device and that general controls would not provide a reasonable assurance of the safety and effectiveness of the device”

Under Section 513(f)(1), 21 U.S.C. § 360c(f)(1), a device such as the B-P Ankle, which was not introduced for commercial distribution before the enactment of these regulations, is automatically designated as a class III device. However, under section 513(f)(2), 21 U.S.C. § 360c(f)(2), “[a]ny person who submits a report under section 510(k) for a type of device that has not been previously classified under this Act, and that is [automatically] classified into class III under paragraph (1),” may request FDA to classify the device in accordance with the criteria established under the regulations. Endotec argues for reclassification of the B-P Ankle from class III (Premarket Approval) to class II (Special Controls). Section 513(a)(1)(B), 21 U.S.C. § 360c(a)(1)(B), sets forth the criteria for class II designation. It provides for class II designation if sufficient information exists to establish special controls that will provide a reasonable assurance of the safety and effectiveness of the device. Such special controls include “the promulgation of performance standards, postmarket surveillance, patient registries, the development and dissemination of guidelines (including those for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance.” 21 C.F.R. § 513(a)(1)(B), 21 U.S.C. § 360c(a)(1)(B).

We disagree with Endotec's assertion that such special controls would provide a reasonable assurance of safety and effectiveness of the B-P Ankle. Sufficient information does not exist in the current literature to make such a determination and, therefore, the continued classification of the B-P Ankle as a class III device is appropriate.

III. Insufficient Public Information Exists to Provide a Reasonable Assurance of Safety and Efficacy of the B-P Ankle Based on Special Controls Alone

A. Clinical Studies Using the B-P Ankle

The central issue to be considered is whether the data within Endotec's petition support the reclassification of the B-P Ankle prosthesis into class II. This question requires a determination as to whether adequate special controls can be established to address the risks identified with this type of device.

In its petition, Endotec identifies several specific health hazards associated with the B-P Ankle, including wear-debris induced osteolysis, aseptic loosening of components, infection, fracture of the bones supporting the device, migration or subsidence of the device, failure of the implant or any individual implant component, vascular and nerve damage, pulmonary embolism, sprains or strains, and sensitivity to implant materials. In addition, use of the B-P Ankle poses general risks, including those associated with the surgical procedure and implantation of the artificial joint.

When the foregoing risks are considered, Endotec fails to present sufficient clinical data to show that special controls are sufficient to reasonably ensure safety and effectiveness of the B-P Ankle. As discussed below, current literature on clinical experiences with ankle arthroplasty remains preliminary. The majority of published studies are retrospective, non-comparative, involve relatively short-term follow-up periods, and have small sample sizes. Further, many are not independently run, but instead are conducted by the developers of the devices themselves.

Examining Endotec's petition, we note initially that the literature review of clinical experiences with the B-P Ankle is incomplete. Endotec cites only four clinical studies involving the current model of the B-P Ankle, the "deep-sulcus" design, which is the model relevant to Endotec's petition. Further, of the four clinical analyses cited by Endotec, one is the Progress Report of its own IDE study,¹

¹ Endotec Inc. 2003 IDE Annual Progress Report: Results of 51 cases. IDE #G970158 FDA Submittal, December 2003.

and a second is a study run by the developers of the B-P device themselves.² A third publication, Su *et al.*,³ reports the results of one of the IDE study investigators. Thus, Endotec cites only one truly “independent” clinical study, that conducted by Rippstein in 2002.¹

The Rippstein study, discussed more fully below, was a retrospective analysis that used a small sample size of 25 B-P implants. Although Endotec states that the prostheses were implanted over a ten-year time span, the authors in fact sequentially implanted three different designs, including the Scandinavian Total Ankle Replacement (“S.T.A.R. Ankle”) in 1996, the DePuy “Agility” Ankle between 1997 and 1999, and finally the B-P Ankle between 1999 and 2002. In the series of B-P Ankles implanted, the authors report on the first 25 cases “with a follow-up period greater than one year.” The article states that these 25 prostheses “were reviewed in 2001,” indicating a maximum follow-up period of only 2 years for the B-P cases at issue in this study. Thus, this report represents a single surgeon’s early experience with the B-P Ankle, with fairly short-term follow-up. Further, this study reported severe complications in 3 cases, including one oversized talar component, one deep infection, and one tibial nerve entrapment. These occurrences, along with other “disappointing” results including postoperative stiffness and reports of diffuse pain, led Rippstein to conclude that there was still much to be learned about ankle arthroplasty.

The Su study was also retrospective, reporting on a small sample size of only 19 implants, 5 of which had been used in Endotec’s IDE study; the remaining 14 were implanted on a “customized” basis. As with the Rippstein study, Endotec emphasizes that the prostheses on which Su reported were implanted over a ten-year time span. However, the Su study also had a relatively short mean follow-up period of only 4.4 years. In addition, the Su study raised particular concerns about the occurrence of osteolysis. Of the 19 B-P Ankles implanted, there were 3 (15.8%) reported occurrences of osteolysis. A fourth case, although asymptomatic, developed a linear lucency around the tibial component. Su also reported 2 occurrences of subsidence of the tibial component. Another patient sustained a dislocated polyethylene bearing 3 years after surgery, and radiographs revealed that the bearing component was extruded. This patient required revision surgery.

² Buechel, F.F., Beuchel, F.F., Pappas, M.J. (2004) Twenty-Year Evaluation of Cementless Mobile-Bearing Total Ankle Replacements. *Clin Orthop* 424:19-26.

³ Su, E.P., Kahn, B., Figgie, M.P. (2004) Total ankle replacement in patients with rheumatoid arthritis. *Clin Orthop* 434:32-8.

¹ Rippstein, P.F. (2002) Clinical experiences with three different designs of ankle prostheses. *Foot Ankle Clin N Am* 7:817-831.

The results from Endotec's IDE study are also preliminary, reporting on 51 cases, with a mean follow-up of 3 years. Still, 3 of these cases resulted in removal of the B-P implant due to infection. It should be noted that Endotec provides no control data for comparison of the B-P results, and Endotec does not state whether the IDE study was a concurrently controlled clinical trial. Further, we note that in February 2002, after conducting inspections of Endotec's facility and two of its clinical sites, the FDA found Endotec's data collection procedures to be unreliable.⁵ The FDA consequently suspended review of Endotec's submissions until the inadequacies were corrected. While FDA later lifted the suspension, the fact that it considered Endotec's data collection procedures unreliable cautions against relying on these results to determine whether premarket approval is necessary for the B-P Ankle.

Finally, the study cited by Endotec of 75 implants performed by Buechel *et al.*⁶ had a mean follow-up period of 5 years, despite Endotec again emphasizing the longer time-span during which the implants were performed. The Buechel study reported complications with 38 (51%) of the implants. Notably, and of particular concern, 10 (13.3%) of the implants resulted in osteolysis, 6 of the tibia, 2 of the fibula, and 2 of the talus. In addition, 11 ankles showed delayed wound healing and 6 suffered malleolar fracture. There were also 3 reports of talar component subsidence, 3 reports of severe bearing wear, 3 cases of reflex sympathetic dystrophy, and 2 cases in which infections developed.

In total, Endotec's petition cites only 170 reported cases of current generation B-P Ankle implants. Of these, 56 (32.9%) came from its own IDE study, including 5 IDE cases apparently described twice. The single largest group, 75 cases (44.1%), came from a study conducted by the developers of the B-P Ankle themselves. These data are hardly sufficient to determine that special controls would provide a reasonable assurance of safety and efficacy of the B-P device, particularly in light of the seriousness and prevalence of certain complications reported in these studies.

The occurrence of osteolysis with ankle arthroplasty is of particular concern. As noted above, Su *et al.*⁷ reported evidence of tibial osteolysis in 3 (15.8%)

⁵ Endotec Calls FDA's AIP Decision "Extreme," Probes Appeal Mechanisms. *The Gray Sheet*. 28(10). March 11, 2002.

⁶ Buechel, F.F., Beuchel, F.F., Pappas, M.J. (2004) Twenty-Year Evaluation of Cementless Mobile-Bearing Total Ankle Replacements. *Clin Orthop* 424:19-26.

⁷ Su, E.P., Kahn, B., Figgie, M.P. (2004) Total ankle replacement in patients with rheumatoid arthritis. *Clin Orthop* 434:32-8.

of 19 implants, an incidence that the authors viewed as necessitating close follow-up. As discussed further in the following section, emerging data indicate that osteolysis may be a more common problem than previously anticipated. Osteolysis was noted in these patients at 4.7, 6.4, and 7.7 year follow-up, highlighting the fact that short-term data are likely to underestimate the incidence of this complication. Because most of the available B-P data are short- to intermediate-term, the long-term incidence of osteolysis with this device is as yet unknown.

Drzala *et al.*⁸ revealed further complications with the B-P Ankle in a report on the intermediate results of 38 B-P Ankles. Results showed that 3 of the ankles underwent revision, 2 suffered eccentric wear and lateral bearing subluxation, and 2 patients with preoperative osteonecrosis sustained lateral talar collapse.

Finally, in a study in which 50 B-P Ankles were implanted, Buechel *et al.*⁹ reported a variety of complications. We note that the patient population in this study may overlap with that of the later 75 implant study by Buechel *et al.* cited above. However, reported complications included 2 cases of revision surgery for malalignment, 2 cases of reflex sympathetic dystrophy, and one case of meniscal bearing wear with component malalignment. In addition, 2 patients with a preoperative diagnosis of avascular necrosis were included in this sample; one of these patients suffered talar component subsidence. Regarding the avascular necrosis patients, it should also be noted that one of these patients suffered moderate postoperative pain, and the second experienced severe pain.

Given the poor clinical course in avascular necrosis patients described above, Endotec's inclusion of avascular necrosis among the indications for use of the B-P Ankle is particularly troubling. As several of the studies referenced here note, avascular necrosis is widely considered to be a contraindication for ankle arthroplasty. The development of avascular necrosis is also a potential risk of ankle replacement, and below-knee amputation may be a catastrophic sequella of avascular necrosis. It is incongruous for Endotec to claim avascular necrosis as an indication for the B-P Ankle, particularly given the complications that developed in both of the avascular necrosis patients in the Buechel study, and in both of the avascular necrosis patients in the Drzala study. It is impossible to determine at

⁸ Drzala, M. & Engh, K.O. (1998) Abstract: Independent evaluation of Buechel-Pappas second-generation cementless total ankle arthroplasty intermediate term results. *AOFAS 28th Annual Meeting: Scientific Papers* 11.

⁹ Buechel, F.F. Sr., Buechel, F.F. Jr., Pappas, M.J. (2003) Ten-year evaluation of cementless Buechel-Pappas meniscal bearing total ankle replacement. *Foot Ankle Int* 24(6):462-72.

this point whether special controls could be established to reasonably assure the safety and effectiveness of the device in this patient population and, in fact, Endotec proposes none.

Consistent with the B-P Ankle clinical data presented above, researchers continue to observe that “there are currently limited data on the clinical outcomes of uncemented total ankle replacements.”¹⁰ Although the literature has shown arthroplasty to be a potentially viable alternative to traditional arthrodesis, the types of complications revealed in recent studies are sufficiently serious to warrant PMA review for the B-P Ankle. The available clinical data reveal several safety risks that continue to be significantly associated with B-P Ankle arthroplasty. Continued clinical and biomechanical testing is the only adequate means of ascertaining the causes of these complications and accordingly improving the device and the surgical techniques used for implantation. Special controls are not adequate for providing the specific, clinically-based data necessary to evaluate the complications being reported with the B-P Ankle.

B. Mechanical Testing Data

In addition to reporting an inadequate amount of clinical data, the report on mechanical testing presented in Endotec’s petition is also surprisingly thin. For example, in describing torsion and shear testing on the B-P Ankle, Endotec cites only one study, conducted in 2000.¹¹ Similarly, for testing of device coating, Endotec includes only one study, performed in 1988.¹²

Further, in its discussion of wear testing, Endotec cites two studies,^{13,14} both of which provide a comparison of Co-Cr and TiN femoral heads using a hip-

¹⁰ Lewis, G. (2004) Biomechanics of and research challenges in uncemented total ankle replacement. *Clin Orthop* 424:89-97.

¹¹ Raikin, S.M., Heim, C.S., Plaxton, N.A., *et al.* (2000) Mobility Characteristics of Total Ankle Replacements. Orthopedic Research Laboratories, Lutheran Hospital, Cleveland Clinic Health System, Cleveland, OH.

¹² Coll, B.F. & Jacquet, P. Surface Modification of Medical Implants and Surgical Devices Using TiN Layers. 15th International Conference on Metallurgical Coatings, San Diego, CA, USA. April 11-15, 1988.

¹³ Pappas, M.J., Makris, G.M., Buechel, F.F. (1995) Titanium Nitride Ceramic Film Against Polyethylene: A 48 million Cycle Wear Test. *Clin Orthop* 317:64-70.

¹⁴ Pappas, M.J., Makris, G.M., Buechel, F.F. (1990) Comparison of wear of cups articulating with Co-Cr and TiN coated femoral heads. *Trans Biomat* 13:36.

resurfacing test. However, the level of impact on the hip joint is not comparable to the impact one would expect to be placed on the ankle. Thus, these data are grossly inadequate for purposes of evaluating wear in ankle prostheses. It should also be noted that wear testing data may be particularly important in assessing the safety of the B-P Ankle, given the incidence of osteolysis described in several clinical studies of the device.

Finally, in analyzing contact stress, Endotec claims that it is infeasible to perform certain contact stress tests, in particular the Fuji-Film Method, on the B-P Ankle. Endotec makes this claim despite the fact that other similarly designed mobile-bearing total ankle replacements have undergone both finite element modeling and contact stress testing. Instead, Endotec presents a mathematical calculation to estimate contact stress. Results from such calculations alone, rather than from actual testing, are hardly adequate for determining whether special controls are sufficient to ensure that the B-P Ankle is reasonably safe and effective with regard to contact stress.

C. Comparison with the “Agility” Ankle

As part of its argument for downclassification, Endotec draws a comparison between the B-P Ankle and the DePuy “Agility” Ankle, which has been given class II designation and 510(k) clearance. 21 C.F.R. § 888.3110. Endotec argues that, despite having been designated as class II, the Agility Ankle poses several safety risks due to its poor stability characteristics. Endotec claims that because the B-P Ankle was designed with improved stability characteristics over the Agility Ankle, it is in fact safer than the Agility and should therefore also be given class II designation.

As discussed below, clinical data have revealed several significant safety hazards associated with use of the Agility Ankle. Accordingly, the Agility Ankle serves as a prime example of the necessity of the PMA process for ankle prostheses. Had the Agility Ankle been subject to further premarket clinical and biomechanical testing, the dangers that came to light in postmarket clinical experiences could perhaps have been identified and avoided. A major flaw in Endotec’s argument is in presupposing that the B-P Ankle is reasonably safe and effective simply because its design is different from that of the Agility. Classifying the B-P Ankle requires an independent examination of the available data on the B-P Ankle itself. As evidenced by the clinical studies discussed above, this examination falls far short of providing sufficient information to establish the reasonable safety and effectiveness of the B-P Ankle.

Although the relatively poor safety profile of the Agility Ankle offers weak support for Endotec’s proposed downclassification of the B-P Ankle, we highlight some of the safety hazards that have been reported on Agility to stress the

importance of requiring premarket approval for ankle prostheses generally, and for the B-P Ankle in particular.

In 2003, Saltzman, *et al.*¹⁵ published a 90 patient multi-center series focusing on perioperative complications in surgeons' initial arthroplasties using the Agility Ankle. Three patients (3.3%) in the study ultimately required below-knee amputation because of deep infections, intractable pain, and postoperative wound problems. Intra-operative complications noted in this series included malleolar fractures, which occurred in 12 patients (13.3%). These malleolar fractures were attributed to difficulties with tibial component size selection and positioning, minor wound problems related to skin vascularity, and the use of limited approaches requiring tension with retraction.

Two recent publications reported longer-term results with the Agility Ankle.¹⁶ At mean follow-up period of 9 years, Knecht and colleagues found that 11% of 132 ankles implanted required a revision or an ankle arthrodesis. In addition, 76% had some evidence of peri-implant radiolucency, and 15% developed late-onset lysis, appearing, on average, 35 months post-implant. The authors opined that the later onset of the lysis and expansile bone loss suggested a wear-particle inflammatory reaction similar to that found in the peri-implant interfaces of hip and knee prostheses.

The surgical team of Dr. Sigvard Hansen reported results for 306 Agility Ankle replacements at mean follow-up period of 33 months.¹⁷ Eighty-five patients (28%) underwent 127 reoperations, including 41 component replacements or removals (13.4%) in 33 ankles (10.8%). Among the 41 revisions were 8 below-knee amputations and one arthrodesis. Seven of the 8 amputations, however, were in patients with a history of severe trauma and multiple surgical procedures prior to the Agility arthroplasty. Still, these complications reinforce the need for clearly determined indications and contraindications before ankle arthroplasty can be considered reasonably safe and effective. Without further clinical studies to generate data on appropriate indications and potential contraindications, surgeons are apt to perform arthroplasty on patients with histories similar to those in this study without sufficient knowledge of the risks that could be involved for such patients.

¹⁵ Saltzman, C.L., Amendola, A., Anderson, R., *et al.* (2003) Surgeon training and complications in total ankle arthroplasty. *Foot & Ankle Intl* 24(6):514-518.

¹⁶ Knecht, S.I., Estin, M., Callaghan, J.J., *et al.* (2004) The Agility total ankle arthroplasty: Seven to sixteen-year follow-up. *JBJS* 86A:1161-71.

¹⁷ Spirt, A.A., Assal, M., Hansen, S.T. (2004) Complications and failure after total ankle arthroplasty. *JBJS* 86A:1172-78.

Rippstein, discussed above, also reported results with the Agility Ankle. He found the Agility appropriate only for patients with the most severe anatomical deformities, usually involving post-traumatic arthrosis. Because he found the clinical benefits of arthroplasty in these patients to be “low or even nonexistent,” Rippstein eventually abandoned the use of the Agility prosthesis entirely.

In a retrospective study, McGarvey *et al.*¹⁸ examined the first 25 Agility total ankle arthroplasties performed by a particular surgeon. They examined the fracture rate, the timing, location, and treatment of the fracture, and the outcome. They reported 5 fractures (20%), all of which occurred intra-operatively. Four of the fractures involved the medial malleolus and one involved the lateral malleolus. All fractures required some form of fixation as implant stability was compromised.

Meyerson, *et al.*¹⁹ also performed a retrospective radiographic and chart review of 50 Agility implants, focusing on perioperative complications. The authors reported 7 intra-operative fractures, 2 tendon lacerations, and 2 nerve lacerations. The authors suggest that more information and clinical experience is needed to avoid the complications associated with the Agility Ankle, despite the fact that the Agility device has already been cleared as a class II device.

Assal, *et al.*²⁰ described an incidence of complete polyethylene insert fracture in a patient who underwent total ankle replacement with varus malpositioning. To avoid such a “catastrophic complication,” the authors highlight the importance of ankle alignment in arthroplasty, and stress the need for additional procedures to correct malalignment before implanting a total ankle prosthesis. The authors conclude that “the use of the Agility Total Ankle System is in its infancy. Most patients are only a few years postsurgery, and a significant number of them have some malalignment.” They note that the life span of polyethylene inserts is still unknown, and that their survival is even less likely if alignment problems are not corrected before surgery.

¹⁸ McGarvey, W.C., Clanton, T.O., Lunz, D. (2004) Malleolar fracture after total ankle arthroplasty: a comparison of two designs. *Clin Orthop* 424:104-10.

¹⁹ Meyerson, M.S. & Mroczek, K. (2003) Perioperative Complications of Total Ankle Arthroplasty. *Foot & Ankle Intl* 24(1):17-20.

²⁰ Assal, M., Al-Shaikh, R., Reiber, B.H., *et al.* (2003) Fracture of the Polyethylene Component in an Ankle Arthroplasty: A Case Report. *Foot & Ankle Intl* 24(1):901-903.

Finally, we note the reporting of several adverse events on the Agility Ankle in FDA's Manufacturer User Facility and Distributor Experience ("MAUDE") database. Reported adverse events include revision due to wear and implant fractures, infection, and pain and swelling with weightbearing. An amputation was also reported.

In its review of the Agility Ankle, and other first-generation ankle prostheses, Endotec attempts to argue that premarket approval for the B-P Ankle is unnecessary because the device has certain characteristics that could make it safer and more effective than earlier devices. However, it is misguided to presume that the B-P Ankle is sufficiently safe simply because Endotec has made design adjustments intended to improve upon deficiencies of the first-generation prostheses. Endotec clearly makes this erroneous presumption. For example, the petition states: "[S]ubsidence and wear reduction is really an issue of design. A good, sound design is in itself a safeguard against subsidence and unacceptable wear" (Endotec Petition at 35). However, the effectiveness of such design modifications to improve safety is merely theoretical until the device is tested in clinical use. Endotec has failed to support its claims with clinical data showing that its design modifications improve safety and effectiveness sufficiently to warrant downclassification.

We also note that, according to expert clinicians, the Agility Ankle is used almost exclusively as an uncemented ankle replacement, which constitutes "off-label" use of a device cleared only for use with bone cement. For example, the Agility implants used in the Spirt study between 1995 and 2001 were implanted without cement. Conceivably, the deficiencies of the Agility Ankle that have resulted in its abandonment in clinical practice except in an off-label configuration may have been more readily apparent had this device been subject to the rigors of the PMA process.

In discussing the clinical history of the failed first-generation prostheses, Endotec notes: "It may be seen that the decisions of the panel and the FDA to designate semi-constrained ankles as class II were founded on relatively short-term encouraging results of early ankle designs based on presentations and publications of the developers of these ankles. Longer-term studies, however, clearly demonstrate that the ankle types are failures" (Endotec Petition at 54). We agree with this assessment, and note that the Agility Ankle was cleared in 1982 with clinical studies dating back only to 1976. However, we believe that Endotec is now urging the FDA to take a similar course with the B-P Ankle, despite the absence of long-term, independent data on the device's clinical performance.

D. Comparison with Class II Total Hip and Knee Replacements

The safety profile of total ankle replacements has historically been weaker than that for other major lower extremity joint replacements.²¹ For example, certain hip and knee replacements (however, not mobile-bearing designs) have been given class II designation because the safety of these devices can be reasonably ensured through special controls. Comparing the safety profiles of these devices to that of class III ankle prostheses, it is clear that total ankle replacement poses significantly greater risks and therefore requires more stringent protections than those currently required for class II joint replacements.

Clinical data on the use of hip and knee prostheses are significantly more extensive than that on the use of ankle replacements. As a Guidance Document Submission (“GDS”) on hip replacements reports: “Currently, there is considerable cumulative experience on prosthetic hip joint clinical performance, given the 40 years of clinical evolution and an implantation rate of approximately 300,000 or more devices/year.”²² This vast amount of clinical knowledge has provided a solid basis on which to establish special controls for hip replacements. No such knowledge base currently exists for ankle prostheses.

In addition, the GDS proposes a clinical study design for evaluating both conventional hip arthroplasty prostheses and modern technological improvements on conventional designs. The proposed primary endpoints for this design include 0% device related complications and 0% revision surgeries. Patient success is attained when a patient meets these endpoints at one year. Study success is achieved when 95% of patients are deemed successes at one year. The endpoints proposed here demonstrate the extremely high level of performance that has come to be expected of hip prostheses. There is currently no data on ankle replacements that even approach this degree of success in clinical use. It is clear that the safety of current ankle prostheses still lags far behind that of class II hip replacements, indicating that for the time being class III designation remains appropriate for ankles prostheses.

Similarly, long-term study of knee replacements has generated a pool of clinical data far more extensive than that available for ankle replacement. To

²¹ Saltzman, C.L., Amendola, A., Anderson, R., *et al.* (2003) Surgeon training and complications in total ankle arthroplasty. *Foot & Ankle Intl* 24(6):514-518.

²² Department of Health and Human Services, Division of General and Restorative Devices Orthopedic Devices Branch. Hip Guidance Document Submission: Clinical Trial Design for Hip replacement Systems. April 19, 2004. *Citing* National Center for Health Statistics, 1991 to 2000 National Hospital Discharge Survey.

illustrate, in a 2004 petition for reclassification of class III mobile-bearing knee prostheses,²³ an extensive bibliography of 193 citations was included. These citations referenced well-controlled trials, investigations without matched controls, non-clinical bench studies, retrieval studies, and case studies. In addition, the company provided unpublished data from 7 ongoing IDE studies, and an amendment with 43 articles on wear. When the Orthopedic Advisory Panel reviewed this petition,²⁴ the sponsor presented results of a meta analysis of 21 studies reporting the outcome of 22 cohorts which enrolled a total of 2,490 patients (2,870 knees). In addition, a panel member noted that FDA has approved 3 PMAs for mobile-bearing knees, but cautioned that this “is not a very big experience set.”²⁵ By contrast, no PMAs have yet been approved for mobile-bearing ankle replacements. Another panel member termed the overall amount of knowledge accumulated over 30 years about mobile-bearing knees “extraordinary.”²⁶ This degree of knowledge on the clinical and biomechanical performance of the B-P Ankle does not currently exist in the literature. Thus, the clinical data provided in Endotec’s petition are extremely thin compared to that of petitions for devices such as knee prostheses, which have much longer clinical track records in the United States.

Given the longer clinical track records of knee joint patellofemoral and femorotibial (uni-compartmental) porous-coated uncemented prostheses, FDA recommended reclassification of these devices from class III to class II in March, 2000.²⁷ The clinical experience with these devices allowed FDA to identify four risks to health associated with their use: adverse tissue reaction, infection, pain and/or loss of function, and revision. FDA proceeded to develop a Special Controls Guidance which outlined the measures recommended by the Agency to mitigate

²³ Orthopedic Devices Branch, Division of General, Restorative and Neurological Devices. Memorandum. Summary of information regarding OSMA’s reclassification petition for the post-amendments Class III Mobile Bearing Knee. November 29, 2004.

²⁴ Orthopedic Devices Branch, Division of General, Restorative and Neurological Devices. Memorandum. Reclassification Petition: Mobile Bearing Knees. April 26, 2004.

²⁵ Orthopedic and Rehabilitation Devices Panel Medical Devices Advisory Committee Meeting, Transcript at 109, June 3, 2004 (available at <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4049t2.htm>).

²⁶ *Id.* at 116.

²⁷ 65 Fed. Reg. 12015 (March 7, 2000).

these risks.²⁸ These measures included provision of the following information: preclinical testing as outlined in the guidance, to evaluate the material and performance characteristics of the final, worst case, sterilized device, including conformance to applicable FDA guidance documents and consensus standards; sterilization information; and detailed labeling.

Following the model of the knee joint Special Controls Guidance, Endotec proposes the adoption of similar special controls for the B-P Ankle: preclinical testing; adherence to guidance documents and consensus standards; provision of sterilization information; and detailed labeling. However, the risks identified by Endotec are more numerous and more serious than those identified for prosthetic knees in FDA's guidance document. This list includes: infection; component loosening; revision of components including revision secondary to dislocation/subluxation; implant failure; implant fracture; wear osteolysis; sensitivity to implant materials; nerve impingement; nerve damage; pain; vascular disorders; pulmonary embolism; and surgical error.

Moreover, this list of risks, albeit extensive, is incomplete. Additional arthroplasty risks may be divided into operative and postoperative categories. Additional operative risks include: fractures of the ankle and/or lower extremity bones, which, in rare instances, may lead to avascular necrosis and even amputation; tendon damage; ligament damage; improper device placement; instrument malfunction; and hemorrhage/bleeding. Postoperative risks include: the need for additional stabilization; device migration (with or without reoperation); arthrodesis or other surgical intervention; ligament instability; thrombophlebitis; soft tissue edema; wound dehiscence; and skin slough or breakdown.

Considering the seriousness of several of these identified risks, the special controls proposed by Endotec are clearly inadequate to reasonably ensure the safety and efficacy of the B-P device. Significantly, the proposed controls lack specificity, focusing on relatively standard checks, such as preclinical testing, consensus standards, sterilization, and labeling. Accordingly, they fail to provide effective measures for mitigating the particular risks, including the risk of device failure, that have been associated with clinical use of the B-P Ankle thus far. Developing specific measures requires a broader knowledge of the clinical performance of the B-P Ankle than is currently available. Thus, Endotec's advocated special controls are not based on a sufficiently extensive knowledge of its device's potential risks, unlike the special controls for class II hip and knee replacements. Particularly in comparison to these current class II implants, ankle

²⁸ Class II Special Controls Guidance Document: Knee Joint Patellofemorotibial and Femorotibial Metal/Polymer Porous-Coated Uncemented Prostheses; Guidance for Industry and FDA, issued January 16, 2003.

replacements continue to reveal safety concerns that may only be adequately evaluated through the added rigor of PMA review.

IV. Conclusion

Clinical data on the second-generation, "deep-sulcus" B-P Ankle are still preliminary, and studies that have been published show significant risks associated with use of the device. There are presently no complete reports of prospective, controlled comparisons of total ankle replacements in the literature. Accordingly, Endotec is unable in its petition to provide such reports on use of the B-P Ankle. Instead, Endotec presents only four clinical studies, including the Progress Report of its own IDE study, a retrospective case series reported by the developers of the B-P device, and a retrospective study by an IDE investigator. The fourth study was one surgeon's retrospective review of his first cases with the B-P device, and comprised a small number of cases with a relatively short follow-up period. Further, Endotec fails to supplement this meager clinical data with significant reports on mechanical testing of the B-P Ankle. Continued, comprehensive clinical trials and biomechanical studies are still needed to better identify the seriousness and frequency of the risks that have been associated with use of the B-P Ankle thus far. Moreover, clinical experiences with the Agility Ankle, described above, caution strongly in favor of PMA review to allow for long-term follow-up of ankle implants, which could reveal unanticipated problems, allow better estimates of the frequency of known complications, and result in the development of better strategies to address these complications.

The special controls advocated by Endotec are simply inadequate to control the identified arthroplasty risks and to reasonably assure the safety and effectiveness of ankle prostheses. A number of these potential adverse events, such as osteolysis, device migration, device breakage, bony fractures, and the need for (and feasibility of) salvage fusion procedures, may only be adequately assessed through the added rigor of evaluation that is part of the PMA process. Because this added rigor can be time-consuming and onerous, manufacturers often prefer to have their devices reviewed via the 510(k), rather than the PMA, regulatory pathway. However, for devices such as ankle replacements, the added rigor of the PMA process is necessary to ensure patient safety.

Compared to 510(k)s, PMAs require a more detailed and more lengthy application and a substantially larger volume of information. FDA also has the authority to impose certain postapproval requirements as a condition to approval of a device submitted under the PMA process. These requirements include the filing of annual reports that contain potentially significant information about device safety and efficacy including unpublished data from any clinical or nonclinical studies involving the device, and reports in the scientific literature concerning the device. Postapproval conditions also can include restrictions on the sale,

distribution, or use of a device; and additional labeling requirements. These requirements may include, under the authority of Section 515(d)(1)(B)(ii) of the FDCA, requirements that apply to the training of practitioners who may use the device. FDA may also review the adequacy and comprehensiveness of physician training materials during the course of the PMA review.

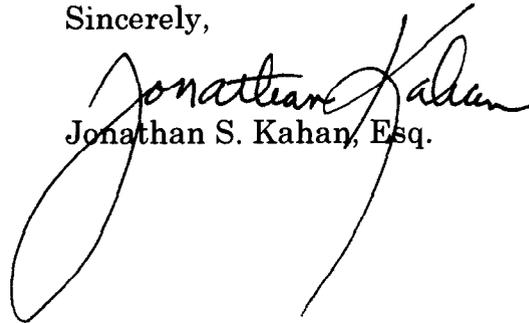
Moreover, PMAs almost always require extensive clinical data, whereas many 510(k)s are cleared without clinical data, and others are cleared with less clinical data than would be required for a PMA. This is a critical issue with ankle replacements, where the adverse events described above can only be adequately assessed through long-term clinical follow-up. For example, the incidence of osteolysis is only now being fully appreciated as more clinical reports are being published with longer follow-up periods. This risk cannot be adequately assessed through mechanical testing alone. Nor can the risk of intra-operative ankle or lower extremity fractures be appreciated absent clinical data. Expert clinicians agree that there is no substitute for clinical experience in assessing the risk that bony fractures may occur during surgery due to difficulties with ankle prosthesis placement, surgical instruments, and peculiarities of local anatomy. Indeed, the extent of this problem, and how to mitigate it through modifications to the surgical procedure and surgical instruments, is only becoming apparent as clinical experience continues to accumulate with these implants. Similarly, risks of device migration and device subsidence may only be appreciated with extensive clinical experience.

It should also be noted that adverse events such as osteolysis, intra-operative fractures, and subsidence, may vary greatly among different ankle replacements, even among those in the same general category as the B-P Ankle. Should these devices be placed in class II, new arthroplasty devices, many of which have been studied for even shorter periods of time and have accumulated less preclinical and clinical information than the B-P Ankle, will be able to claim substantial equivalence to previously-cleared devices, thereby obviating the need to provide the scientific evidence of safety and efficacy required by the PMA process. The requirement to provide clinical trial data utilizing control groups to elucidate the risk-benefit ratio of the new device compared to existing treatments also may be rendered unnecessary. As Endotec aptly points out in its petition, only preliminary data were available on constrained arthroplasties when FDA placed these devices in class II, and the history of the Agility Ankle demonstrates that downclassification was premature. Available data for the B-P Ankle, both preclinical and clinical, are similarly limited, and are in no way commensurate with the volumes of data amassed on class II prosthetic hip and knee replacements. Therefore, given the preliminary nature of the information that exists on arthroplasty devices such the B-P Ankle, special controls alone are inadequate to ensure the safety and efficacy of these devices, and the requirement that these devices undergo the rigor of the PMA review process remains necessary.

HOGAN & HARTSON L.L.P.

We, therefore, oppose Endotec's petition to downclassify the B-P Ankle, and urge the Commissioner to require premarket approval for the device as the only means of reasonably assuring its safety and effectiveness in clinical use.

Sincerely,



Jonathan S. Kahan, Esq.

cc: Gerard J. Prud'homme, Esq.
Steven B. Datlof, M.D., Esq.